AAOS
American Academy of Orthopaedic Surgeons

Management of Osteoarthritis of the Knee (Non-Arthroplasty)

Evidence-Based Clinical Practice Guideline

Adopted by:
The American Academy of Orthopaedic Surgeons Board of Directors
August 31, 2021

Endorsed by:

AAHKS
American Association of Hip and Knee Surgeons

APTA
American Physical Therapy Association

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Disclaimer

This clinical practice guideline (CPG) was developed by a physician volunteer clinical practice guideline development group based on a formal systematic review of the available scientific and clinical information and accepted approaches to treatment and/or diagnosis. This clinical practice guideline is not intended to be a fixed protocol, as some patients may require more or less treatment or different means of diagnosis. Clinical patients may not necessarily be the same as those found in a clinical trial. Patient care and treatment should always be based on a clinician's independent medical judgment, given the individual patient's specific clinical circumstances.

Disclosure Requirement

In accordance with AAOS policy, all individuals whose names appear as authors or contributors to this clinical practice guideline filed a disclosure statement as part of the submission process. All panel members provided full disclosure of potential conflicts of interest prior to voting on the recommendations contained within this clinical practice guideline.

Funding Source

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FDA Clearance

Some drugs or medical devices referenced or described in this Clinical practice guideline may not have been cleared by the Food and Drug Administration (FDA) or may have been cleared for a specific use only. The FDA has stated that it is the responsibility of the physician to determine the FDA clearance status of each drug or device he or she wishes to use in clinical practice.

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SUMMARY OF RECOMMENDATIONS

Lateral Wedge Insoles

Lateral wedge insoles are not recommended for patients with knee osteoarthritis.

Strength of Recommendation: Strong ★★★★

Evidence from two or more "High" quality studies with consistent findings for recommending for or against the intervention. Also requires no reasons to downgrade from the EtD framework.

Canes

Canes could be used to improve pain and function in patients with knee osteoarthritis.

Strength of Recommendation: Moderate ★★★☆

Evidence from two or more "Moderate" quality studies with consistent findings, or evidence from a single "High" quality study for recommending for or against the intervention. Also requires no or only minor concerns addressed in the EtD framework.

Braces

Brace treatment could be used to improve function, pain, and quality of life in patients with knee osteoarthritis

Strength of Recommendation: Moderate ★★★☆ (downgrade)

Evidence from two or more "Moderate" quality studies with consistent findings, or evidence from a single "High" quality study for recommending for or against the intervention. Also requires no or only minor concerns addressed in the EtD framework.

Oral/Dietary Supplements

The following supplements may be helpful in reducing pain and improving function for patients with mild to moderate knee osteoarthritis; however, the evidence is inconsistent/limited and additional research clarifying the efficacy of each supplement is needed.

- **Turmeric**
- **Ginger extract**
- **Glucosamine**
- **Chondroitin**
- **Vitamin D**

Strength of Recommendation: Limited ★★☆☆ (downgrade)

Description: Evidence from one or more "Low" quality studies with consistent findings or evidence from a single "Moderate" quality study recommending for or against the intervention. Also, higher strength evidence can be downgraded to limited due to major concerns addressed in the EtD Framework.

Topical Treatments

Topical NSAIDs should be used to improve function and quality of life for treatment of osteoarthritis of the knee, when not contraindicated.

Strength of Recommendation: Strong ★★★★

Evidence from two or more "High" quality studies with consistent findings for recommending for or against the intervention. Also requires no reasons to downgrade from the EtD framework.

Supervised Exercise

Supervised exercise, unsupervised exercise, and/or aquatic exercise are recommended over no exercise to improve pain and function for treatment of knee osteoarthritis.

Strength of Recommendation: Strong ★★★★

Evidence from two or more "High" quality studies with consistent findings for recommending for or against the intervention. Also requires no reasons to downgrade from the EtD framework.

Neuromuscular Training

Neuromuscular training (i.e. balance, agility, coordination) programs in combination with traditional exercise could be used to improve performance-based function and walking speed for treatment of knee osteoarthritis.

Strength of Recommendation: Moderate ★★★☆ (downgrade)

Evidence from two or more "Moderate" quality studies with consistent findings, or evidence from a single "High" quality study for recommending for or against the intervention. Also requires no or only minor concerns addressed in the EtD framework.

Self-Management

Self- management programs are recommended to improve pain and function for patients with knee osteoarthritis.

Strength of Recommendation: Strong ★★★★

Evidence from two or more "High" quality studies with consistent findings for recommending for or against the intervention. Also requires no reasons to downgrade from the EtD framework.

Patient Education

Patient education programs are recommended to improve pain in patients with knee osteoarthritis.

Strength of Recommendation: Strong ★★★★

Evidence from two or more "High" quality studies with consistent findings for recommending for or against the intervention. Also requires no reasons to downgrade from the EtD framework.

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Weight Loss Intervention

Sustained weight loss is recommended to improve pain and function in overweight and obese patients with knee osteoarthritis.

Strength of Recommendation: Moderate ★★★☆ (downgrade)
Evidence from two or more "Moderate" quality studies with consistent findings, or evidence from a single "High" quality study for recommending for or against the intervention. Also requires no or only minor concerns addressed in the EtD framework.

Manual Therapy

Manual therapy in addition to an exercise program may be used to improve pain and function in patients with knee osteoarthritis.

Strength of Recommendation: Limited ★★☆☆ (downgrade)
Evidence from two or more "Moderate" quality studies with consistent findings, or evidence from a single "High" quality study for recommending for or against the intervention. Also requires no or only minor concerns addressed in the EtD framework.

Massage

Massage may be used in addition to usual care to improve pain and function in patients with knee osteoarthritis.

Strength of Recommendation: Limited ★★☆☆ (downgrade)
Evidence from two or more "Moderate" quality studies with consistent findings, or evidence from a single "High" quality study for recommending for or against the intervention. Also requires no or only minor concerns addressed in the EtD framework.

Laser Treatment

FDA-approved laser treatment may be used to improve pain and function in patients with knee osteoarthritis.

Strength of Recommendation: Limited ★★☆☆ (downgrade)
Evidence from two or more "Moderate" quality studies with consistent findings, or evidence from a single "High" quality study for recommending for or against the intervention. Also requires no or only minor concerns addressed in the EtD framework.

Acupuncture

Acupuncture may improve pain and function in patients with knee osteoarthritis.

Strength of Recommendation: Limited ★★☆☆ (downgrade)
Evidence from two or more "Moderate" quality studies with consistent findings, or evidence from a single "High" quality study for recommending for or against the intervention. Also requires no or only minor concerns addressed in the EtD framework.

Transcutaneous Electrical Nerve Stimulation

Modalities that may be used to improve pain and/or function in patients with knee osteoarthritis include:

a. **Transcutaneous Electrical Nerve Stimulation (pain)**

Strength of Recommendation: Limited ★★☆☆ (downgrade)
Evidence from two or more "High" quality studies with consistent findings for recommending for or against the intervention. Also requires no reasons to downgrade from the EtD framework.

Percutaneous Electrical Nerve Stimulation/Pulsed Electromagnetic Field Therapy

Modalities that may be used to improve pain and/or function in patients with knee osteoarthritis include:

a. **Percutaneous Electrical Nerve Stimulation (pain and function)**
b. **Pulsed Electromagnetic Field Therapy (pain)**

Strength of Recommendation: Limited ★★☆☆ (downgrade)
Evidence from two or more "Moderate" quality studies with consistent findings, or evidence from a single "High" quality study for recommending for or against the intervention. Also requires no or only minor concerns addressed in the EtD framework.

Extracorporeal Shockwave Therapy

Extracorporeal shockwave therapy may be used to improve pain and function for treatment of osteoarthritis of the knee.

Strength of Recommendation: Limited ★★☆☆ (downgrade)
Evidence from two or more "Moderate" quality studies with consistent findings, or evidence from a single "High" quality study for recommending for or against the intervention. Also requires no or only minor concerns addressed in the EtD framework.

Oral NSAIDs

Oral NSAIDs are recommended to improve pain and function in the treatment of knee osteoarthritis when not contraindicated.

Strength of Recommendation: Strong ★★★★
Evidence from two or more "High" quality studies with consistent findings for recommending for or against the intervention. Also requires no reasons to downgrade from the EtD framework.

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Oral Acetaminophen

Oral acetaminophen is recommended to improve pain and function in the treatment of knee osteoarthritis when not contraindicated.

Strength of Recommendation: Strong ★★★★

Evidence from two or more "High" quality studies with consistent findings for recommending for or against the intervention. Also requires no reasons to downgrade from the EtD framework.

Oral Narcotics

Oral narcotics, including tramadol, result in a significant increase of adverse events and are not effective at improving pain or function for treatment of osteoarthritis of the knee.

Strength of Recommendation: Strong ★★★★

Evidence from two or more "High" quality studies with consistent findings for recommending for or against the intervention. Also requires no reasons to downgrade from the EtD framework.

Hyaluronic Acid

Hyaluronic acid intra-articular injection(s) is not recommended for routine use in the treatment of symptomatic osteoarthritis of the knee.

Strength of Recommendation: Moderate ★★★☆ (downgrade)

Evidence from two or more "Moderate" quality studies with consistent findings, or evidence from a single "High" quality study for recommending for or against the intervention. Also requires no or only minor concerns addressed in the EtD framework.

Intra-articular Corticosteroids

Intra-articular (IA) corticosteroids could provide short-term relief for patients with symptomatic osteoarthritis of the knee.

Strength of Recommendation: Moderate ★★★☆ (downgrade)

Evidence from two or more "Moderate" quality studies with consistent findings, or evidence from a single "High" quality study for recommending for or against the intervention. Also requires no or only minor concerns addressed in the EtD framework.

Platelet-rich Plasma

Platelet-rich plasma (PRP) may reduce pain and improve function in patients with symptomatic osteoarthritis of the knee.

Strength of Recommendation: Limited ★★☆☆(downgrade)

Description: Evidence from one or more "Low" quality studies with consistent findings or evidence from a single "Moderate" quality study recommending for or against the intervention. Also, higher strength evidence can be downgraded to limited due to major concerns addressed in the EtD Framework.

Denervation Therapy

Denervation therapy may reduce pain and improve function in patients with symptomatic osteoarthritis of the knee.

Strength of Recommendation: Limited ★★☆☆ (downgrade)
Description: Evidence from one or more "Low" quality studies with consistent findings or evidence from a single "Moderate" quality study recommending for or against the intervention. Also, higher strength evidence can be downgraded to limited due to major concerns addressed in the EtD Framework.

Lavage/Debridement

Arthroscopy with lavage and/or debridement in patients with a primary diagnosis of knee osteoarthritis is not recommended.

Strength of Recommendation: Moderate ★★★☆
Description: Evidence from two or more "Moderate" quality studies with consistent findings, or evidence from a single "High" quality study for recommending for or against the intervention. Also requires no or only minor concerns addressed in the EtD framework.

Partial Meniscectomy

Arthroscopic partial meniscectomy can be used for the treatment of meniscal tears in patients with concomitant mild to moderate osteoarthritis who have failed physical therapy or other nonsurgical treatments.

Strength of Recommendation: Moderate ★★★☆
Evidence from two or more "Moderate" quality studies with consistent findings, or evidence from a single "High" quality study for recommending for or against the intervention. Also requires no or only minor concerns addressed in the EtD framework.

Tibial Osteotomy

High tibial osteotomy may be considered to improve pain and function in properly indicated patients with unicompartmental knee osteoarthritis.

Strength of Recommendation: Limited ★★☆☆ (downgrade)
Description: Evidence from one or more "Low" quality studies with consistent findings or evidence from a single "Moderate" quality study recommending for or against the intervention. Also, higher strength evidence can be downgraded to limited due to major concerns addressed in the EtD Framework.

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Summary of Consensus Statement

There is no evidence or only conflicting supporting evidence for the following recommendations. In the absence of reliable evidence, the systematic literature review development group is making a recommendation based on their clinical opinion.

Dry Needling

In the absence of reliable evidence, it is the opinion of the workgroup that the utility/efficacy of dry needling is unclear and requires additional evidence.

Strength of Recommendation: Consensus ★☆☆☆

Description: Evidence there is no supporting evidence, or limited level evidence was downgraded due to major concerns addressed in the EtD framework. In the absence of reliable evidence, the guideline work group is making a recommendation based on their clinical opinion.

Free Floating Interpositional Devices

In the absence of reliable or new evidence, it is the opinion of the work group not to use free-floating (un-fixed) interpositional devices in patients with symptomatic medial compartment osteoarthritis of the knee.

Strength of Recommendation: Consensus ★☆☆☆

Description: Evidence there is no supporting evidence, or limited level evidence was downgraded due to major concerns addressed in the EtD framework. In the absence of reliable evidence, the guideline work group is making a recommendation based on their clinical opinion.

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INTRODUCTION

OVERVIEW

This clinical practice guideline is based on a systematic review of published studies examining the non-arthroplasty treatment of knee osteoarthritis in adults. It provides recommendations that will help practitioners to integrate the current evidence and clinical practice, and it highlights gaps in the literature in need of future research. This guideline is intended to be used by appropriately trained physicians and clinicians who manage the treatment of osteoarthritis of the knee. It also serves as an information resource for developers and applied users of clinical practice guidelines.

GOALS AND RATIONALE

The purpose of this clinical practice guideline is to evaluate the current best evidence associated with treatment. Evidence-based medicine (EBM) standards advocate for use of empirical evidence by physicians in their clinical decision making. To assist with access to the large resources of information, a systematic review of the literature in publication was conducted between March 2018 and April 28, 2020. It highlights where there is good evidence, where evidence is lacking, and what topics future research will need to target in order to help facilitate evidence-based decision making in the treatment of patients with osteoarthritis of the knee. AAOS staff methodologists assisted the physician/clinician work group in evaluating the existing literature so that they could formulate the following recommendations based on a rigorous systematic process. Musculoskeletal care is provided in many different settings and by a variety of providers. We created this guideline as an educational tool to guide qualified physicians and clinicians in making treatment decisions that improve the quality and efficacy of care. This guideline should not be construed as including all possible methods of care or excluding acceptable interventions similarly directed at obtaining favorable outcomes. The final decision to use a specific procedure must be made after assessing all concerns presented by the patient and consideration of locality-specific resources.

INTENDED USERS

This guideline is intended to be used by orthopaedic surgeons and other healthcare providers managing patients with osteoarthritis of the knee. It serves as an information resource for medical practitioners. In general, individual practicing physicians and clinicians do not have the resources required to complete a project of comparable scope and duration involving the evaluation of an extensive literature base. In April 2019, the AAOS adopted the use of the GRADE Evidence-to-Decision Framework into its clinical practice guideline development methodology. This Framework enables work group members to incorporate additional factors into the strength of each recommendation and move away from the rigidity of previous AAOS recommendation language stems. The AAOS intends for this guideline to assist treatment providers not only in making shared clinical decisions with their patients, but also in describing to patients and their loved ones why a selected intervention represents the best available course of treatment. This guideline is not intended for use as a benefits determination document. It does not cover allocation of resources, business and ethical considerations, and other factors needed to determine the material value of orthopaedic care. Users of this guideline may also want to consider the appropriate use criteria (AUC) related to the treatment of osteoarthritis of the knee.

PATIENT POPULATION

This guideline is intended for use with adults (ages 17 years and older) who have been diagnosed by a trained healthcare provider with osteoarthritis of the knee and are undergoing treatment.

SCOPE

The scope of this guideline includes non-pharmacologic and pharmacologic interventions for symptomatic osteoarthritis of the knee as well as operative procedures less invasive than knee

replacement (arthroplasty). It does not provide recommendations for patients diagnosed with rheumatoid arthritis, osteoarthritis of other joints, or other inflammatory arthropathies.

ETIOLOGY

Osteoarthritis results from an imbalance between breakdown and repair of the tissues in the synovial joint organ and occurs as a result of multiple risk factors including trauma, overuse, and genetic predisposition.

INCIDENCE AND PREVALENCE

The incidence of knee osteoarthritis in the United States is estimated at 240 persons per 100,000 per year. Worldwide prevalence of radiographically confirmed symptomatic knee OA is estimated to be 3.8% overall, increasing with age to over 10% in the population over the age of 60.

BURDEN OF DISEASE

Osteoarthritis (of any joint) was the primary diagnosis for 23.7 million ambulatory care visits in 2013. An estimated 32.5 million adults in American, 14% of that population, suffered from symptomatic knee osteoarthritis between 2008 and 2014. Risk factors of the condition increase with age, especially in women. Although women represent 51% of the general population in the United States, they represent 78% of the patients diagnosed with osteoarthritis between 2008 and 2014. Genetics and hereditary vulnerability, elevated body mass, certain occupations, and traumatic knee injuries are other factors that increase one's risk of developing the disease.

EMOTIONAL AND PHYSICAL IMPACT

Older adults with self-reported osteoarthritis visit their physicians more frequently and experience greater functional limitations than others in the same age group. The aging of the baby boomers, rise in rates of obesity, and greater emphasis on staying active suggest that the social and physical impact of knee osteoarthritis will continue to be widespread.

POTENTIAL BENEFITS, HARM, AND CONTRAINDICATIONS

Individuals with osteoarthritis of the knee often complain of joint pain, stiffness, and difficulty with purposeful movement. The aim of treatment is to provide pain relief and improve the patient's functioning. Most interventions are associated with some potential for adverse outcomes, especially if invasive or operative. Because the clinical research does not differentiate between the sexes, it is possible future research may result in a better understanding of how a patient's sex alters treatment benefits and harms. Contraindications vary widely by procedure. Reducing risks improves treatment efficacy and is accomplished through collaboration between patient and physician.

DIFFERENCES BETWEEN THE PRESENT AND PREVIOUS GUIDELINES

This updated clinical practice guideline replaces the second edition that was completed in 2013, "Treatment of Osteoarthritis of the Knee (Non-Arthroplasty) 2nd edition." This update considered the literature that we previously examined as well as the empirical evidence published since the 2013 guideline. In April 2019, the AAOS adopted the use of the GRADE Evidence-to-Decision Framework into its clinical practice guideline development methodology. This Framework enables work group members to incorporate additional factors into the strength of each recommendation and move away from the rigidity of previous AAOS recommendation language stems. The complete listing of inclusion criteria for this guideline is detailed in the section, "Study Selection Criteria," (eAppendix 1).

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METHODS

The methods used to perform this systematic review were employed to minimize bias and enhance transparency in the selection, appraisal, and analysis of the available evidence. These processes are vital to the development of reliable, transparent, and accurate clinical recommendations. To view the full AAOS clinical practice guideline methodology please visit https://www.aaos.org/additonalresources/ .

This clinical practice guideline evaluates the management of osteoarthritis of the knee (non-arthroplasty) patient outcomes. The AAOS approach incorporates practicing physicians (clinical experts) and methodologists who are free of potential conflicts of interest relevant to the topic under study, as recommended by clinical practice guideline development experts.[1]

This clinical practice guideline was prepared by the AAOS Osteoarthritis of the Knee Guideline physician development group (clinical experts) with the assistance of the AAOS Clinical Quality and Value (CQV) Department (methodologists). To develop this clinical practice guideline, the clinical practice guideline development group held an introductory meeting on February 23, 2018 to establish the scope of the clinical practice guideline. As the physician experts, the clinical practice guideline development group defined the scope of the clinical practice guideline by creating PICO Questions (i.e. population, intervention, comparison, and outcome) that directed the literature search. The AAOS Medical Librarian created and executed the search (see Appendix III for search strategy).

LITERATURE SEARCHES

We begin the systematic review with a comprehensive search of the literature. Articles we consider were published prior to the start date of the search in a minimum of three electronic databases; PubMed, EMBASE, and the Cochrane Central Register of Controlled Trials. The medical librarian conducts the search using key terms determined from the guideline development group's PICO questions.

A CQV methodologist will review/include only primary literature but will supplement the electronic search with a manual search of the bibliographies of secondary literature sources, such as systematic reviews, as available. The methodologist will then evaluate all recalled articles for possible inclusion based on the study selection criteria and will summarize the evidence for the guideline work group who assist with reconciling possible errors and omissions.
A study attrition diagram is provided in the appendix of each document that details the numbers of identified abstracts, recalled and selected studies, and excluded studies that were evaluated in the CPG. The search strategies used to identify the abstracts is also included in the appendix of each CPG document.

DEFINING THE STRENGTH OF RECOMMENDATION

Judging the quality of evidence is only a steppingstone towards arriving at the strength of a CPG recommendation. The strength of recommendation also takes into account the quality, quantity, and the trade-off between the benefits and harms of a treatment, the magnitude of a treatment's effect, and whether data exists on critical outcomes.

Strength of recommendation expresses the degree of confidence one can have in a recommendation. As such, the strength expresses how possible it is that a recommendation will be overturned by future evidence. It is very difficult for future evidence to overturn a recommendation that is based on many high quality randomized controlled trials that show a large effect. It is much more likely that future evidence will overturn recommendations derived from a few small retrospective comparative studies. Consequently, recommendations based on the former kind of evidence are given a "strong" strength of recommendation and recommendations based on the latter kind of evidence are given a "limited" strength.

To develop the strength of a recommendation, AAOS staff first assigned a preliminary strength for each recommendation that took only the final quality and the quantity of evidence (see Table 1). The recommendations can be further downgraded or upgraded based on the GRADE and Evidence-to-Decision Framework criteria described above.

VOTING ON THE RECOMMENDATIONS

The recommendations and their strength were voted on by the guideline development group members during the final meeting. If disagreement between the guideline development group occurred, there was further discussion to see whether the disagreement(s) could be resolved. Recommendations were approved and adopted in instances where a simple majority (60%) of the guideline development group voted to approve; however, the guideline development group had consensus (100% approval) when voting on every recommendation for this guideline. Any recommendation strength upgrade or downgrade based on the Evidence-to-Decision Framework requires a super majority (75%) approval of the work group.

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INTERPRETING THE STRENGTH OF EVIDENCE

Table I. LEVEL OF EVIDENCE DESCRIPTIONS

Strength	Overall Strength of Evidence	Description of Evidence Quality	Strength Visual
Strong	Strong or Moderate	Evidence from two or more "High" quality studies with consistent findings for recommending for or against the intervention. Or Rec is upgrade from Moderate using the EtD framework	
Moderate	Strong, Moderate or Limited	Evidence from two or more "Moderate" quality studies with consistent findings, or evidence from a single "High" quality study for recommending for or against the intervention. Or Rec is upgraded or downgraded from Limited or Strong using the EtD framework.	
Limited	Limited or Moderate	Evidence from one or more "Low" quality studies with consistent findings or evidence from a single "Moderate" quality study recommending for or against the intervention. Or Rec is downgraded from Moderate using the EtD Framework.	
Consensus*	No Evidence	There is no supporting evidence, or higher quality evidence was downgraded due to major concerns addressed in the EtD framework. In the absence of reliable evidence, the guideline work group is making a recommendation based on their clinical opinion.	

Table II. INTERPRETING THE STRENGTH OF A RECOMMENDATION

Strength of Recommendation	Patient Counseling (Time)	Decision Aids	Impact of Future Research
Strong	Least	Least Important, unless the evidence supports no difference between two alternative interventions	Not likely to change
Moderate	Less	Less Important	Less likely to change
Limited	More	Important	Change possible/anticipated
Consensus	Most	Most Important	Impact unknown

REVIEW PERIOD

Following the final meeting, the CPG draft undergoes a 3-week review period for additional input from external content experts. Written comments are provided on the structured review form. All reviewers are required to disclose their conflicts of interest.

To guide who participates, the CPG work group identifies specialty societies at the introductory meeting. Organizations, not individuals, are specified.

The specialty societies are solicited for nominations of individual reviewers approximately six weeks before the final meeting. The review period is announced as it approaches, and others interested are able to volunteer to review the draft. The chairs of the guideline work group review the draft of the guideline prior to dissemination.

Some specialty societies (both orthopaedic and non-orthopaedic) ask their evidence-based practice (EBP) committee to provide review of the guideline. The organization is responsible for coordinating the distribution of our materials and consolidating their comments onto one form. The chair of the external EBP committees provides disclosure of their conflicts of interest (COI) and manages the potential conflicts of their members.

Again, the AAOS asks for comments to be assembled into a single response form by the specialty society and for the individual submitting the review to provide disclosure of potentially conflicting interests. The review stage gives external stakeholders an opportunity to provide evidence-based direction for modifications that they believe have been overlooked. Since the draft is subject to revisions until its approval by the AAOS Board of Directors as the final step in the guideline development process, confidentiality of all working drafts is essential.

The CPG is also provided to members of the AAOS Board of Directors (BOD), members of the Council on Research and Quality (CORQ), members of the Board of Councilors (BOC), and members of the Board of Specialty Societies (BOS) and members of the Committee on Evidence-Based Quality and Value (EBQV) for review and comment. The CPG is automatically forwarded to the AAOS BOD and CORQ so that they may review it and provide comment prior to being asked to approve the document. Members of the BOC and BOS are solicited for interest. If they request to see the document, it is forwarded to them for comment. Based on these bodies, over 200 commentators have the opportunity to provide input into each CPG.

The chairs of the guideline work group and the manager of the AAOS CQV unit drafts the initial responses to comments that address methodology. These responses are then reviewed by the chair and co-chair, who respond to questions concerning clinical practice and techniques. The Senior Manager of Clinical Quality and Value may provide input as well. All comments received and the initial drafts of the responses are also reviewed by all members of the guideline development group. All proposed changes to recommendation language as a result of the review period are based on the evidence. Final revisions are summarized in a report that is provided alongside the guideline document throughout the remainder of the approval processes and final publication.

The AAOS believes in the importance of demonstrating responsiveness to input received during the review process and welcomes the critiques of external specialty societies. Following final approval of the guideline, all individual responses are posted on our website http://www.aaos.org/quality with a point-by-point reply to each non-editorial comment. Reviewers who wish to remain anonymous notify the AAOS to have their names de-identified; their comments, our responses, and their COI disclosures are still posted.

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THE AAOS CPG APPROVAL PROCESS

This final clinical practice guideline draft must be approved by the AAOS Committee on Evidence Based Quality and Value Committee, and subsequently the AAOS Council on Research and Quality, and the AAOS Board of Directors. These decision-making bodies are described in the OAK CPG eAppendix. Their charge is to approve or reject its publication by majority vote.

REVISION PLANS

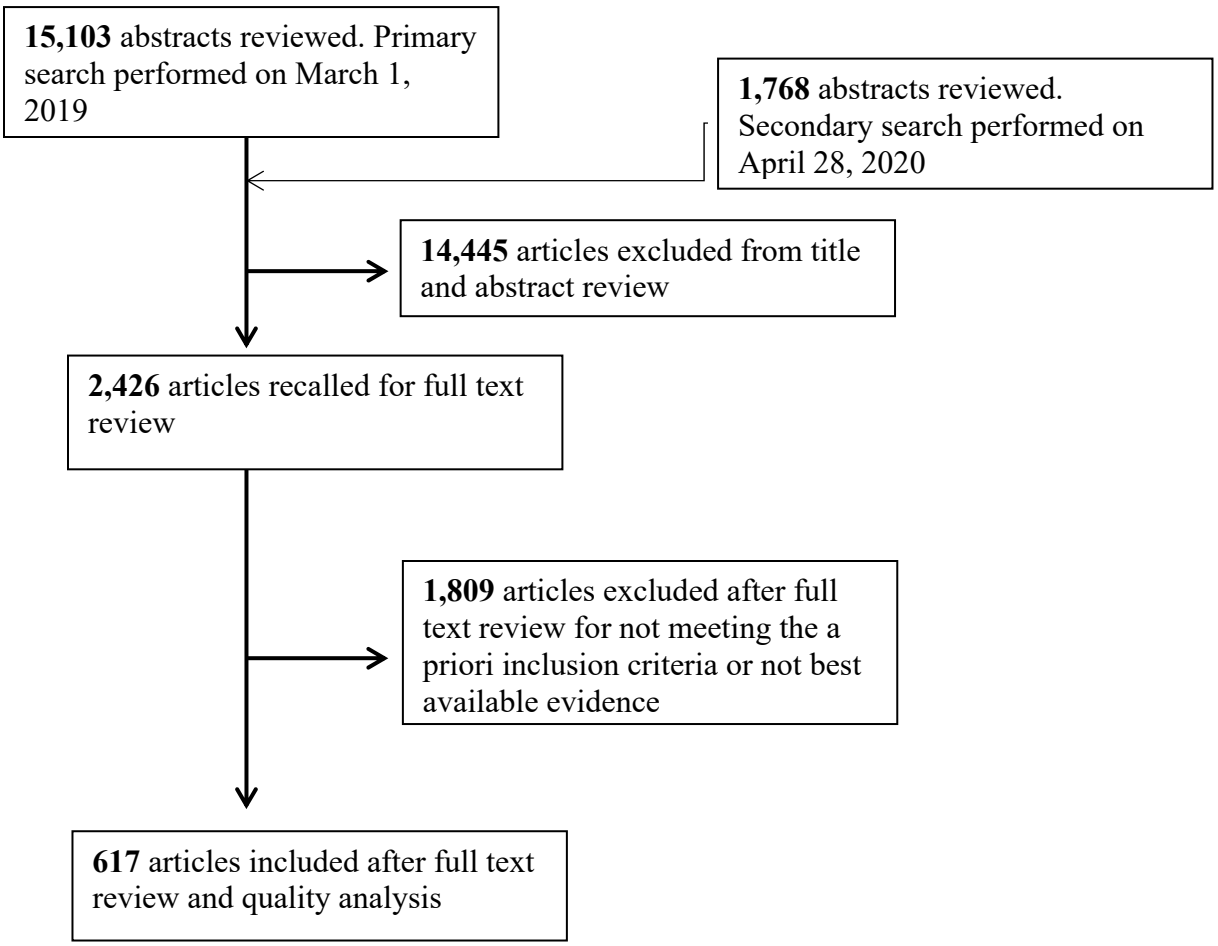
This clinical practice guideline represents a cross-sectional view of current treatment and may become outdated as new evidence becomes available. This clinical practice guideline will be revised in accordance with new evidence, changing practice, rapidly emerging treatment options, and new technology. This clinical practice guideline will be updated or withdrawn in five years.

CPG DISSEMINATION PLANS

The primary purpose of the present document is to provide interested readers with full documentation of the best available evidence for various procedures associated with the topic of this review. Publication of most clinical practice guidelines is announced by an Academy press release, articles authored by the clinical practice guideline development group and published in the Journal of the American Academy of Orthopaedic Surgeons, and articles published in AAOS *Now*. Most clinical practice guidelines are also distributed at the AAOS Annual Meeting in various venues such as on Academy Row and at Committee Scientific Exhibits. The final guideline recommendations and their supporting rationales will be hosted on www.OrthoGuidelines.org.

Selected clinical practice guidelines are disseminated by webinar, an Online Module for the Orthopaedic Knowledge Online website, Radio Media Tours, Media Briefings, and by distributing them at relevant Continuing Medical Education (CME) courses and at the AAOS Resource Center.

Study Attrition Flowchart



View background material via the OAK3 CPG eAppendix 1
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RECOMMENDATIONS

Lateral Wedge Insoles

Lateral wedge insoles are not recommended for patients with knee osteoarthritis.

Strength of Recommendation: Strong ★★★★

Evidence from two or more "High" quality studies with consistent findings for recommending for or against the intervention. Also requires no reasons to downgrade from the EtD framework.

Rationale

Although lateral heel wedges had historical support for their use in knee arthritis, contemporary studies have not shown a reliable improvement in pain relief and no contemporary studies have shown sufficient functional improvement for patients suffering from knee arthritis to recommend using lateral wedge insoles. Lateral heel wedges can be prepared as an insert for the heel alone, or included in the heel of an independent arch support (i.e. lateral heel wedge arch support of LWAS) or built into shoe itself (as was used by Hinman et al 2016). In the arthritic knee, medial compartment compression forces are commonly increased, especially in the knee with varus tibiofemoral alignment. The knee adduction moment can be calculated by gait analysis. The lateral wedge is thought to change the knee adduction moment thus relieving medial compartment pressure, hence relieving arthritic pain.

Our literature review screening culled several papers for analysis. Baker and Goggins 2007 was a high-quality study finding no important differences between insole and wedged insole. 90 patients were randomized to one treatment for 6 weeks followed by a 4-week washout period and then the opposite treatment. There were no major differences in pain during either phase of the study. More musculoskeletal symptoms and more blisters occurred with neutral insoles. No patient falls were attributed to the treatment alternatives.

Felson and Parke 2019 prescreened patients to eliminate those with patellofemoral OA and biomechanical non-responders. Lateral wedge insoles reduced knee pain, but the effect of treatment was small and was considered likely of clinical significance in only a minority of patients. 21 of 83 of patients did not show sufficient biomechanical correction. Only 28% of patients in the active phase of treatment had minimally important improvement whereas 22% of patients wearing neutral insoles reached the same level of improvement. 2 patients stopped treatment while wearing lateral wedge insoles (calf pain at night and increased knee pain) and 2 stopped while wearing neutral insoles (toe blister and increased knee pain). They also looked at volume of arthritic bone marrow lesions (BML) found by MRI and saw no significant difference in BML change between study and control groups.

In Bennell 2011, 89 patients with mild to moderate knee arthritis completed follow up with lateral insoles worn daily for 12 months. 90 patients completed follow up as the control group wearing neutral insoles. Pain relief after 12 months showed no significant difference between the groups.

In Hsieh 2016, 90 patients with Kellgren-Lawrence Grade 2 or higher radiographic changes were randomized to either a rigid insole with lateral wedge arch support (LWAS) or a soft insole with lateral wedge. Dropout rate was 20% with rigid and 15.6% with soft insoles over the 3-month long study. They concluded that patients using the soft insole LWAS had improved pain and function. However, their primary data suggests better walking time and speed going up and down stairs with rigid LWAS.

Furthermore, pain was improved with soft LWAS only at the 3-month mark. Authors suggested longer term follow up for soft insoles.

Hinman 2016 evaluated an unloading shoe with stiff lateral midsole and 5 degree lateral wedge insole in comparison to a standard walking shoe. 164 patients were enrolled with 96% retention during the 6 months study. 83 patients received the unloading shoes and the control shoes. 14 of 83 stopped wearing the unloading shoes for various reasons and 8 of 81 stopped wearing the control shoes. 160 completed primary outcome measures at 6 months. There was no significant difference between groups with regard to pain or function, although both groups did show improvement.

20% of participants with the study shoes reported ankle and foot pain whereas 9% of control shoe participants did so. There was no difference in reason to discontinue treatment (unloading shoe 4% versus 2% control). Other reported adverse events were back pain, hip pain, knee pain, knee stiffness/swelling and shin/calf pain. 2 of 83 experimental group patients reported increase in knee pain with the unloading shoe and 2 or 81 control patients reported that the conventional shoe did not relieve knee pain.

Toda 2004 followed 84 knee female arthritis patients were followed for one month wearing either a hard rubber insole or urethane insole secured to the foot with a subtalar strap used for ankle sprains. 12 mm lateral wedge was manufactured for both. 17 of the 42 rubber insole patients had complications (foot pain in 8; popliteal pain in 6; low back pain in 3) versus 8 of the 42 using urethane insoles (popliteal pain in 4; foot pain in 3; low back pain in 1). All patients improved by the Lequesne Index with the urethane group achieving statistically significant improvement.

Niazi 2014 was a comparison of off-loading knee brace versus lateral wedge insole. 120 patients with both radiographic medial compartment arthritis and gene varum were randomized to either knee brace or lateral wedge insole. Pain improvement with the knee brace group was statistically significant compared to the lateral wedge insole, but clinically minor (VAS 3.97 in the study group compared to 4.53 in controls).

In Hatef 2013, 118 of 150 patients completed the 2-month long study (101 women and 17 men). Half were given LWAS and the control group wore neutral insoles. Patient compliance was much worse in the LWAS group. They noted statistically significant decline in knee pain and EKFS in women in the LWAS, but not men. Overall, there was improvement in the LWAS group. There was a much higher non-compliance rate in the LWAS than with the neutral insoles with 29 of 57 patients stopping use of the insoles by weeks 5 to 6 of an 8-week study.

We identified one potential study within our literature which addressed the question of special shoe versus a conventional shoe. Nigg 2006 evaluated a training shoe which purports to convert a flat hard surface into “natural uneven ground”, thus prompting increased muscle activity in the lower extremity. The control shoe was a standard walking shoe. 58 patients were enrolled in the study group and 67 in the control group. Both groups had one patient drop out (cumbersome shoes in the study group and increased knee pain with the control shoe). Pain with walking was improved at 12 weeks in both groups, without between groups difference. The study shoe showed increased pain relief at 3, 6 and 12 weeks. The control shoe showed increased pain relief at 3 and 12 weeks. They also reported improved balance from baseline in the study shoe at 12 weeks which was not statistically significant.

Benefits/Harms of Implementation

Although lower extremity pain might be increased with either neutral insole or LWAS, there is no significant harm to the patient trying either option.

View background material via the OAK3 CPG eAppendix 1
View data summaries via the OAK3 CPG eAppendix 2

Cost Effectiveness/Resource Utilization
A standard insole or conventional walking shoe provided equivalent improvement in pain compared to lateral wedge arch support. Although the lateral wedge modifications are more expensive, the increased cost is not prohibitive and a patient attempting self-treatment could discontinue at any time with little loss of time effort or out of pocket cost.

Acceptability
Insoles are already commercially available and have long history of orthopaedic use. They can fit or be adapted to a variety of shoes, commonly already owned by the patient. Some studies reviewed (Hsieh 2016 and Hatef 2013) also described a relatively high dropout or non-compliance rate. While this does not imply frank harm to the patient, such data do suggest distinct potential for patient dissatisfaction with the treatment.

Feasibility
Although there are no immediately obvious limits to feasibility of implementing neutral insoles or LWAS for knee pain, Felson 2019 confirmed previous studies by showing 25% of their potential subjects did not correct knee adduction when using the lateral wedge.

Future Research
We did not identify any studies of sufficient size comparing a “walking shoe” versus a random or conventional shoe. The studies reviewed by the workgroup suggest that a walking shoe or a soft neutral insole might provide some degree of pain relief. Future studies addressing this treatment option could confirm some type of specialized yet commercially available shoe as beneficial to the patient with knee arthritis.

Canes

Canes could be used to improve pain and function in patients with knee osteoarthritis.

Strength of Recommendation: Moderate ★★★☆
Evidence from two or more "Moderate" quality studies with consistent findings, or evidence from a single "High" quality study for recommending for or against the intervention. Also requires no or only minor concerns addressed in the EtD framework.

Rationale

Canes have been used since antiquity for lower extremity orthopaedic disorders. With that in mind, only a small number of modern studies have formally investigated use of a cane for knee osteoarthritis. Our literature review found one high quality study (Jones 2012) showing support for use regarding moderate pain relief and another study (Van Ginckel 2019) of moderate quality showing no major improvement in pain.

Jones 2012 performed a comprehensive study of use of a cane for knee osteoarthritis. Their primary outcome was pain, but they also looked at function, general health, consumption of NSAIDs and energy expenditure. 64 patients were selected out a total of 323 patients nominated from a rheumatology clinic. The majority of possible patients (168 out of 323) refused to participate in the study. 32 patients were randomized to use of a cane for 60 days (EG, experimental group). The cane was cut to appropriate height and they received instructions on its use. The 32 control patients (CG) were instructed to maintain normal lifestyle and not to use auxiliary gait devices. At 30 and 60 days the EG patients had less pain compared to controls. The greatest improvement was in the VAS (10 cm scale): EG averaging 3.84 cm and CG 5.95 cm at 60 days). The Lequesne scale (0-24) difference was only 2.53 (CG 15.09 and EG 12.56 at 60 days). At 60 days, the study group consumed fewer NSAIDs than control.

Van Ginckel 2019 evaluated use of a cane in patients with medial compartment knee osteoarthritis and bone marrow lesions (BML) on MRI. The primary intent of their study was to identify an effect on the size of BML by using a cane. Out of 1989 potential patients (contacted by phone or online) 231 were considered eligible for radiographic screening and of those, only 79 showed arthritic changes on plain films and BML on MRI and chose to continue with the study. 40 patients were assigned to use a cane whenever walking for the next 12 weeks. 39 control patients were instructed to maintain their usual lifestyle without any gait aids. Only one patient in the control group was lost to follow up. After 3 months there was no significant improvement in BML size. Secondary information was obtained relative to clinical characteristics. There was no significant difference between the two groups with regards to knee pain (WOMAC scale) or quality of life (AQoL 6-D scale) although there was improvement in global knee pain in the group using the cane.

Benefits/Harms of Implementation

Jones 2012 addressed the increased oxygen demand for ambulation using a cane. Initially all patients had decreased ambulation distance with a cane and increased heart rate and increased oxygen consumption. After 60 days patients who had been using the cane (EG) were able to ambulate a similar distance with or without the cane suggesting an ability to adapt to the cane. Also, EG patients using the cane had more normal oxygen consumption after walking again suggesting physiologic adaptation to the cane with time.

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Outcome Importance
Our review shows moderate confirmation that canes can relieve the pain of knee arthritis and improve function in those patients.

Cost Effectiveness/Resource Utilization
Use of a cane is a common low-cost treatment which is readily available with many options and typically covered by third party payers.

Acceptability
Van Ginckel noted “patient vanity” as a common reason for non-compliance.

Feasibility
Canes have been used since antiquity although comparison studies are only being produced in the last generation. There is little downside to extended use of the cane as patients appear to adapt to the increased oxygen consumption demands.

Future Research
More studies would be beneficial to the knowledge base confirming value to patients with knee osteoarthritis.

Braces

Brace treatment could be used to improve function, pain and quality of life in patients with knee osteoarthritis.

Strength of Recommendation: Moderate★★★☆ (downgrade)
Evidence from two or more "Moderate" quality studies with consistent findings, or evidence from a single "High" quality study for recommending for or against the intervention. Also requires no or only minor concerns addressed in the EtD framework.

Rationale

Four high, four moderate and two low quality studies were included for review, following the application of exclusion criteria by committee (Brouwer 2006b; Kirkley 1999; Callaghan 2015; Van Raaij 2010; Thoumie 2018; Hjartarson 2018; Petersen 2018; Niazi 2014; Hungerford 2013; Yu 2016). Three prospective randomized controlled trials compared bracing to control groups for treatment of symptomatic OA of the knee joint and found statistically significant and clinically meaningful improvement in patient symptoms related to symptomatic OA of the knee (Callaghan 2015; Thoumie 2018; Brouwer 2006b). Kirkley et al compared outcomes between valgus offloading brace, neoprene sleeve, and non-brace control for symptomatic OA and Varus alignment. This study reported statistically significant improvement in disease specific quality of life and function in both study groups (Kirkley 1999). The study by Brouwer et al., comparing valgus bracing to a non-braced control, and reported no significant difference in functional assessment, PRO or pain; however, clinically significant improvements were noted in walking distance (1.25km[0.15,2.35]) for the brace group. Subgroup analysis demonstrated greater positive effect of bracing in patients with varus alignment and more severe symptoms. Callaghan et al examined the effects of bracing for patella-femoral OA and found significant improvement from baseline VAS and KOOS pain scores. Finally, Hjartarson et al examined outcomes of bracing vs. placebo by removing valgus tension straps from the control group brace. In their study they reported statistically significant and clinically meaningful improvements in KOOS sub scores: symptoms, ADL, sports and recreation, and quality of life.

The Braces recommendation has been downgraded one level because of heterogeneity.

Benefits/Harms of Implementation

Braces can provide significant pain relief and improved function to patients that have unicompartmental knee osteoarthritis. Braces can provide a subjective feeling of more normal tibiofemoral kinematics, preventing excessive strain on the affected compartment while protecting against preexistent concomitant meniscal and chondral injuries. There is also a theoretical benefit of increased confidence in the knee during the different activities by providing a sense of security to the knee. There are almost no harms in trialing a brace besides some skin irritation, or the brace being uncomfortable.

Future Research

Future high-quality studies that are well powered are required to assess the real efficacy of unloader braces vs knee sleeves in a population with similar mechanical axis with a similar degree of OA.

View background material via the OAK3 CPG eAppendix 1
View data summaries via the OAK3 CPG eAppendix 2

Oral/Dietary Supplements

The following supplements may be helpful in reducing pain and improving function for patients with mild to moderate knee osteoarthritis; however, the evidence is inconsistent/limited and additional research clarifying the efficacy of each supplement is needed.

a) **Turmeric**
b) **Ginger extract**
c) **Glucosamine**
d) **Chondroitin**
e) **Vitamin D**

Strength of Recommendation: Limited ★★☆☆ (downgrade)
Description: Evidence from one or more "Low" quality studies with consistent findings or evidence from a single "Moderate" quality study recommending for or against the intervention. Also, higher strength evidence can be downgraded to limited due to major concerns addressed in the EtD Framework.

Rationale

The majority of 6 high quality trials (Reginster 2001, Cibere 2004, McAlindon 2004, Clegg 2006, Herrero-Beaumont 2007, Fransen 2015), the majority of 6 moderate quality trials (Noack 1994, Houpt 1999, Rindone 2000, Pavelka 2002, Giordano 2009, and Shahine 2014), and 1 low quality study that met inclusion criteria showed either improvement or no change in patient outcomes for those with osteoarthritis of the knee when taking glucosamine versus control.

The majority of 8 high quality trials (Fransen 2015, Clegg 2006, Uebelhart 2004, Reginster 2017, Morita 2018, Zegels 2013, Kahan 2009, Rondanelli 2019) and 6 moderate quality trials (Mazieres 2007, Moller 2010, Rondanelli 2019, Bourgeois 1998, Mazieres 2001, Bucsi 1998) that met inclusion criteria showed either improvement or no change in patient outcomes for those with osteoarthritis of the knee when taking chondroitin.

One high quality study (Srivastava 2016) that met inclusion criteria showed that Turmeric extract could be used over control to improve adverse events, function, and pain in patient with osteoarthritis of the knee.

One high study (Zakeri 2011) and one moderate quality study (Altman 2001) that met inclusion criteria showed that ginger extract may be used to improve pain in patients with osteoarthritis of the knee. However, there was no significant difference in function between ginger extract and control.

Three high quality studies (McAlindon 2013, Sanghi 2013, and Jin 2016) and 1 moderate quality study (Arden 2016) that met inclusion criteria showed either improvement or no significant difference in patient outcomes for those with osteoarthritis of the knee between Vitamin D and control.

The Oral/ Dietary Supplements recommendation has been downgraded two levels because of inconsistency and need for additional clarity of efficacy.

Benefits/Harms of Implementation

The United States Food and Drug Administration does not hold dietary supplements to the same standards as prescription medication. As a result, variability can exist between producers of dietary supplements.

The patient's medications should be evaluated for potential drug-supplement interactions prior to initiating any dietary supplement.

Outcome Importance
Improvement in the predictability of the treatment effect for specific dietary supplements will either reduce an unnecessary out-of-pocket expense or provide patients with a relatively safe method for reducing pain and improving function in the treatment of mild to moderate osteoarthritis of the knee. Knowing which supplements have evidence-based support for effective treatment will reduce unnecessary out-of-pocket expenses and provide patients with a safe method for reducing pain and improving function in the treatment of mild to moderate osteoarthritis of the knee.

Cost Effectiveness/Resource Utilization
Dietary supplements are typically an out-of-pocket expense not covered by medical insurance. As a result, patients must individually consider the expense associated with utilization of dietary supplements. We did not have the analysis to comment on the cost-benefit ratio of dietary supplements compared to other over the counter or prescription medications.

Acceptability
The limited evidence supporting dietary supplements and out-of-pocket expense associated with their use will limit broader acceptance. For patients without a medication interaction, dietary supplements pose limited physical harm as it is typically difficult to consume a toxic quantity. Therefore, it is believed to be an acceptable means to potentially achieve benefit in the treatment of mild to moderate osteoarthritis of the knee.

Feasibility
Dietary supplements are widely available to patients. The associated out-of-pocket expense is the primary barrier to access.

Future Research
The most important future research will need to provide multiple investigations demonstrating reproducible results illustrating the effectiveness of dietary supplements. Additionally, future research is necessary to determine the appropriate dose, frequency, and duration of treatment with dietary supplements.

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View data summaries via the OAK3 CPG eAppendix 2

Topical Treatments

Topical NSAIDs should be used to improve function and quality of life for treatment of osteoarthritis of the knee, when not contraindicated.

Strength of Recommendation: Strong ★★★★

Evidence from two or more "High" quality studies with consistent findings for recommending for or against the intervention. Also requires no reasons to downgrade from the EtD framework.

Rationale

Twelve high quality studies (Baer 2005, Roth 2004, Conaghan 2013, Simon 2009, Kneer 2013, Rother 2013, Bookman 2004, Wadsworth 2016, Sandelin 1997, Dehghan 2019, Dehghan 2020, Rother 2007) and two moderate quality studies (Barthel 2009, Ottillinger 2001) show that topical NSAIDs could result in improved function and quality of life over placebo gel. However, inconsistent evidence suggests no significant difference in pain and adverse events between topical NSAIDs and control.

Benefits/Harms of Implementation

Topical NSAIDs are now available over the counter for patients to buy and use. Topical NSAIDs should be used with caution in certain health conditions such as stage 4-5 chronic kidney disease, coronary artery disease, and congestive heart failure. There is a risk for skin sensitivity.

Outcome Importance

Improved function and quality of life improvement are the important outcomes from Topical NSAID use.

Cost Effectiveness/Resource Utilization

Since this will now be available over the counter, prescription coverage will be less. This could pose as a barrier to those without health savings accounts or without insurance. Also, patients might not be willing to apply a topical gel multiple times a day.

Acceptability

The use of a topical gel for osteoarthritis of the knee should be an acceptable method of treatment if cost is not prohibitive and the patient does not have any skin irritation from the gel.

Feasibility

Topical NSAIDs will be available at pharmacies over the counter. The main barrier will be cost and having to apply the gel multiple times a day.

Future Research

Future research might be directed at determining if continued topical NSAID use is required to sustain benefits or if benefits continue after usage for a defined period of time.

Supervised Exercise

Supervised exercise, unsupervised exercise, and/or aquatic exercise are recommended over no exercise to improve pain and function for treatment of knee osteoarthritis.

Strength of Recommendation: Strong ★★★★
Evidence from two or more "High" quality studies with consistent findings for recommending for or against the intervention. Also requires no reasons to downgrade from the EtD framework.

Rationale

Ten high quality studies were reviewed that compared a supervised exercise program to a non-exercise control (e.g., no treatment, heat only, education, usual primary care). (Christensen 2015,Holsgaard-Larsen 2018, Oliveira 2012, Willamson 2007, de Rooij 2017, Imoto 2012, Topp 2002, Hu 2020, Kim 2013, Chen 2014) Seven of these studies found greater improvements in pain, function, or both pain and function over the non-exercise control group (Oliveira 2012, de Rooij 2017, Imoto 2012, Topp 2002, Hu 2020, Kim 2013, Chen 2014).

One high quality study and four moderate quality studies were reviewed that compared supervised exercise to a non-supervised exercise program (e.g., home program, internet-based program, exercise brochure). (McCarthy 2004, Allen 2018, Yilmaz 2019, Tunay 2010, Bennell 2014). Patients from both groups received benefit from the interventions but there were mixed results as to whether supervised exercise was superior to the non-supervised exercise programs. It appears that both supervised or non-supervised exercise programs can result in improved pain and function in people with knee osteoarthritis.

Four high quality studies and one moderate quality study were reviewed that compared aquatic exercise to either usual primary care, education, or self-management. (Kuptniratsaikul 2019, Rewald 2020, Waller 2017, Munukka 2020, Dias 2017.) Three high quality studies reported greater improvements in pain, function, or global ratings of improvement for the aquatic groups over the control groups. (Kuptniratsaikul 2019, Rewald 2020, Dias 2017) One high quality study reported increased leisure time activity for the aquatic group compared to the control. (Waller 2017) One moderate quality study compared aquatic exercise to land-based exercise. (Silva 2008) There was no difference in WOMAC pain and function scores reported between groups for this study, but the aquatic exercise group had less pain with walking compared to the land-based group. Although there may be some benefit from aquatic exercise, inconsistent results do not allow us to recommend aquatic exercise over land-based exercise at this time.

Several studies examined clinical outcomes for different modes of exercise in patients with knee osteoarthritis. Ebnezar 2012 reported some improvement in anxiety measures when comparing yoga to non-yoga exercise. (Ebnezar 2012) Other studies compared weightbearing to non-weightbearing exercise (Bennell 2020, Jan 2009), high versus low resistance training (Jan 2008), isokinetic, isometric, and isotonic exercise (Huang 2005), and leg versus hip exercise (Lun 2015) and did not find substantial differences in the mode of exercise. It appears that exercise is beneficial, but the mode of exercise may not matter as much as engaging in any exercise program.

Benefits/Harms of Implementation

Most patients can expect an improvement in pain and function with exercise. Patients may experience a temporary increase in knee pain or muscle soreness when engaging in an exercise program.

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View data summaries via the OAK3 CPG eAppendix 2

Cost Effectiveness/Resource Utilization

One study by Bove, et al, 2018 examined the cost-effectiveness of delivering physical therapy supervised exercise and manual therapy in booster (treatment sessions spread out periodically over 1 year) vs no-booster (treatment sessions delivered consecutively over 9 weeks) session approaches. It appeared that the booster delivery approach may be more cost-effective than the non-booster delivery approach.

Feasibility

Most exercise programs would be considered feasible. However, some patients may have difficulty with access to supervised exercise due to travel or co-pay concerns. Aquatic programs would not be feasible for patients who do not have access to a pool or walking tank.

Future Research

Identifying factors that could discriminate between people who would likely benefit from supervised programs vs independent exercise programs is an area of research that could improve clinical decision-making for prescribing exercise. More studies are also needed to examine delivery of exercise through telerehabilitation compared with in-person supervised programs. Studies should also examine differences in outcomes between varying modes of delivering telerehabilitation exercise programs. More research would also be beneficial in examining the role of booster session delivery of exercise programs.

Neuromuscular Training

Neuromuscular training (i.e. balance, agility, coordination) programs in combination with traditional exercise could be used to improve performance-based function and walking speed for treatment of knee osteoarthritis.

Strength of Recommendation: Moderate ★★★☆ (downgrade)
Evidence from two or more "Moderate" quality studies with consistent findings, or evidence from a single "High" quality study for recommending for or against the intervention. Also requires no or only minor concerns addressed in the EtD framework.

Rationale
Three high quality studies (Fitzgerald 2011, Gomiero 2018, Apparao 2017) and two moderate quality studies (Bennell 2014 and Diracoglu 2005) comparing neuromuscular training combined with traditional strength and joint mobility exercise programs to strength and joint mobility exercise alone were reviewed. There were no differences in knee pain reported between groups in any of the studies. There were mixed results on function measures with two studies reporting greater improvements in self-reported function (Apparao 2017, Diracoglu 2005) and two studies reporting greater improvements in walking speed (Bennell 2014, Diracoglu 2005) for the neuromuscular training group.

The Neuromuscular training recommendation has been downgraded one level because of inconsistent evidence.

Benefits/Harms of Implementation
Some patients can expect an improvement in function and walking speed with neuromuscular training. Some patients may experience a temporary increase in knee pain or muscle soreness when engaging in the exercise program.

Feasibility
Neuromuscular exercise programs would be considered feasible. However, some patients may have difficulty with access to supervised exercise due to travel or co-pay concerns.

Future Research
Given the mixed results between exercise programs with and without neuromuscular exercise programs, it would be beneficial for future research to identify factors that would discriminate between patients who would have better success with a neuromuscular exercise program versus those who would have better success with a traditional strength and joint mobility exercise program.

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View data summaries via the OAK3 CPG eAppendix 2

Self-Management

Self-management programs are recommended to improve pain and function for patients with knee osteoarthritis.

Strength of Recommendation: Strong ★★★★

Evidence from two or more "High" quality studies with consistent findings for recommending for or against the intervention. Also requires no reasons to downgrade from the EtD framework.

Rationale

Self-management programs refer to formalized training and education programs that are taught by both healthcare professionals and trained layperson instructors. They typically include several sessions over several weeks. These programs train people in several elements of self-management for osteoarthritis including medication compliance, pain management and pain coping strategies, joint protection strategies during physical activity, exercise advice, problem solving approaches and stress management techniques.

Four high quality studies (Saffari 2018, Somers 2012, Hurley 2007, Omidi 2018) and one moderate quality study (Coleman 2012) compared self-management to usual care or no treatment. These studies reported greater improvements in pain, function, or both compared to the control groups. In addition, some of these studies reported greater improvements in quality of life, pain catastrophizing, and self-efficacy in the self-management groups (Saffari 2018, Somers 2012).

One high quality (Marconcin 2018) and three moderate quality studies examined the combined use of self-management and exercise to either groups that received self-management or exercise alone (Bennell 2016) or usual care (Yip 2007, Kao 2012). Yip et al. reported greater improvements in pain, time spent in leisure activities, and self-efficacy, compared to usual care. (Yip 2007) reported greater improvements in pain and function compared to the control groups. Bennell, et al, reported improvements in pain and function in all groups. There were no differences between groups on pain measures but the combined use of self-management (i.e., pain coping skills training) and exercise had greater improvements in function compared to those receiving only self-management or exercise (Bennell 2016).

An attempt was made to examine the literature on cognitive behavioral therapy (CBT) in the management of people with knee osteoarthritis. One high quality (Helminen 2015) and 4 moderate quality (Focht 2012, Focht 2017, Smith 2015, Lerman 2017) studies were reviewed. Control groups consisted of usual care (Helminen 2015), traditional exercise approaches for knee osteoarthritis, (Focht 2012, Focht 2017) or behavioral desensitization (Smith 2015, Lerman 2017). Inconsistency in outcome results across studies made it difficult to provide a recommendation for this intervention approach at this time.

Benefits/Harms of Implementation

Patients may expect improvements in pain and function, problem-solving abilities, and self-efficacy from participating in these programs. Engagement in exercise recommendations could result in some temporary increased knee pain or muscle soreness.

Outcome Importance

Pain, function, self-efficacy in managing osteoarthritis.

Feasibility

Self-management programs are feasible for patients provided they have appropriate access. Some patients may have limited access for participation, making the programs less feasible.

Future Research

Future research should examine delivery methods designed to increase access for patients (e.g., online delivered programs). Given that some patients with severe symptoms and disability may not be able to respond to self-management programs, future research should assess whether the outcomes of self-management programs vary with disease severity. This research should determine if there is a threshold of disease or disability severity that discriminates between responders and non-responders of this treatment approach.

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Patient Education

Patient education programs are recommended to improve pain in patients with knee osteoarthritis.

Strength of Recommendation: Strong ★★★★

Evidence from two or more "High" quality studies with consistent findings for recommending for or against the intervention. Also requires no reasons to downgrade from the EtD framework.

Rationale

Six high-quality studies (Saffari 2018, Somers 2012, Cagnin 2019, Gilbert 2018, Baker 2019, Berman 2004) thirteen moderate quality study (Brosseau 2012, Allen 2010, O'Brien 2018, Allen 2010, Bennell 2017, Marra 2012, Rezende 2017, Sandeghi 2019, Rodriguez da Silva 2017, Rini 2015, Moseng 2020, Chen 2020, Ravaud 2009) and two limited quality studies compared patient education and control. These studies reported more significant improvements in pain compared to the control groups.

Patient education programs in studies overlap with self-management programs. Patient education programs vary from patient handout, 2+ hour DVD, one-day education to multiple sessions over a month (Saffari 2018, Cagnin 2019, Brosseau 2012, O'Brien 2018, Rezende 2017, Rodriguez da Silva 2017, Rini 2015). Many studies are challenging to evaluate the effects of education because they involve exercise classes and other proven interventions (Marra 2012, Ravaud 2009). Self-management programs train people in several elements of self-management for osteoarthritis (1148), including medication compliance, pain management, and pain coping strategies, joint protection strategies (1149) during physical activity, exercise advice, problem-solving approaches, and stress management techniques. Patient education programs may not be as labor-intensive, and further work is needed to identify the amount of education needed to improve patient-related outcome measures, like pain.

Programs that focused on education are two high quality (Saffari 2018, Cagnin 2019) and four moderate quality (Brosseau 2012, O'Brien 2018, Rodriguez da Silva 2017, Rini 2015). Saffari used seven (7) group sessions over one month and provided a CD-ROM and booklet describing preventive lifestyle procedures and the importance of treatment adherence (Saffari 2018). They found improvement in SF-12 and pain scores. Cagnin used an educational session with a physical therapist who demonstrated how recommended exercises should be performed and how patients can manage their pain. They demonstrated improvement in KOOS pain scores (Cagnin 2019). Brousseau looked at education (educational pamphlet) vs. walking and education vs. walking and behavioral intervention (Brouseau 2012). There was a non-clinically significant improvement in pain in the education-only group at 12 months compared to walking and behavioral intervention. O'Brien used weight loss education, where trained telephone interviewers provided brief advice and education about the benefits of weight loss and physical activity for knee osteoarthritis immediately after randomization [O'Brien 2018]. The intervention group provided an evidence-based public health non-disease-specific telephone-based coaching service funded by the local Australian state government to support adults in making sustained lifestyle improvements, including diet, physical activity, and achieving a healthy weight and, where appropriate, access smoking cessation services. They did not find an added benefit from the coaching service over the brief telephone education in pain nor WOMAC scores. Rini compared an internet-based app (PainCoach) [http://tri.ad/projects-2/] to usual care and found a non-clinically significant reduction in VAS pain scores (Rini 2015). Rodriguez da Silva used a single day (Saturday, from 8 a.m. to 5 p.m.), which included seven lectures of 30 min by each professional team, and 60-min workshops by the physical education, physical therapy, and occupational therapy professionals, approaching the importance of their area in knee OA treatment/management. The study did not report pain scores but did note an increase in mobility with improvements in the get-up and go test. The two high-quality and four moderate-quality studies showed

improved pain scores from the education given during educational sessions. Most studies (15 of the 21) incorporate education with other interventions; therefore, it is impossible to isolate the effects of education in these other 15 studies.

One high quality (Gilbert 2018) and three moderate quality (Rezende 2017, Chen 202, Ravaud 2009) used the transtheoretical model (TTM) and motivational interviewing to improve osteoarthritis treatment adherence. These studies showed improvement in WOMAC pain scores. TTM has been used successfully in other conditions that benefit from lifestyle changes [PMID: 24500864].

Future Research

Further research is needed to determine the best practice of education for reducing pain and other PROM for knee OA and the delivery method. Since many studies use different components and delivery methods and multiple interventions, it is impossible to recommend one particular educational module or particular component.

View background material via the OAK3 CPG eAppendix 1
View data summaries via the OAK3 CPG eAppendix 2

Weight Loss Intervention

Sustained weight loss is recommended to improve pain and function in overweight and obese patients with knee osteoarthritis.

Strength of Recommendation: Moderate ★★★☆ (downgrade)
Evidence from two or more "Moderate" quality studies with consistent findings, or evidence from a single "High" quality study for recommending for or against the intervention. Also requires no or only minor concerns addressed in the EtD framework.

Rationale

There were 1 high (Jenkinson et. al 2009),1 moderate (Miller 2006), and 2 low strength (Focht 2005, Rejeski 2002) studies evaluating diet and exercise as weight loss interventions to treat knee osteoarthritis. Overall pain and function improved with weight loss achieved through a combination of diet and exercise. However, when evaluating only diet vs control, 2 high (Bliddal 2011, Christensen 2015), 2 moderate (Messier 2013, Mihalko 2018) and 2 low strength (Rejeski 2002, Fochyt 2005) there was no clear clinically significant change in patient outcomes. Specifically, Christensen et al, 2015 published a high-quality study investigating the effect of weight on symptoms of knee osteoarthritis. They showed no significant difference in pain and function at 1 year. Bliddal et al, 2010 published another high quality study which investigated the effect of weight loss on symptoms of knee OA in the obese patient, showing that perceived pain (via WOMAC) was significantly lessened despite not being able to show improvement in function and quality of life at 1 year.

There were 2 moderate strength studies (Messier 2013, Mihalko 2018) which evaluated diet vs exercise, which favored exercises. To note, Messier et al 2013 published results of the IDEA trial with moderate quality study which was an attempt to determine if a 10% reduction in body weight (induced by diet, with or without exercise) would improve "clinical and mechanistic" outcomes in sedentary lifestyle patients (BMI 27 thru 41). Interestingly, in this primary study, they were unable to show an improvement in WOMAC pain but they did show improvement in the WOMAC function subscale, and also showed improvements in the 6 minute walk test.
Given the current evidence, it is at the discretion of the surgeon as to which approach is utilized to address weight loss, however a combination of diet and exercises appears to be the preferred alternative.

The Weight Loss Intervention recommendation has been downgraded one level because of inconsistent evidence.

Benefits/Harms of Implementation

There are no known or anticipated harms associated with implementing this recommendation.

Outcome Importance

Management of obesity and overweight through weight loss may have high impact on symptoms and overall health.

Cost Effectiveness/Resource Utilization

Weight loss presents a potentially high level of cost effectiveness compared to other surgical and nonsurgical approaches; however, the cost-effectiveness of different weight loss approaches is still to be determined.

Acceptability
Currently weight loss is a commonly utilized approach in the optimization of patient who present with obesity and knee osteoarthritis, hence there should be no issues implementing this recommendation as it does not influence a major change in clinical practice. To note, patients often are reluctant or unwilling to accept referrals for weight loss as a suggestion for a path to improvement.

Feasibility
This recommendation does not interfere with other interventions or clinical practice therefore it is deemed very feasible in a subset of overweight and obese patients.

Future Research
Future research should focus on large randomized clinical trials and should focus more on function and quality of life measures since it appears obvious that pain improved through weight loss.

View background material via the OAK3 CPG eAppendix 1
View data summaries via the OAK3 CPG eAppendix 2

Manual Therapy

Manual therapy in addition to an exercise program may be used to improve pain and function in patients with knee osteoarthritis.

Strength of Recommendation: Limited ★★☆☆ (downgrade)
Description: Evidence from one or more "Low" quality studies with consistent findings or evidence from a single "Moderate" quality study recommending for or against the intervention. Also, higher strength evidence can be downgraded to limited due to major concerns addressed in the EtD Framework.

Rationale
Manual therapy consists of maneuvers applied with manual force from the treating therapist to the patient's body to improve joint mobility and/or relieve pain. The techniques may generally consist of manually applied joint mobilization techniques, manually applied joint range of motion and/or muscle stretching, and soft tissue massage. One high quality study (Fitzgerald 2016) and one moderate quality study (Deyle 2000) were reviewed that examined manual therapy combined with exercise compared to exercise alone (Fitzgerald 2016) or non-therapeutic ultrasound (placebo physical therapy) in subjects with knee osteoarthritis. (Deyle 2000) Fitzgerald, et al, reported that both groups yielded significant improvements in clinical outcomes from baseline but the manual therapy group had greater improvements in the WOMAC total score and were more likely to meet the OMERACT-OARSI Responder Criteria at the 9 week follow-up. (Fitzgerald 2016) While both groups demonstrated sustained improvements in clinical outcomes at 1 year there was no difference between groups on any measures at this timepoint. Deyle et al. reported similar findings with the manual therapy and exercise group demonstrating greater improvements at 8 weeks but no significant differences between groups at 1 year (Deyle 2000).

The Manual Therapy recommendation has been downgraded one level because of inconsistent evidence and to lack of internal consistency with recommendations of equal supporting evidence.

Benefits/Harms of Implementation
Most patients can expect an improvement in pain and function with the interventions. Patients may experience a temporary increase in knee pain or muscle soreness when engaging in a manual therapy and exercise program.

Cost Effectiveness/Resource Utilization
Bove, et al 2018 found manual therapy and exercise delivered with periodic booster sessions was more cost-effective than delivery of this same intervention without booster sessions. (Bove 2018) The cost effectiveness assessment was over a 2-year follow-up (Bove 2018).

Feasibility
The manual therapy interventions are feasible for patients who have access to in-person physical therapy. The exercise interventions are feasible both from an in-person and home program perspective.

Future Research
Future studies should examine ways to sustain the effects of manual therapy and exercise for extended follow-up periods. Research is needed to determine the effectiveness of self-applied manual therapy and telerehabilitation applications of manual therapy and exercise interventions for improving pain and function in patients with knee osteoarthritis.

Massage

Massage may be used in addition to usual care to improve pain and function in patients with knee osteoarthritis.

Strength of Recommendation: Limited ★★☆☆ (downgrade)
Description: Evidence from one or more "Low" quality studies with consistent findings or evidence from a single "Moderate" quality study recommending for or against the intervention. Also, higher strength evidence can be downgraded to limited due to major concerns addressed in the EtD Framework.

Rationale

Two high quality study (Pehlivan 2018, Sansila 2019) and one moderate quality study (Perlman 2018) were reviewed that examined massage plus usual care to a usual care control group. Pehlivan et al. applied a leg massage focusing primarily on tissues around the knee for a total of 6 sessions over 3 weeks (Pehlivan 2018). Subjects receiving massage had greater improvements in knee pain at 4 weeks follow-up compared to the usual care control group but there was no difference between groups at 8 weeks. There were also no differences in function between groups at either time point. Perlman et al. applied a 60-minute total body massage one time per week for 8 weeks, followed by bi-weekly sessions for 52 weeks (Perlman 2018). There was greater improvement in pain and function in the massage group at the 8-week follow-up, but these effects were not sustained for any of the longer-term follow-up timepoints.

The Massage recommendation has been downgraded one level because of inconsistent evidence and due to lack of internal consistency with recommendations of equal supporting evidence.

Benefits/Harms of Implementation

Patients receiving massage may experience some short-term improvements in pain and function. Massage treatments are generally safe but common side effects may include skin redness or irritation, bruising, muscle soreness, fatigue, and nausea.

Feasibility

The interventions are considered feasible and relatively accessible to the general public. Patients who have transportation issues may have difficulty with obtaining access to treatment.

Future Research

Future research may be warranted to determine how massage could be combined with other interventions for knee osteoarthritis to sustain longer term effects on pain and function.

View background material via the OAK3 CPG eAppendix 1
View data summaries via the OAK3 CPG eAppendix 2

Laser Treatment

FDA-approved laser treatment may be used to improve pain and function in patients with knee osteoarthritis

Strength of Recommendation: Limited ★★☆☆ (downgrade)
Description: Evidence from one or more "Low" quality studies with consistent findings or evidence from a single "Moderate" quality study recommending for or against the intervention. Also, higher strength evidence can be downgraded to limited due to major concerns addressed in the EtD Framework.

Rationale

A meta-analysis was performed using pain data from two high quality studies (Gur 2003, Nazari 2018) and one moderate quality (Marquina 2012) study examining high intensity laser treatment compared to either placebo laser treatment or no treatment groups. The results of the analysis are provided in Figure 10 in appendix. The overall findings were in favor of the laser intervention over the sham or no-treatment groups. In addition, two of these studies reported greater improvements in function. (Gur 2003, Nazari 2018) Gur 2003 also compared high dose vs. low dose laser treatment on clinical outcomes and found no significant difference between the groups. (Gur 2003)

The Laser Treatment recommendation has been downgraded two levels because of feasibility, usage in practice and a lack of internal consistency with recommendations of equal supporting evidence.

Benefits/Harms of Implementation

Patients should expect to experience improvements in pain and function with the treatment. There have been no reports of serious side effects from laser treatment for pain control. Long-term exposure of the laser beam to the eyes can cause eye damage.

Feasibility

Access to the laser treatment may not be available in all clinics.

Future Research

Continued study of laser treatment for pain control, improving function and cost-effectiveness in people with knee osteoarthritis is encouraged.

Acupuncture

Acupuncture may improve pain and function in patients with knee osteoarthritis.

Strength of Recommendation: Limited ★★☆☆ (downgrade)
Description: Evidence from one or more "Low" quality studies with consistent findings or evidence from a single "Moderate" quality study recommending for or against the intervention. Also, higher strength evidence can be downgraded to limited due to major concerns addressed in the EtD Framework.

Rationale

A meta-analysis was performed using pain data from five high quality studies (Chen 2013, Suarez-Almazor 2010, Mavrommatis 2012, Berman 2004, Hinman 2014) and two moderate quality studies (Vas 2007, Berman 1999). Acupuncture treatments were either traditional (Chen 2013, Hinman 2014) or electro-acupuncture. (Suarez-Almazor 2010, Mavrommatis 2012, Vas 2007, Berman 2004, Berman 1999) Control groups consisted of either no acupuncture, (Hinman 2014) sham acupuncture, (Mavrommatis 2012, Suarez-Almazor 2010, Vas 2007, Berman 2004) sham TENS (Chen 2013), or usual care. (Berman 1999) The meta-analysis also accounted for the degree of blinding effectiveness of the studies. The results of the meta-analysis can be seen in Figure 11 in the appendix. The overall findings were in favor of acupuncture for reducing pain in subjects with knee osteoarthritis. There appeared to be no effect in two studies where blinding was effective. In studies where there was no blinding or the effects of blinding were unclear, there were greater effects favoring acupuncture. This prompted our decision to apply a limited strength of recommendation in favor of acupuncture for pain control.

A similar meta-analysis was performed using the same studies for measures of function. The results of this meta-analysis can be seen in Figure 12 in appendix. The overall findings were in favor of acupuncture for improving measures of function in subjects with knee osteoarthritis. However, the effects of blinding effectiveness on the results were similar to that described above for pain. Again, this prompted our decision to apply a limited strength of recommendation in favor of acupuncture for improving function.

Some investigators examined variations in delivery of acupuncture treatment. Ju et al. examined high intensity vs low intensity electro-acupuncture and found no difference between these approaches for pain but possibly better improvements in function favoring the high intensity group. (Ju 2015) Others found no meaningful differences between using 2-point, 4-point, or 6-point acupuncture approaches. (Qi 2016, Taechaarpornkul 2009).

The Acupuncture recommendation has been downgraded two levels because of inconsistent evidence and a lack of internal consistency with recommendations of equal supporting evidence.

Benefits/Harms of Implementation

Many patients receive benefit such as reduced pain and improved function but not all patients respond favorably to treatment. The treatment should be administered by a certified acupuncture practitioner. Common side effects can include soreness and minor bleeding or bruising where needles are inserted. Risk of infection is low if proper procedures are followed. Patients who have a bleeding disorder, pacemaker, or could be pregnant may not be safe candidates for acupuncture and should consult with their physician before having the treatment.

View background material via the OAK3 CPG eAppendix 1
View data summaries via the OAK3 CPG eAppendix 2

Acceptability
The interventions are considered acceptable, but some individuals may not be enthusiastic about having needles inserted into their skin.

Feasibility
The intervention is feasible provided there is access to a trained practitioner. Not all clinics can provide such access.

Future Research
Continued research is encouraged, with more studies that improve blinding effectiveness in the methodology and studies that may identify patient characteristics that could discriminate between responders and non-responders of this treatment approach.

Transcutaneous Electrical Nerve Stimulation

Modalities that may be used to improve pain and/or function in patients with knee osteoarthritis include:

a) Transcutaneous Electrical Nerve Stimulation (pain)

Strength of Recommendation: Limited ★★☆☆ (downgrade)

Description: Evidence from one or more "Low" quality studies with consistent findings or evidence from a single "Moderate" quality study recommending for or against the intervention. Also, higher strength evidence can be downgraded to limited due to major concerns addressed in the EtD Framework.

Rationale

A meta-analysis was performed using pain data from two high quality studies (Palmer 2014, Inal 2016) and one moderate quality study (Atamaz 2012) in which Transcutaneous Electrical Nerve Stimulation (TENS) was compared to sham TENS in subjects with knee osteoarthritis. Blinding effectiveness was considered fair in all three studies. The results of the meta-analysis can be seen in Figure 15 in the appendix. The overall findings were in favor of receiving TENS for reducing pain in subjects with knee osteoarthritis. A similar meta-analysis was performed using the same studies for measures of function. The results of this meta-analysis can be seen in Figure 16 in the appendix. The overall findings did not favor the use of TENS to improve measures of function in subjects with knee osteoarthritis.

The Transcutaneous Electrical Nerve Stimulation recommendation has been downgraded two levels because of inconsistent evidence and a lack of internal consistency with recommendations of equal supporting evidence.

Benefits/Harms of Implementation

TENS units are small, portable, non-invasive devices that could provide pain relief and may allow some patients to reduce pain medication use. Some patients may experience skin irritations or allergic reactions to the adhesive pads used to deliver the stimulation. Use of TENS is not recommended in people with pacemakers and women who are pregnant should not apply TENS in the abdominal or pelvic regions.

Acceptability

The interventions appear to be acceptable to most patients however some patients may not like the sensation of electrical or electro-magnetic energy being applied to their bodies.

Future Research

Continued research with larger randomized trials that examine long-term effectiveness of the interventions is warranted. Studies that identify factors discriminating between responders and non-responders to the interventions would also be important.

View background material via the OAK3 CPG eAppendix 1
View data summaries via the OAK3 CPG eAppendix 2

Percutaneous Electrical Nerve Stimulation

Modalities that may be used to improve pain and/or function in patients with knee osteoarthritis include:

a) **Percutaneous Electrical Nerve Stimulation (pain and function)**
b) **Pulsed Electromagnetic Field Therapy (pain)**

Strength of Recommendation: Limited ★★☆☆ (downgrade)
Description: Evidence from one or more "Low" quality studies with consistent findings or evidence from a single "Moderate" quality study recommending for or against the intervention. Also, higher strength evidence can be downgraded to limited due to major concerns addressed in the EtD Framework.

Rationale

One high quality study was reviewed that examined the use of Percutaneous Electrical Nerve Stimulation (PENS) combined with a Cox-2 inhibitor to sham PENS combined with a Cox-2 inhibitor in subjects with knee osteoarthritis. (He 2019) The results indicated greater improvements in pain and function measures in subjects receiving PENS compared to sham PENS.

One high quality study was reviewed that examined the use of a wearable Pulsed Electomagnetic Field (PEMF) device for pain management in subjects with knee osteoarthritis. (Bagnato 2016) Subjects were randomized to either the PEMF group or a sham PEMF group. PEMF was applied 12 hours per day for a period of 4 weeks. The results indicated greater improvement in WOMAC pain and VAS pain scores for subjects receiving PEMF over sham PEMF. There was no difference between groups on WOMAC function scores.

The Percutaneous Electrical Nerve Stimulation/Pulsed Electromagnetic Field Therapy recommendation has been downgraded one level because of feasibility issues.

Benefits/Harms of Implementation

PENS is a minimally invasive procedure. Patients may experience reduction in pain and improvement in function after receiving the intervention. Because the intervention involves the insertion of very thin needles, side effects are similar to acupuncture and include bleeding, bruising, or skin irritation at the insertion site. Infection or nerve damage are possible but very rare side effects.

PEMF devices are generally safe and can reduce pain and inflammation. The treatment often results in an increase in blood flow which, in some circumstances, could temporarily trigger an increase in pain and discomfort and oxidative stress. Some patients may report fatigue and loss of energy, sleep disturbances, dizziness, and increased urination. PEMF treatment may induce a decrease in blood pressure and heart rate so caution must be taken in patients with cardiovascular deficiencies. A fall in blood sugar levels can also result in some people with PEMF treatment so caution should be taken in patients who have difficulty regulating blood sugar. PEMF may affect blood coagulation and is not recommended in people who are taking anti-coagulant therapies.

Acceptability

The interventions appear to be acceptable to most patients however some patients may not like the sensation of electrical or electro-magnetic energy being applied to their bodies.

Feasibility
PENS is feasible but requires a practitioner trained in the technique which could limit access for some patients. PEMF is not widely used in clinics treating patients for knee osteoarthritis and thus could limit access for some patients.

Future Research
Continued research with larger randomized trials that examine long-term effectiveness of the interventions is warranted. Studies that identify factors discriminating between responders and non-responders to the interventions would also be important.

View background material via the OAK3 CPG eAppendix 1
View data summaries via the OAK3 CPG eAppendix 2

Extracorporeal Shockwave Therapy

Extracorporeal shockwave therapy may be used to improve pain and function for treatment of osteoarthritis of the knee.

Strength of Recommendation: Limited ★★☆☆ (downgrade)
Description: Evidence from one or more "Low" quality studies with consistent findings or evidence from a single "Moderate" quality study recommending for or against the intervention. Also, higher strength evidence can be downgraded to limited due to major concerns addressed in the EtD Framework.

Rationale
A meta-analysis was performed using pain data from three high quality studies (Zhong 2019, Ediz 2018, and Uysal 2020) in which Extracorpeal Shockwave Therapy (ESWT) was compared to sham ESWT in subjects with knee osteoarthritis. The results of the meta-analysis can be seen in Figure 19 in the appendix. The overall findings were in favor of receiving ESWT for reducing pain in subjects with knee osteoarthritis. In addition, four high quality studies reported greater improvements in function scores in subjects receiving ESWT compared to the sham group at 4 to 12 weeks but not at 1-year follow-up. (Zhao 2013, Ediz 2018, Zhong 2019, Uysal 2020).

The Extracorporeal shockwave Therapy recommendation has been downgraded two levels because of inconsistent evidence and a lack of internal consistency with recommendations of equal supporting evidence.

Benefits/Harms of Implementation
Patients receiving this treatment may experience improvements in pain and function. Side effects may include redness or mild bruising, swelling, pain, numbness or tingling in the treated area, migraine headaches, and syncope.

Acceptability
Generally tolerated well but some patients may experience side-effects listed above.

Feasibility
The intervention is considered feasible but may not be widely available in clinics managing patients with knee osteoarthritis and therefore may not be accessible for all patients.

Future Research
Future studies should examine methods to sustain longer term effects of the intervention (e.g., optimal dosage, use of booster interventions), investigate the potential of ESWT as an osteoarthritis disease-modifying agent, and identify characteristics of patients that may discriminate between responders and non-responders of the intervention. The mechanisms of action of these interventions in human subjects is not well understood. Future studies investigating the mechanisms of action of these interventions in human subjects would be helpful.

Oral NSAIDs

Oral NSAIDs are recommended to improve pain and function in the treatment of knee osteoarthritis when not contraindicated.

Strength of Recommendation: Strong ★★★★

Evidence from two or more "High" quality studies with consistent findings for recommending for or against the intervention. Also requires no reasons to downgrade from the EtD framework.

Rationale

Among the 34 high-quality, 23 moderate-quality, and 1 low-quality studies that met the inclusion criteria, non-selective and selective clyclooxygenase-2 (COX-2) oral nonsteroidal anti-inflammatory drugs (NSAID) consistently improved pain and function compared to controls in the treatment of osteoarthritis of the knee (Reginster 2017; Lee 2017; Gordo 2017; Strand 2017; Essex 2014; Kongtharvonskul 2016; Altman 2015; Gibofsky 2014; Ishijima 2014; Conaghan 2013; Essex 2012; Singh 2012; Elsaman 2016; Schnitzer 2011; Kivitz 2004; Fleischmann 1997; Lee 1986; Davies 1999; Sandelin 1997; Puopolo 2007; Gibofsky 2003; Bensen 1999; Kivits 2002; Clegg 2006; Sangdee 2002; Sheldon 2005; Tannenbaum 2004; Lehmann 2005; Rother 2007; Simon 2009; Svensson 2006; Schnitzer 2010; Doherty 2011; McKenna 2001 (a); Paul 2009; Bolten 2015; Essex 2015; Ekman 2014; Ohtori 2013; Selvan 2012; Pavelka 2007; Ehrich 1999; Lee 1985; Dwicandra 2018; Asmus 2014; Smugar 2006; Bingham 2007; Altman 1998; Schnitzer 1999; Birbara 2006; Williams 2001; Miceli 2004; Mckenna 2001 (b); Pincus 2004; Lohmander 2005; Schnitzer 2005b; Williams 2000; Fleischmann 2006). Although meta-analysis of non-selective oral NSAIDs compared to controls demonstrated a meaningful reduction in pain, the results need to be interpreted with caution due to the relatively high degree of heterogeneity. The meta-analysis of non-selective oral NSAIDs compared to controls demonstrated a meaningful improvement in function with an acceptable degree of heterogeneity. In terms of selective COX-2 oral NSAIDs, the meta-analysis of celecoxib, the only available selective COX-2 oral NSAID on the United States market, demonstrated a meaningful reduction in pain and improved function with an acceptable degree of heterogeneity. The comparison of non-selective and selective COX-2 oral NSAIDs shows no significant difference in the effectiveness between the types of oral NSAIDs (Gordo 2017; Essex 2014; Essex 2016; Essex 2012; Bensen 1999; Kivits 2002; Kivitz 2004; Puopolo 2007; Hochberg 2011; Mckenna 2001 (b); Schnitzer 2005b; Malik 2017). Although NSAIDs effectively reduce pain and improve function in the treatment of osteoarthritis of the knee, providers should consider patient comorbidities, the type of NSAID administered, dose, and duration of administration. In fact, the United States Food and Drug Administration (FDA) has a black-box warning for NSAIDs citing an increased risk of serious cardiovascular thrombotic events and serious gastrointestinal events. Therefore, we recommend the lowest effective dose for the shortest duration possible for the patient. Although selective COX-2 oral NSAIDs were developed to reduce gastrointestinal adverse events compared to non-selective oral NSAIDs, meta-analysis did not reveal a significant reduction in gastrointestinal adverse events.

Benefits/Harms of Implementation

Although oral NSAIDs are widely used to treat osteoarthritis of the knee, providers must recognize the specific risks associated with each medication. Specific patient contraindications need to be assessed on an individual basis (Example: patient with cardiac conditions have an increased risk of myocardial infarction).

View background material via the OAK3 CPG eAppendix 1
View data summaries via the OAK3 CPG eAppendix 2

Outcome Importance
The most important consideration will be removal of oral narcotics from the medications prescribed in the treatment of osteoarthritis of the knee. This becomes particularly significant due to the rise of the opioid epidemic in the United States.

Cost Effectiveness/Resource Utilization
Evidence based decision making in selecting the optimal systemic treatment for the treatment of symptomatic knee osteoarthritis should result in improved pain and function. For a given systematic treatments as effectiveness increases without raising the risk of adverse events so will its cost effectiveness. To date, the most cost-effective systemic treatment is still to be determined.

Acceptability
Currently oral NSAIDs are commonly utilized approach in treating symptomatic knee osteoarthritis, hence there should be no issues implementing this recommendation as it does not influence a major change in clinical practice, and it provides further evidence to support and guide these practices.

Feasibility
This recommendation may be implemented immediately having a potential positive impact in clinical practice.

Future Research
Most important future research will provide high quality investigation through either prospective randomized trials or prospective cohort studies to establish efficacy within specific subgroups and populations to tailor systemic medications increasing efficacy and decreasing risk of adverse effects.

Oral Acetaminophen

Oral Acetaminophen is recommended to improve pain and function in the treatment of knee osteoarthritis when not contraindicated.

Strength of Recommendation: Strong ★★★★

Evidence from two or more "High" quality studies with consistent findings for recommending for or against the intervention. Also requires no reasons to downgrade from the EtD framework.

Rationale

Among the 4 high-quality and 3 moderate quality studies that met the inclusion criteria, oral acetaminophen consistently improved pain and function compared to controls in the treatment of osteoarthritis of the knee (Herrero-Beaumont 2007; Doherty 2011; Reed 2018; Prior 2014; Micelli 2004; Pincus 2004; Altman 2007). The meta-analysis of oral acetaminophen compared to controls demonstrated a meaningful reduction in pain and improved function with no evidence of confounding heterogeneity. Overall, acetaminophen is considered a safe medication with no evidence of significantly increased adverse events among the included studies. However, the United States FDA has a black-box warning for acetaminophen secondary to concern of overdose leading to hepatoxicity or death. When oral acetaminophen was compared to NSAIDs, the use of oral NSAIDs provided a significant reduction in pain and improved function. As a result, providers may consider using oral NSAIDs instead of acetaminophen when a contraindication to oral NSAIDs does not exist in the patient.

Benefits/Harms of Implementation

Although oral acetaminophen is widely used to treat osteoarthritis of the knee, providers must recognize the specific risks associated with each medication. Specific patient contraindications to need to be assessed in an individual basis (Example: patient with renal failure).

Outcome Importance

The most important consideration will be removal of oral narcotics from the medications prescribed in the treatment of osteoarthritis of the knee. This becomes particularly significant due to the rise of the opioid epidemic in the United States.

Cost Effectiveness/Resource Utilization

Evidence based decision making in selecting the optimal systemic treatment for the treatment of symptomatic knee osteoarthritis should result in improved pain and function. For a given systematic treatments as effectiveness increases without raising the risk of adverse events so will its cost effectiveness. To date, the most cost-effective systemic treatment is still to be determined.

Acceptability

Currently acetaminophen is commonly utilized approach in treating symptomatic knee osteoarthritis, hence there should be no issues implementing this recommendation as it does not influence a major change in clinical practice, and it provides further evidence to support and guide these practices.

Feasibility

This recommendation may be implemented immediately having a potential positive impact in clinical practice.

View background material via the OAK3 CPG eAppendix 1
View data summaries via the OAK3 CPG eAppendix 2

Future Research

Most important future research will provide high quality investigation through either prospective randomized trials or prospective cohort studies to establish efficacy within specific subgroups and populations to tailor systemic medications increasing efficacy and decreasing risk of adverse effects.

Oral Narcotics

Oral narcotics, including tramadol, result in a significant increase of adverse events and are not effective at improving pain or function for treatment of osteoarthritis of the knee.

Strength of Recommendation: Strong ★★★★

Evidence from two or more "High" quality studies with consistent findings for recommending for or against the intervention. Also requires no reasons to downgrade from the EtD framework.

Rationale

Among the 5 high-quality and 2 moderate quality studies that met the inclusion criteria, oral narcotic medications are not an effective treatment to reduce pain and improve function in osteoarthritis of the knee (Serrie 2017; Afilalo 2010; Mayorga 2016; Fishman 2007; Fleischmann 2001; Burch 2007; Babul 2004). In fact, the use of narcotics to treat osteoarthritis of the knee is consistently associated with a significantly high risk of adverse events. Due to the lack of efficacy and increase of adverse event, we would recommend against the use of narcotics for the treatment of osteoarthritis of the knee. Given the effective and relatively safe alternatives of oral NSAIDs and acetaminophen, oral narcotics should be avoided when the provider is considering the recommendation of an oral medication.

Benefits/Harms of Implementation

The removal of oral narcotics from the medications prescribed in the treatment of osteoarthritis of the knee will have further beneficial effects if patients fail non-surgical management and eventually progress to replacement of the knee, as they have been associated with adverse events after surgery as well.

Outcome Importance

The most important consideration will be removal of oral narcotics from the medications prescribed in the treatment of osteoarthritis of the knee. This becomes particularly significant due to the rise of the opioid epidemic in the United States.

Cost Effectiveness/Resource Utilization

Evidence based decision making in selecting the optimal systemic treatment for the treatment of symptomatic knee osteoarthritis should result in improved pain and function. For a given systematic treatments as effectiveness increases without raising the risk of adverse events so will its cost effectiveness. To date, the most cost-effective systemic treatment is still to be determined.

Acceptability

Due to the lack of efficacy and increase of adverse event, a recommendation against the use of narcotics for the treatment of osteoarthritis of the knee was made and this could present some resistance from patients who have failed oral NSAIDS and acetaminophen. Nonetheless, patients should be counseled on the risks associated with narcotics and their lack of efficacy for the purpose of treating knee osteoarthritis.

Feasibility

This recommendation may be implemented immediately having a potential positive impact in clinical practice.

View background material via the OAK3 CPG eAppendix 1
View data summaries via the OAK3 CPG eAppendix 2

Future Research

Most important future research will provide high quality investigation through either prospective randomized trials or prospective cohort studies to establish efficacy within specific subgroups and populations to tailor systemic medications increasing efficacy and decreasing risk of adverse effects.

Hyaluronic Acid

Hyaluronic acid intra-articular injection(s) is not recommended for routine use in the treatment of symptomatic osteoarthritis of the knee.

Strength of Recommendation: Moderate ★★★☆ (downgrade)
Evidence from two or more "Moderate" quality studies with consistent findings, or evidence from a single "High" quality study for recommending for or against the intervention. Also requires no or only minor concerns addressed in the EtD framework.

Rationale

Twenty-eight studies (17 high-strength (Chevalier 2010, Petterson 2018, Maheu 2019, Neustadt 2005, Baltzer 2009, Lundsgaard 2008, Altman 2004, Huang 2011, van der Weergen 2015, Altman 2009, Day 2004, Jorgensen 2010, Henrotin 2017, Henderson 1994, Hangody 2018, Saccomanno 2016, Altman 1998) and 11 moderate-strength (Jubb 2003, Navarro-Sarabia 2011, Farr 2019, Kahan 2003, Kahan 2003, Karlsson 2002, Hermans 2019, Huskisson 1999, Heybeli 2008, Petrella 2006, Takamura 2018, Wobig 1998)) assessed intraarticular hyaluronic acid (HA) injections when compared to controls. A comparison of patients from these studies and from studies validating the MCIDs were used to judge clinical significance. Results revealed that patients were demographically comparable for WOMAC and VAS pain as well as WOMAC function based on age, baseline pain scores, BMI, weight, and gender. Meta-analysis in meaningfully important difference (MID) units showed that the effect was less than 0.5 MID units, indicating a low likelihood that an appreciable number of patients achieved clinically important benefits after intraarticular HA injection (Guyatt et al.). When we differentiated high- versus low-molecular weight viscosupplementation (three high, two moderate and two low quality studies), our analyses demonstrated no significant differences among different viscosupplementation formulations. Crosslinking features of the viscosupplemtation product was assessed in two high quality studies. In patients with OA, there was no difference between cross-linked and non-cross-linked HA.

Some studies demonstrated a statistical benefit with the use of HA but could not reach the significance for a minimally clinical meaningful difference, leading to the conclusion that viscosupplementation can represent a viable option for some patients that failed other treatments when appropriately indicated. The number needed to treat to see a tangible benefit from HA was 17 patients. Furthermore, this difference was most evident at 6 weeks and 3 months. Most of the studies that exist in the literature evaluate low to moderate arthritic knees (Kellgren Lawrence of I-III) with worse results in patients with severely affected knees (KL IV).

The 2013 edition of this guideline strongly recommended against the use of viscosupplementation. In contrast to this updated version, the 2021 version found that statistically significant improvements were associated with high-molecular cross-linked hyaluronic acid but when compared to mid-range molecular weight, statistical significance was not maintained. This newer analysis did not demonstrate clinically relevant differences when compared to controls. However, as previous research reported benefits in their use, the group felt that a specific subset of patients might benefit from its use.

The Hyaluronic Acid recommendation was downgraded one level due to a lack of generalized results.

Benefits/Harms of Implementation

There are no major known or anticipated harms associated with implementing this recommendation.

View background material via the OAK3 CPG eAppendix 1
View data summaries via the OAK3 CPG eAppendix 2

Outcome Importance
Pain and function improvement through intraarticular therapies for the treatment of knee osteoarthritis may have high impact on symptoms and overall health.

Cost Effectiveness/Resource Utilization
The cost-effectiveness of different intra-articular therapies is still to be determined, in comparison to other treatment strategies and among different intra-articular alternatives.

Acceptability
Currently intra-articular treatments are commonly utilized approach in treating symptomatic knee osteoarthritis, hence there should be no issues implementing this recommendation as it does not influence a major change in clinical practice, and it provides further evidence to support and guide these practices.

Feasibility
These recommendations do not interfere with other interventions or clinical practice therefore it is deemed very feasible in patients with symptomatic knee osteoarthritis.

Future Research
Future research in this area should embrace detailed osteoarthritis characterization including sub-group analyses and osteoarthrosis severity stratification. Furthermore, using clinically relevant outcomes and controls for bias are warranted along with cost-effectiveness analysis.

Intra-articular Corticosteroids

Intra-articular (IA) corticosteroids could provide short-term relief for patients with symptomatic osteoarthritis of the knee.

Strength of Recommendation: Moderate ★★★☆ (downgrade)
Evidence from two or more "Moderate" quality studies with consistent findings, or evidence from a single "High" quality study for recommending for or against the intervention. Also requires no or only minor concerns addressed in the EtD framework.

Rationale
Our search found 19 high (Campos 2017, Cai 2019, Abou-Raya 2014, Erturk 2016, de Campos 2013, Shrestha 2018, Mendes 2019, Yilmaz 2019, Chao 2010, Raynauld 2003, McAlindon 2017, Henrikson 2015, Neilsen 2018, Riis 2017, Arden 2014, Delgado-Enciso 2019, Smith 2003, Soriano-Maldonado 2016) and 6 moderate quality studies (Conaghan 2018, Langworthy 2019, Gaffney 1995, Yavuz 2012, Yilmaz 2019, Jones 1996) comparing intra-articular corticosteroids to control to treat knee osteoarthritis. Overall pain and function improved with intra-articular corticosteroids; however, it is important to note that such effect lasted only up to 3 months. When we differentiated intra-articular corticosteroids extended versus immediate release (one high, two moderate quality studies) (Bodick 2015, Conaghan 2018 and Langworthy 2019), our analyses demonstrated that, extended release IA steroids can be used over immediate release to improve patient outcomes (Moderate strength recommendation).

The Intra-Articular Corticosteroids recommendation has been downgraded one level because of potential risk in accelerating osteoarthritis from injections.

Benefits/Harms of Implementation
The AAOS Patient Safety Committee recommends avoiding musculoskeletal corticosteroid injections for two weeks before and one week after COVID vaccine administration.

Outcome Importance
Pain and function improvement through intra-articular therapies for the treatment of knee osteoarthritis may have high impact on symptoms and overall health.

Cost Effectiveness/Resource Utilization
The cost-effectiveness of different intra-articular therapies is still to be determined, in comparison to other treatment strategies and among different intra-articular alternatives.

Acceptability
Currently intra-articular treatments are commonly utilized approach in treating symptomatic knee osteoarthritis, hence there should be no issues implementing this recommendation as it does not influence a major change in clinical practice, and it provides further evidence to support and guide these practices.

Feasibility
These recommendations do not interfere with other interventions or clinical practice therefore it is deemed very feasible in patients with symptomatic knee osteoarthritis.

View background material via the OAK3 CPG eAppendix 1
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Future Research

Future research in this area should embrace detailed osteoarthritis characterization including sub-group analyses and osteoarthrosis severity stratification. Furthermore, using clinically relevant outcomes and controls for bias are warranted along with cost-effectiveness analysis.

Platelet-rich Plasma

Platelet-rich plasma (PRP) may reduce pain and improve function in patients with symptomatic osteoarthritis of the knee.

Strength of Recommendation: Limited ★★☆☆ (downgrade)
Description: Evidence from one or more "Low" quality studies with consistent findings or evidence from a single "Moderate" quality study recommending for or against the intervention. Also, higher strength evidence can be downgraded to limited due to major concerns addressed in the EtD Framework.

Rationale

There were two high (Rayegani; 2014, Gormeli; 2017) and one moderate (Akan; 2018) study with 30 people per group comparing PRP vs. control. There were mixed results in the studies for pain and function. A meta-analysis was not performed due to heterogeneity. Two studies (Akan; 2018, Gormeli; 2017) looked at PRP in severe OA with mixed results. Two studies (Rayegani; 2014, Gormeli; 2017) looked at change in all stages of OA at a six-month timeframe. The studies had mixed results. One study (Gormeli; 2017) looked at Kellgren-Lawrence 1-3 stage OA with improvement in IKDC and EQ-VAS. Therefore, due to the heterogeneity of results and the difference in early and late stage OA results, we downgraded the recommendation to Limited from Strong. We feel these recommendations may change with future research on the use of PRP in different levels of severity of OA.

The number of PRP injections had mixed results with the studies with three PRP injections (Akan; 2018, Gormeli; 2017) having positive results outcomes for pain and function. Studies with one and two PRP injections had mixed results, with the positive being less likely clinically significant changes in pain and function. Further research should be done to determine the number of PRP injections for treatment of KOA. Currently, three IA-PRP injections appear to have more favorable results.

Adverse events from PRP injections has been investigated in one high-quality study (Huang; 2018) reported adverse events for PRP vs. control. They reported hypertension and proteinuria were treatment-related side-effects. These met Common Toxicity Criteria grade ≥3. This raises questions on the safety of PRP, which needs further evaluation. Therefore, the strength of recommendation was downgraded to Limited.

When evaluating the effectiveness of PRP vs HA, there were eight high-quality studies (Sanchez; 2012, Vaquerizo; 2013, Filardo; 2015, Gormeli; 2017, Cole; 2017, Buendia-Lopez; 2018, Di Martino; 2019, Yaradilmis; 2020) and six (6) medium quality studies (Spakova; 2012, Raeissadat; 2015, Lana; 2016, Duymus; 2017, Raeissadat; 2017, Ahmad; 2018) and one low-quality studies (Sanchez; 2008) that investigated IA-PRP vs. IA-HA. Four studies were included in a meta-analysis of Total WOMAC results at the 9- OR 12-months mark. This analysis showed a clinically significant difference for IA-PRP over IA-HA. The results between IA-PRP vs IA-HA diverged after 6 months. Most studies showed similar results between IA-PRP and IA-HA at six months, except one (Yaradilimis 2020) where the LR-PRP total WOMAC was better at all time points than the IA HA. Both the patients in the IA HA and IA PRP improved in total WOMAC at six months. Patients in the IA-PRP-arms maintained improvement after 6 months at the 9- OR 12-months mark for total WOMAC vs. IA-HA which started to have a worsening score. The standard is to inject IA-HA every six months in patients with painful KOA. The preparation of the PRP (LR-PRP vs LP-PRP) was noted to be different with the LR-PRP had higher MID values than LP-PRP vs. IA-HA. The research highlights the prolonged effect of IA-PRP over IA-HA, though both appear to be equivalent at 6 months.

View background material via the OAK3 CPG eAppendix 1
View data summaries via the OAK3 CPG eAppendix 2

Patient-related outcome measures (OARSI-OMERACT responders, percentage of subjects meeting a percentage reduction in VAS Pain OR WOMAC Pain scores) (Sanchez; 2008, Sanchez; 2012, Vaquerizo; 2013, Buendia-Lopez; 2018) more often favorited IA-PRP at both the six month and 12-month time frame. Further, research is needed using standardized PROM's to investigate the effectiveness of IA-PRP to determine if more patients will benefit from IA-PRP at six months over IA-HA.

Adverse events were higher in the PRP group than IA HA, both local soreness and injection pain (two studies (Spakova; 2012, Yaradilmis; 2020)) and one study (Huang; 2018)) systemic events (proteinuria and hypertension). One study (Vaquerizo; 2013) did not find a difference comparing any adverse event, and one study (Raeissadat; 2017) did not see a difference for minor injection-site adverse events. Therefore, there appears to be more studies finding IA-PRP to have more adverse events vs. IA-HA, more research is need to determine if the adverse events outweigh the benefit of IA-PRP over IA-HA at 9 and 12 months. This is another reason for the downgrade in evidence from Strong to Limited.

Comparisons between IA-PRP and IA-CS, there were three high (Joshi Juber; 2017, Khan; 2018, Nabi; 2018) and one moderate quality study (Huang; 2019). One study (Joshi Juber; 2017) was KL IV end-stage OA and did not find a difference. One study (Khan; 2018) was repeat injections every other month (0, 2, 4 months) with follow up at six months in KL II OAK with no difference. One study (Nabi; 2018) used patients with KL II-III given three injections one month apart showed improvement at three months (one month after the last injection) and six months (4 months after the final injection). One study (Huang; 2019) did three PRP injections every three weeks on KL I-II OAK showed improvement in pain and function at six months (4 months after last injection) and 12 months (10 months after last injection). Therefore, the IA-PRP given in three injections evaluated at 4 months post last injection is more likely to show benefit in KL II and III stages of KOA. More research is needed to evaluate long-term benefits of IA-PRP vs IA-CS over a two- or five-year period to determine if IA-PRP is cartilage sparing vs IA-CS concern for possible cartilage damage over time.

PRP is defined in LR-PRP and LP-PRP. There may be a difference in the effectiveness in knee osteoarthritis between these two preparations. Currently, there is limited data from one direct comparison (Yaradilimis; 2020) and our meta-analysis (Figure 45) of IA-PRP and IA-HA that would demonstrate that intra-articular LR-PRP vs. LP-PRP for KOA is more likely to demonstrate a benefit at 9 and 12 months. The number of studies is limited, therefore determining the better choice between LR-PRP vs. LP-PRP is still inconclusive, but at this time appears to favor LR-PRP.

The Platelet-Rich Plasma recommendation has been downgraded two levels because of inconsistent evidence.

Benefits/Harms of Implementation

Some patients may experience temporary local soreness or injection pain.

Outcome Importance

Pain and function improvement through intra-articular therapies for the treatment of knee osteoarthritis may have high impact on symptoms and overall health.

Cost Effectiveness/Resource Utilization

The cost-effectiveness of different intra-articular therapies is still to be determined, in comparison to other treatment strategies and among different intra-articular alternatives.

Acceptability
Currently intra-articular treatments are commonly utilized approach in treating symptomatic knee osteoarthritis, hence there should be no issues implementing this recommendation as it does not influence a major change in clinical practice, and it provides further evidence to support and guide these practices.

Feasibility
These recommendations do not interfere with other interventions or clinical practice therefore it is deemed very feasible in patients with symptomatic knee osteoarthritis.

Future Research
Future research in this area should embrace detailed osteoarthritis characterization including sub-group analyses and osteoarthrosis severity stratification. Furthermore, using clinically relevant outcomes and controls for bias are warranted along with cost-effectiveness analysis. Specifically, to platelet rich plasma it will be of outmost importance to include comprehensive platelet rich plasma characterization and description of platelet rich plasma preparation protocol.

View background material via the OAK3 CPG eAppendix 1
View data summaries via the OAK3 CPG eAppendix 2

Denervation Therapy

Denervation therapy may reduce pain and improve function in patients with symptomatic osteoarthritis of the knee.

Strength of Recommendation: Limited ★★☆☆ (downgrade)
Description: Evidence from one or more "Low" quality studies with consistent findings or evidence from a single "Moderate" quality study recommending for or against the intervention. Also, higher strength evidence can be downgraded to limited due to major concerns addressed in the EtD Framework.

Rationale

For the denervation therapies, there are 2 high quality studies (Radnovic et al 2017 and Mendes et al 2019) and 2 moderate quality studies (McAlindon et al 2017 and El-Hakeim et al 2018) comparing denervation technique with placebo.

One high quality study (Radnovic et al 2017) specifically evaluated the efficacy of cryoneurolysis in comparison to placebo control in patients with knee OA. It was found that the group receiving cryoneurolysis had improved total WOMAC, WOMAC stiffness, WOMAC pain, WOMAC physical function and in VAS pain compared to placebo control group.

Another high-quality study (Mendes et al 2019) evaluated the efficacy of chemical ablation in comparison to placebo control in patients with knee OA. It was found that the group receiving chemical denervation had improved in WOMAC pain compared to placebo control group. Another moderate quality study (McAlindon et al 2017) comparing the efficacy of chemical ablation in comparison to placebo control in patients with knee OA found no major difference between the two groups.

One moderate quality study (El-Hakeim et al 2018) specifically evaluated the efficacy of thermal ablation in comparison to placebo control in patients with knee OA. It was found that the group receiving thermal ablation had improved WOMAC total, WOMAC function and VAS pain compared to placebo control group.

One high quality study (Davis et al) and one moderate evidence study (Davis et al 2018) compared IA HA to thermal ablation in patients with knee OA. The first study (Davis et al 2018) showed worse Oxford Knee Score, Global Perceived Index and Numeric Rating Scale in the HA group compared to the thermal ablation group, while the second study (Davis et al 2018) showed worse Oxford Knee Score, Change in Medication Use (mg) from Baseline, Knee pain-Numeric Rating scale and Mean Reduction in average NRS score in the HA group compared to the thermal ablation.

One high quality study (Gulec et al 2017) compared unipolar to bipolar radiofrequency ablation of the knee in patients with knee OA. In patients with OA, Bipolar intra-articular pulsed radiofrequency thermocoagulation may be used over Unipolar intra-articular pulsed radiofrequency thermocoagulation to improve patient pain.

One moderate quality study (Sari et al 2018) compared IA steroids to thermal ablation of the knee in patients with knee OA. The study showed worse WOMAC total, WOMAC function, WOMAC stiffness and worse VAS pain in the IA steroids group compared to thermal ablation group
In summary, our analysis demonstrates that denervation therapy may reduce pain and improve function in patients with symptomatic osteoarthritis of the knee.

The Denervation Therapy recommendation has been downgraded two levels because of inconsistent evidence and bias.

Benefits/Harms of Implementation
There are no major known or anticipated harms associated with implementing this recommendation anticipated.

Outcome Importance
Pain and function improvement through denervation therapies for the treatment of knee osteoarthritis may have high impact on symptoms and overall health.

Cost Effectiveness/Resource Utilization
The cost-effectiveness of different denervation therapies is still to be determined, in comparison to other treatment strategies and among different denervation alternatives.

Acceptability
Currently denervation treatments are commonly utilized approaches in treating symptomatic knee osteoarthritis, hence there should be no issues implementing this recommendation as it does not influence a major change in clinical practice, and it provides further evidence to support and guide these practices.

Feasibility
These recommendations do not interfere with other interventions or clinical practice therefore it is deemed very feasible in patients with symptomatic knee osteoarthritis.

Future Research
Future research in this area should embrace detailed osteoarthritis characterization including sub-group analyses, osteoarthrosis severity stratification, and end stage disease in patients unable to have total knee arthroplasty (e.g. due to age or comorbities). Furthermore, using clinically relevant outcomes and controls for bias are warranted along with cost-effectiveness analysis.

View background material via the OAK3 CPG eAppendix 1
View data summaries via the OAK3 CPG eAppendix 2

Lavage/Debridement

Arthroscopy with lavage and/or debridement in patients with a primary diagnosis of knee osteoarthritis is not recommended.

Strength of Recommendation: Moderate ★★★☆

Evidence from two or more "Moderate" quality studies with consistent findings, or evidence from a single "High" quality study for recommending for or against the intervention. Also requires no or only minor concerns addressed in the EtD framework.

Rationale

There were four studies that met the inclusion criteria for this recommendation. There was one high strength (Moseley et al 2002), two moderate strength (Kirkley et.al 2008, Kalunian et.al 2000), and one low quality (Saeed et.al 2015).

Kirkely et al 2008 compared arthroscopic surgery which, included lavage and debridement combined with physical therapy and medical treatment versus physical therapy and medical treatment alone. The outcome measures utilized were the total Western Ontario and McMaster Universities Osteoarthritis Index (WOMAC) score, Short Form-36 (SF-36) Physical Component Summary score, McMaster–Toronto Arthritis Patient Preference Disability Questionnaire (MACTAR), and the Arthritis Self-Efficacy Scale (ASES) and standard-gamble utility scores. Six patients assigned to surgery elected not to have the procedure; data from these patients were analyzed, according to the intention to- treat principle, with data from the surgery group. Out of all potential outcomes, only two were statistically significant in favor of surgery. In summary, this randomized controlled trial demonstrated no benefit of arthroscopic lavage and debridement compared to physical therapy and medical treatment for osteoarthritis of the knee.

Kalunian et al. 2000 compared arthroscopic lavage (3000ml) with placebo (250ml). The study was performed at 4 different institutes and included a large number of enrolled patients from one institution with intra-articular crystals in their knee. The arthroscopes used were less than usual caliber in size ranging from 1.7mm to 2.7mm. Outcome measures were WOMAC scores at 12 months. There were not any statistically significant differences in aggregate WOMAC scores between the two treatment groups. The study concludes that irrigation may be helpful in a small subset of patients, especially those with crystals.

Mosley et al 2002 study is an RCT comparing arthroscopic debridement, arthroscopic lavage, versus placebo / sham surgery. The study provides strong evidence that knee arthroscopy with or without debridement is not better and appears to be equivalent to a placebo procedure in improving knee pain and self-reported function. However, the study raised questions regarding its limited sampling (mostly male veterans) as well as the number of potential study participants who declined randomization into a treatment group. They also used a non-validated Knee Specific Pain score. Also, patients with substantial malalignment (varus or valgus deformity) and those with advanced disease, who might have a poorer response to surgical intervention were included in the trial.

Saeed et al 2015 compared HA injections versus arthroscopic debridement in patients with OA in an RCT where only the pain component of the knee society score was utilized. In short term follow up of 6 months, arthroscopy failed to show better pain outcome than injections.

Most of the studies excluded patients with meniscal tear, loose body, or other mechanical derangement, with concomitant diagnosis of osteoarthritis of the knee. The present recommendation does not apply to such patients.

Benefits/Harms of Implementation

Owing to lack of strong evidence in support of clinical benefits from lavage surgery coupled with increased risks from surgery, the workgroup decided to recommend against arthroscopic debridement and/or lavage in patients with a primary diagnosis of osteoarthritis of the knee.

Future Research

Most studies included in this review had compared lavage to variety of nonoperative modalities. However, considering emergence of new modalities and technology it would be worthwhile to do high quality study with arthroscopic lavage done with a standardized size instrument comparing with nonoperative measures which could include PRP injections, nerve ablations, etc. Recent introduction of nanoscopes also warrants further studies of use of such devices in an office setting and comparing it to cost effectiveness of doing procedures in the operating room.

View background material via the OAK3 CPG eAppendix 1
View data summaries via the OAK3 CPG eAppendix 2

Partial Meniscectomy

Arthroscopic partial meniscectomy can be used for the treatment of meniscal tears in patients with concomitant mild to moderate osteoarthritis who have failed physical therapy or other nonsurgical treatments.

Strength of Recommendation: Moderate ★★★☆

Evidence from two or more "Moderate" quality studies with consistent findings, or evidence from a single "High" quality study for recommending for or against the intervention. Also requires no or only minor concerns addressed in the EtD framework.

Rationale

The three studies discussed below compare outcomes following arthroscopic partial meniscectomy with physical therapy and demonstrate that knee arthroscopy with partial meniscectomy is as effective as physical therapy. In PICO 5, this work group recommended supervised or unsupervised exercise as opposed to no exercise to improve pain and function in patients with knee osteoarthritis. Currently, there are no studies that compare outcomes (knee pain and function) following arthroscopic partial meniscectomy versus physical therapy alone in patients who have failed to improve with an initial course of physical therapy. It is important to clearly define the appropriate indications for arthroscopic partial meniscectomy in patients with knee OA. This procedure should be considered in patients with mild-to-moderate knee OA and an MRI confirmed meniscal tear who have previously failed appropriate conservative treatment such as physical therapy, corticosteroid injections, and a course of non-steroidal anti-inflammatory medications.

Katz et al (2013) conducted a multicenter, randomized, controlled trial of symptomatic patients over the age 45 or older with a meniscal tear and evidence of mild-to-moderate knee osteoarthritis to determine efficacy of arthroscopic partial meniscectomy compared to standardized physical therapy in this patient population. Three hundred fifty-one patients were randomly assigned to surgery and postoperative physical therapy or to a standardized physical therapy regimen (with the option to cross over to surgery at the discretion of the patient and surgeon). The patients were evaluated at 6 and 12 months and the primary outcome was the difference between the groups with respect to the change in the Western Ontario and McMaster Universities Osteoarthritis Index (WOMAC) physical function score. The mean improvement in WOMAC score at 6 months was similar between the groups. At 6 months, 51 patients who were randomized to physical therapy alone (30%) had undergone surgery. The authors concluded that in their intention-to-treat analysis, there were no significant differences in functional improvement 6 months after randomization; however, 30% of patients in the physical therapy alone group underwent surgery. These patients were analyzed in their original group, based on the intention-to-treat analysis.

Van de Graaf et al. (2018) performed a multicenter randomized clinical trial in the Netherlands to determine whether physical therapy is inferior to arthroscopic partial meniscectomy (APM) for improving patient-reported knee function in patients with meniscal tears. Three hundred twenty-one patients were randomly assigned to APM or a predefined physical therapy protocol. Patients were excluded if they had locking of the knee, prior knee surgery, instability caused by anterior or posterior cruciate ligament rupture, severe osteoarthritis (Kellgren Lawrence score of 4), and a BMI > 35 kg/m2. Change in patient-reported knee function on the International Knee Documentation Committee Subscale Knee form (IKDC) over a 24-month period was used as the primary outcome. In the PT group, 47 patients (29%) had APM during the 24-month follow-up period. The authors noted a similar level of improvement in knee function between the APM and PT groups. They concluded that PT was noninferior to APM for improving

patient-reported knee function over a 24-month follow-up period in patients with nonobstructive meniscal tears.

In 2007, Herrlin et al performed a prospective randomized study to compare knee function and physical activity following arthroscopic partial meniscectomy followed by supervised exercise or supervised exercise alone in patients with non-traumatic medial meniscal tear. Ninety patients were evaluated using the Knee Injury and Osteoarthritis Outcomes Score (KOOS), the Lysholm Knee Scoring Scale, and Tegner Activity Scale and a Visual Analog Scale (VAS) for pain prior to the intervention and after 8 weeks of exercise and 6 months following intervention. The authors found that after the intervention, both groups reported decreased knee pain, improved knee function, and a high satisfaction ($p<0.0001$). They, therefore, concluded that arthroscopic partial meniscectomy was not superior to supervised exercise alone in terms of reduced knee pain, improved knee function, and improved quality of life.

Benefits/Harms of Implementation

Given the risks associated with surgical intervention, only appropriately indicated patients should be considered for partial meniscectomy in the setting of mild to moderate knee osteoarthritis.

Future Research

We did not identify any studies that compare outcomes (i.e. knee pain and function) following arthroscopic partial meniscectomy versus physical therapy alone in patients who have failed to improve with an initial course of physical therapy, non-steroidal anti-inflammatory medications (NSAIDs), and a possible intra-articular steroid injection. The three studies reviewed by the work group demonstrate that knee arthroscopy with partial meniscectomy is as effective as physical therapy. Future studies should seek to compare outcomes in patients with mild to moderate knee osteoarthritis and an MRI confirmed meniscal tear who have undergone partial meniscectomy after failing to improve with a course of conservative treatment (NSAIDs, steroid injection, and physical therapy) versus those who have undergone partial meniscectomy without a dedicated course of conservative treatment.

View background material via the OAK3 CPG eAppendix 1
View data summaries via the OAK3 CPG eAppendix 2

Tibial Osteotomy

High tibial osteotomy may be considered to improve pain and function in properly indicated patients with unicompartmental knee osteoarthritis.

Strength of Recommendation: Limited ★★☆☆ (downgrade)
Description: Evidence from one or more "Low" quality studies with consistent findings or evidence from a single "Moderate" quality study recommending for or against the intervention. Also, higher strength evidence can be downgraded to limited due to major concerns addressed in the EtD Framework.

Rationale

High tibial osteotomy (HTO) has been used for pain relief of medial compartment knee osteoarthritis. Realigning the varus knee provides mechanical decompression of the medial compartment. An osteotomy line is created in the proximal tibial and either a wedge defect is created by opening the medial cortex and held open with a wedge or plate and screw hardware, or a lateral wedge is removed and secured commonly with staples or wires. In the Nerhus 2017 study, patients continued to show improvement 6 and 12 months post-operatively. Historical studies have reported pain reduction with survival rates approximately 70% at 10 years ("survival" usually interpreted with endpoint conversion to replacement) (van Outeren cites Brouwer 2014 and Niinimaki 2012).

Many studies available for review by the workgroup compared various techniques of osteotomy in randomized studies. Ogawa 2019 found osteotomy distal to the tibial tubercle to be superior to proximal osteotomy for opening wedge procedure with regard to patellofemoral pain. Arthroscopic evaluation of the knee joint at time of osteotomy and second look at time of hardware removal showed less patellar and trochlear degeneration with the distal osteotomy group.

Nerhus 2017 saw no significant functional difference between surgical patients randomized to either opening or closing wedge, with all showing improvement.

Duivenvoorden 2014 reported improved HSS scores from 71 to 81 at 6 years post-op. VAS scores improved from 6.1 baseline to a statistically significant difference at follow up of 4.0 in the opening wedge patients and 3.2 with the closing wedge (albeit no statistical difference between the groups). It should be noted that patients lost to follow up started with a VAS score 6.6, thus tempering analysis of late results.

Brouwer 2006 performed a prospective randomized trial comparing closing wedge and opening wedge techniques. Closing wedge was secured with two surgical staples and opening wedge with a Puddu plate. After one-year VAS score had improved from 6.1 to 3.6.

Van Outeren 2017 is perhaps the closest attempt to a large randomized control trial between surgery and non-operative management. However, this is still not a highest quality randomized control trial. The researchers gathered two different groups of patients at two different hospitals. The first group underwent randomization to valgus bracing versus usual care. The second group was randomized to HTO with either opening wedge or closing wedge osteotomy. The groups were matched for baseline characteristics. They found HTO more effective in pain reduction compared to non-operative methods. VAS changed from baseline 6.2 in the surgery group to 3.8 post-op. Control group improved from 6.4 to 5.0. Function was improved only in comparison of surgical patients to usual care treatment.

The Wu 2017 study evaluated people with bilateral OA with pain around medial part of the knee. The more degenerative knee got proximal tibial osteotomy, and the other knee got usual non-operative care. The study authors included a table of individual patient data, which allowed a model that controlled for differences in baseline knee society function scores between the knees to be run. With this model, the odds ratio of achieving satisfactory knee society function scores (defined as score >= 80) with osteotomy vs. non-operative treatment was 7.51(CI 1.094, 51.6).

The Tibial Osteotomy recommendation has been downgraded one level because of inconsistent evidence.

Benefits/Harms of Implementation

As with any osteotomy surgery, bone healing and hardware complications can occur. Incomplete osteotomy can lead to unexpected fracture at the point of correction (Getgood 2011). Neurologic injury is feared but uncommon. 2 of 35 patients in both closing wedge and opening wedge groups under Nerhus et al. 2017. Duivenvoorden had only one patient with peroneal nerve injury (closing wedge group) and Brouwer only 1 of 92 (also closing wedge group). Hardware removal appeared more common with medial opening wedge techniques. Limb length discrepancy is also increased with the opening wedge technique (Kim et al. 2016). Van Outeren had non-union of the osteotomy site only in 2 opening wedge patients. Duivenvoorden found opening wedge HTO to have more complications. However, non-union of the osteotomy was more common with their closing wedge technique (Duivenvoorden 2014). Brouwer on their other hand concluded their close wedge technique to have achieved more accurate correction with less morbidity.

The increase valgus angle across the knee will change patellar tracking, as noted above by Ogawa et al. 2019. In Song et al. 2012 no patient at baseline reported anterior knee pain. Although no significant difference was seen between their closing wedge and opening wedge groups, 30% of their patients had various levels of anterior knee pain, including 9% with moderate and 6% with severe anterior knee pain (minimum follow up 3 years).
Nerhus 2017 at two years follow up reported only 1 (closing wedge group) of their total 70 patients as revision to arthroplasty. Duivenvoorden 2014 had six year follow up and reported conversion to TKA in 10 of 45 closing wedge HTO patients and 3 of 45 in the opening wedge group.

Outcome Importance

Despite the lack of a true RCT comparing HTO to non-operative management, the studies reviewed by the workgroup all agree with the premise that pain is reduced by HTO. There appear to be relatively equal outcomes whether HTO is achieved with lateral or opening wedge surgical technique. Opening wedge osteotomy distal to the tibial tubercle appears to be preferred, according to the single study examining this aspect of surgical technique (Ogawa 2019).

Cost Effectiveness/Resource Utilization

Hardware removal was relatively common, and the second surgery will add expense to the total endeavor. For reference, Brouwer reported hardware removal in 11 of 47 closing wedge cases and 27 of 45 with opening wedge HTO. Nerhus reported metal removal in 4 of 35 closing wedge cases and 8 of 35 in the opening wedge group.

Conversion to knee arthroplasty is the most expensive late effect of the procedure. As years increase post-op, conversion rates to TKA increase. No studies were identified which adequately addressed the cost-benefit of knee replacement options versus osteotomy.

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Acceptability
In select patients with isolated medial compartment arthritis, there appear to be adequate short-term results with regard to pain and function in those patients undergoing surgery.

The quality of HTO results will be dependent upon the skill and experience of the operating surgeon and the cooperation of a patient to understand he or she is entering into a post-op state with altered anatomy and a prognosis imperfectly known in comparison to other options.

Feasibility
Van Outeren rightly questions the benefits of surgical treatment versus brace treatment. Their study had only one-year follow-up and 25 of 60 patients initially in the brace group dropped. They were not optimistic for long term utility and/or compliance of brace treatment.

Future Research
Previous studies have addressed outcomes when converting UKA to TKA and likewise for converting HTO to TKA. Studies looking at functional improvement and pain relief of HTO in direct comparison to knee replacement surgery (total or partial) would be of great value to our collective knowledge base, especially if such a study could track patients from baseline into HTO versus UKA and then long term to TKA. It is unlikely such a study could be performed prospectively over such a long time, yet data from a registry might prove fruitful.

Dry Needling

In the absence of reliable evidence, it is the opinion of the workgroup that the utility/efficacy of dry needling is unclear and requires additional evidence.

Strength of Recommendation: Consensus ★☆☆☆

Description: Evidence there is no supporting evidence, or limited level evidence was downgraded due to major concerns addressed in the EtD framework. In the absence of reliable evidence, the guideline work group is making a recommendation based on their clinical opinion.

Rationale

Two high quality studies examining the effectiveness of dry needling in combination with either exercise versus sham dry needling and exercise, (Sanchez, 2019) or dry needling combined with manual therapy and exercise versus manual therapy and exercise alone (Dunning, 2018) were reviewed. Sanchez et al. 2019 found no difference in clinical outcomes of pain or function between treatment groups. In contrast, Dunning et al. found greater improvements in measures of pain and function in the group receiving dry needling. The inconsistency in the results of these studies has prompted the workgroup not to make a recommendation for or against dry needling at this time. Additional evidence will be required before a recommendation can be made.

Future Research

Continued research with larger studies to examine the effectiveness of dry needling for reducing pain and improving function in patients with knee osteoarthritis is warranted.

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Free Floating Interpositional Devices

In the absence of reliable or new evidence, it is the opinion of the work group not to use free-floating (un-fixed) interpositional devices in patients with symptomatic medial compartment osteoarthritis of the knee.

Strength of Recommendation: Consensus 

Description: Evidence there is no supporting evidence, or limited level evidence was downgraded due to major concerns addressed in the EtD framework. In the absence of reliable evidence, the guideline work group is making a recommendation based on their clinical opinion.

Rationale

One study met inclusion criteria, and no additional studies were available for review since the prior edition OAK CPG was published. The single study was a case series and retrospective review of outcomes in patients receiving the surgical intervention for isolated medial compartment OA. The study indicated high reoperation rates in the patients who were followed, with 32% of patients being revised to total knee arthroplasty during the study period. Regarding pain and functional improvement, the study reported no statistical difference in preoperative and postoperative Knee Society Scores. Given the lack of evidence to support use, the AAOS workgroup modified the grade of this recommendation to consensus, because of the high revision rates in this study, and the potential harm associated with surgical intervention (anesthesia risks, VTE, infection, and reoperation).

Cost Effectiveness/Resource Utilization

No economic analyses or resource utilization studies have been reported on this treatment option.

Future Research

Future research should be aimed at producing level one randomized control trials to define clinical efficacy and risk of complication.

APPENDICES

Appendix I: References for Included Literature

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Appendix II: PICO Questions Used to Define Literature Search

1. In adult (>17) patients with symptomatic osteoarthritis of the knee, do assistive devices (canes, shoe inserts, etc.) improve patient outcomes?

2. In adult (>17) patients with symptomatic osteoarthritis of the knee, do braces improve patient outcomes?

3. In adult (>17) patients with symptomatic osteoarthritis of the knee, do oral/dietary supplements improve patient outcomes?

4. In adult (>17) patients with symptomatic osteoarthritis of the knee, do topical treatments improve patient outcomes?

5. In adult (>17) patients with symptomatic osteoarthritis of the knee, does exercise and activity improve patient outcomes?

6. In adult (>17) patients with symptomatic osteoarthritis of the knee, do weight loss interventions improve patient outcomes?

7. In adult (>17) patients with symptomatic osteoarthritis of the knee, is the extent of weight lost associated with improved patient outcomes?

8. In adult (>17) patients with symptomatic osteoarthritis of the knee, do manual therapies (manipulation, mobilization, massage, etc.) improve patient outcomes?

9. In adult (>17) patients with symptomatic osteoarthritis of the knee, do physical/electrotherapeutic agents (acupuncture, heat, ice, TENS, etc.) improve patient outcomes?

10. In adult (>17) patients with symptomatic osteoarthritis of the knee, what systemic treatments are most effective for improving patient outcomes?

11. In adult (>17) patients with symptomatic osteoarthritis of the knee, what locally invasive treatments are most effective for improving patient outcomes?

12. In adult (>17) patients with symptomatic osteoarthritis of the knee, does arthroscopic debridement improve patient outcomes?

13. In adult (>17) patients with symptomatic osteoarthritis of the knee, does partial meniscectomy improve patient outcomes?

14. In adult (>17) patients with symptomatic osteoarthritis of the knee, does osteotomy improve patient outcomes?

Appendix III: Literature Search Strategy

LINE	SEARCH SYNTAX
1	((animals not humans) or cadaver).sh. or cadaver*.ti.
2	(((comment or editorial or letter or historical article) not "clinical trial") or address or news or newspaper article or case reports).pt. or case report.ti.
3	((Adolescent OR Child OR Infant) NOT Adult).sh.
4	1 or 2 or 3
5	exp "Osteoarthritis, Knee"/ or (gonitis or gonarthritis or gonarthros*).ti,ab.
6	exp "Knee Joint"/ or exp "Knee"/ or (knee or knees or femorotibial or tibial or patella or patellar).ti,ab.
7	"Osteoarthritis"/ or "Arthritis"/ or (osteoarthriti* or osteo-arthriti* or osteo-arthros* or osteoarthros*).ti,ab. or ((non-inflamm* or noninflamm* or degenerat* or hypertropic) and (arthriti* or joint* or disease*)).ti,ab.
8	5 or (6 and 7)
9	"Self-Help Devices"/ or "Orthopedic Equipment"/ or "Canes"/ or (cane or canes).ti,ab. or "Crutches"/ or (crutch or crutches).ti,ab. or exp "Orthotic Devices"/ or (orthotic or orthotics or orthoses or orthosis or braces or bracing or shoes or insole or insoles).ti,ab. or "Walkers"/ or ("assistive device" or "assistive devices" or "walking aids" or walker or walkers or splints or sleeves).ti,ab.
10	8 and 9
11	exp "Intercellular Signaling Peptides and Proteins"/ or ("growth factors" or "growth factor").ti,ab. or ((biological or biologic or cell or cell-based or cellular) ADJ2 (therapy or therapies)).ti,ab. or ("platelet rich plasma" or "platelet-rich plasma" or "PRP" or "stem cell" or "stem cells").ti,ab. or "biologics".ti,ab. or exp "Biological Therapy"/ or exp "Biological Products"/ or ("minimally manipulated" or "minimal manipulation" or "blood product" or "blood products").ti,ab. or exp "Platelet-Rich Plasma"/ or exp "Stem Cells"/ or exp "Prolotherapy"/ or (prolotherapy or prolotherapies).ti,ab. or orthobiologics.ti,ab.
12	8 and 11
13	exp "Injections, Intra-Articular"/ or exp "Viscosupplementation"/ or ((intraarticular or "intra articular") and (delivery OR administration OR injection* OR infusion or injectable)).ti,ab. or exp "Hyaluronic Acid"/ or (hyaluron* OR "hylan").ti,ab. or exp "Adrenal Cortex Hormones"/ or (corticoid* or cortical or corticostseroid* or "cortico steroid" or corticotherapy).ti,ab. or viscosupplement*.ti,ab.
14	8 and 13
15	exp "Acetaminophen"/ or ("paracetamol" or "acetaminophen" or "Tylenol").ti,ab. or exp "Anti-Inflammatory Agents, Non-Steroidal"/ or "NSAIDs".ti,ab. or exp "Cyclooxygenase 2 Inhibitors"/ or ((nonsteroidal or non-steroidal or "non steroidal") and (anti-inflammatory or "anti inflammatory" or antiinflammatory)).ti,ab. or exp "Ibuprofen"/ or ("ibuprofen" or "ibuprophen" or Advil or flurbiprofen).ti,ab. or exp "Naproxen"/ or (naproxen or Aleve).ti,ab. or exp "Celecoxib"/ OR (celecoxib or "COX-2 inhibitor" or "COX-2 inhibitors" or "COX2 inhibitor" or "COX2 inhibitors" or Celebrex).ti,ab. or exp "Diclofenac"/ or (diclofenac or misoprostol or sulindac or

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	ketoprofen or tolmetin or etodolac or fenoprofen or piroxicam or etodolac or indomethacin or meloxicam or Mobic or ketorolac or Toradol).ti,ab.
16	8 and 15
17	exp Narcotics/ or exp "Analgesics, Opioid"/ or (narcotic* or opioid* or opiate* or papaver* or oxycodone or Oxycontin or OxyER or "Oxy-ER" or "Oxy-CRF" or "OxyIR" or "Oxy-IR" or Percodan or Percocet or Endocet or Roxicet or hydrocodone or dihydrocodeinone or Vicodin or Vicoprofen or Norco or Lortrab or Lorcet or oxymorphone or Opana or morphine or Kadian or Avinza or "MS Contin" or Duramorph or Roxanol or codeine or fentanyl or Duragesic or Actiq or Sublimaze or hydromorphone or Dilaudid or meperidine or Demerol or tramadol or Ultram or buprenorphine or propoxyphene or Darvocet or Omnopon or methadone or Dolopphine or Methadose or suboxone).ti,ab.
18	8 and 17
19	exp "Weight Loss"/ or exp "Weight Reduction Programs"/ or ("weight loss" or "weight reduction" or "body weight" or "lose weight").ti,ab. or exp "Body Mass Index"/
20	8 and 19
21	"Therapeutic Irrigation"/ or ("lavage").ti,ab. or "Arthroscopy"/ or (arthroscopy or arthroscopic or arthroendoscopy).ti,ab. or exp "Meniscectomy"/ or (meniscectomy or meniscectomies or menisectomy).ti,ab. or ((meniscus or meniscal) ADJ3 (repair or resection or resections or removal or excision)).ti,ab.
22	8 and 21
23	(exp "Acupuncture Therapy"/ or (acupuncture or pharmacoacupuncture or acupotomy or auriculotherapy or "dry needling").ti,ab. or exp "Physical Therapy Modalities"/ or exp "Musculoskeletal Manipulations"/ or (physiotherap* or "physical therapy" or "physical therapies" or manipulation or manipulations or massage or "manual therapy" or "manual therapies" or mobilization).ti,ab. or exp "Electromyography"/ or exp "Electric Stimulation Therapy"/ or ("transcutaneous electric nerve stimulation" or "TENS" or "NMES" or "electrical stimulation" or electrostimulation or "electric stimulation" or "electronic stimulation" or electrotherapy or "nerve stimulation" or "muscle stimulation" or electromyograph*).ti,ab. or exp "Ultrasonic Therapy"/ or (ultrasound or laser or shockwave or "shock wave").ti,ab. or exp "Laser Therapy"/ or exp "Cryotherapy"/ or Hot Temperature/tu or (cryotherapy or cryotherapies or ice or heat or "cold therapy").ti,ab. or exp exercise/ or exp "exercise therapy"/ or ("strength training" or muscle or force or resistance or resistive or exercise or isometric* or isokinetic* or flexibility or dynamic or stretching).ti,ab.) not exp *Arthroplasty, Replacement, Knee/
24	8 and 23
25	"Osteotomy"/ or (osteotom*).ti,ab.

26	8 and 25
27	exp "Ablation Techniques"/ or exp "Catheter ablation"/ or exp "Pulsed radiofrequency treatment"/ or Radio waves/tu or ("radiofrequency ablation" or "radiofrequency neurotomy" or "Radiofrequency denervation" or "radiofrequency thermocoagulation" or "pulsed radiofrequency" or "catheter ablation" or "thermo-ablation" or "thermal ablation" or (nerve)adj3(ablation)).ti,ab. or exp "Denervation"/ or (neurolysis or denervation or denervated or "nerve block" or "nerve blocks" or "nerve blockade" or "nerve blockades" or neurectom* or neurotom*).ti,ab.
28	8 and 27
29	exp "Glucosamine"/ or glucosamine.ti,ab. or exp "Chondroitin"/ or chondroitin.ti,ab. or exp "Dietary Supplements"/ or (supplement or supplements or nutraceutical* or neutraceutical* or nutriceutical* or neutriceutical*).ti,ab. or Ginger/ or ginger.ti,ab. or exp "Cannabinoids"/ or (cannabidiol or CBD).ti,ab. or Curcumin/ or Curcuma/ or (curcumin or curcuma or turmeric).ti,ab.
30	8 and 29
31	(10 or 12 or 14 or 16 or 18 or 20 or 22 or 24 or 26 or 28 or 30) not 4
32	31 and English.lg.
33	Limit 32 to yr="2012-Current"

Database: Embase
Interface: Elsevier (https://embase.com)
Date Searched: *April 28, 2020*

LINE	SEARCH QUERY
1	knee osteoarthritis'/exp OR gonitis:ti,ab OR gonoarthritis:ti,ab OR gonarthros*:ti,ab
2	knee'/exp OR knee:ti,ab OR knees:ti,ab OR femorotibial:ti,ab OR tibial:ti,ab OR patella:ti,ab OR patellar:ti,ab
3	osteoarthritis'/exp OR osteoarthriti*:ti,ab OR 'osteo arthriti*':ti,ab OR 'osteo arthros*':ti,ab OR osteoarthros*:ti,ab OR (('non inflamm*':ti,ab OR noninflamm*:ti,ab OR degenerat*:ti,ab OR hypertropic:ti,ab) AND (arthriti*:ti,ab OR joint*:ti,ab OR disease*:ti,ab))
4	cadaver'/de OR 'in vitro study'/exp OR 'abstract report'/de OR 'book'/de OR 'editorial'/de OR 'note'/de OR 'letter'/it OR 'case study'/de OR 'case report'/de OR 'conference abstract'/it OR 'chapter'/it OR 'conference paper'/it OR 'conference review'/it
5	(#1 OR (#2 AND #3)) NOT #4
6	self help device'/exp OR 'orthopedic equipment'/exp OR 'walking aid'/exp OR 'orthosis'/exp OR 'orthotics'/exp OR cane:ti,ab OR canes:ti,ab OR crutch:ti,ab OR crutches:ti,ab OR orthotic:ti,ab OR orthotics:ti,ab OR orthoses:ti,ab OR orthosis:ti,ab OR braces:ti,ab OR bracing:ti,ab OR shoes:ti,ab OR insole:ti,ab OR insoles:ti,ab OR 'assistive device':ti,ab OR 'assistive devices':ti,ab OR 'walking aids':ti,ab OR walker:ti,ab OR walkers:ti,ab OR splints:ti,ab OR sleeves:ti,ab

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7	signal peptide'/exp OR 'biological therapy'/exp OR 'biological product'/exp OR 'biological products therapeutic use'/exp OR 'thrombocyte rich plasma'/exp OR 'stem cell'/exp or ('growth factor' or 'growth factors' or 'platelet rich plasma' or 'platelet-rich plasma' or 'PRP' or 'stem cell' or 'stem cells' or 'biologics' or 'minimally manipulated' or 'minimal manipulation' or 'blood product' or 'blood products' or prolotherapy or prolotherapies or orthobiologics):ti,ab or ((biologic or biological or cell or cell-based or cellular)NEAR/2(therapy or therapies)):ti,ab
8	intraarticular drug administration'/exp OR 'viscosupplementation'/exp OR 'viscosupplement'/exp OR 'hyaluronic acid'/exp OR 'corticosteroid'/exp OR hyaluron*:ti,ab OR hylan:ti,ab OR viscosupplement*:ti,ab OR corticoid*:ti,ab OR cortical:ti,ab OR corticosteroid*:ti,ab OR 'cortico steroid':ti,ab OR corticotherapy:ti,ab OR ((intraarticular:ti,ab OR 'intra articular':ti,ab) AND (delivery:ti,ab OR administration:ti,ab OR injection*:ti,ab OR infusion:ti,ab OR injectable:ti,ab))
9	paracetamol'/exp OR 'nonsteroid antiinflammatory agent'/exp OR 'cyclooxygenase 2 inhibitor'/exp OR 'ibuprofen'/exp OR 'naproxen'/exp OR 'celecoxib'/exp OR 'diclofenac'/exp OR acetaminophen:ti,ab OR paracetamol:ti,ab OR tylenol:ti,ab OR nsaids:ti,ab OR ibuprofen:ti,ab OR ibuprophen:ti,ab OR advil:ti,ab OR flurbiprofen:ti,ab OR naproxen:ti,ab OR aleve:ti,ab OR celecoxib:ti,ab OR 'cox-2 inhibitor':ti,ab OR 'cox-2 inhibitors':ti,ab OR 'cox2 inhibitor':ti,ab OR 'cox2 inhibitors':ti,ab OR celebrex:ti,ab OR diclofenac:ti,ab OR misprostol:ti,ab OR sulindac:ti,ab OR ketoprofen:ti,ab OR tolmetin:ti,ab OR fenorpofen:ti,ab OR piroxicam:ti,ab OR etodolac:ti,ab OR indomethacin:ti,ab OR meloxicam:ti,ab OR mobic:ti,ab OR ketorolac:ti,ab OR toradol:ti,ab OR ((nonsteroidal:ti,ab OR 'non steroidal':ti,ab) AND ('anti inflammatory':ti,ab OR antiinflammatory:ti,ab))
10	narcotic agent'/exp OR 'narcotic analgesic agent'/exp OR narcotic*:ti,ab OR opioid*:ti,ab OR opiate*:ti,ab OR papaver*:ti,ab OR oxycodone:ti,ab OR oxycontin:ti,ab OR oxyer:ti,ab OR 'oxy-er':ti,ab OR 'oxy-crf':ti,ab OR 'oxyir':ti,ab OR 'oxy-ir':ti,ab OR percodan:ti,ab OR percocet:ti,ab OR endocet:ti,ab OR roxicet:ti,ab OR hydrocodone:ti,ab OR dihydrocodeinone:ti,ab OR vicodin:ti,ab OR vicoprofen:ti,ab OR norco:ti,ab OR lortrab:ti,ab OR lorcet:ti,ab OR oxymorphone:ti,ab OR opana:ti,ab OR morphine:ti,ab OR kadian:ti,ab OR avinza:ti,ab OR 'ms contin':ti,ab OR duramorph:ti,ab OR roxanol:ti,ab OR codeine:ti,ab OR fentanyl:ti,ab OR duragesic:ti,ab OR actiq:ti,ab OR sublimaze:ti,ab OR hydromorphone:ti,ab OR dilaudid:ti,ab OR meperidine:ti,ab OR demerol:ti,ab OR tramadol:ti,ab OR ultram:ti,ab OR buprenorphine:ti,ab OR propoxyphene:ti,ab OR darvocet:ti,ab OR omnopon:ti,ab OR methadone:ti,ab OR dolopphine:ti,ab OR methadose:ti,ab OR suboxone:ti,ab
11	body weight loss'/exp OR 'weight loss program'/exp OR 'body mass'/exp OR 'weight loss':ti,ab OR 'weight reduction':ti,ab OR 'body weight':ti,ab OR 'lose weight':ti,ab

12	lavage'/de OR 'knee arthroscopy'/exp OR 'meniscectomy'/exp OR lavage:ti,ab OR arthroscopy:ti,ab OR arthroscopic:ti,ab OR arthroendoscopy:ti,ab OR meniscectomy:ti,ab OR meniscectomies:ti,ab OR menisectomy:ti,ab OR ((meniscal:ti,ab OR meniscus:ti,ab) AND near3:ti,ab AND (repair:ti,ab OR resection:ti,ab OR resections:ti,ab OR removal:ti,ab OR excision:ti,ab))
13	acupuncture'/exp OR 'physiotherapy'/exp OR 'musculoskeletal manipulation'/exp OR 'electromyography'/exp OR 'electrotherapy'/exp OR 'ultrasound therapy'/exp OR 'low level laser therapy'/exp OR 'cryotherapy'/exp OR 'kinesiotherapy'/exp OR acupuncture OR pharmacoacupuncture OR acupotomy OR auriculotherapy OR 'dry needling' OR physiotherap* OR 'physical therapy' OR 'physical therapies' OR manipulation OR manipulations OR massage OR 'manual therapy' OR 'manual therapies' OR mobilization OR 'transcutaneous electric nerve stimulation' OR 'tens' OR 'nmes' OR 'electrical stimulation' OR electrostimulation OR 'electric stimulation' OR 'electronic stimulation' OR electrotherapy OR 'nerve stimulation' OR 'muscle stimulation' OR electromyograph* OR ultrasound OR laser OR shockwave OR 'shock wave' OR cryotherapy OR cryotherapies OR ice OR heat OR 'cold therapy' OR (('strength training':ti,ab OR muscle:ti,ab OR force:ti,ab OR resistance:ti,ab OR resistive:ti,ab OR exercise:ti,ab OR isometric*:ti,ab OR isokinetic*:ti,ab OR flexibility:ti,ab OR dynamic:ti,ab OR stretching:ti,ab) NOT 'knee arthroplasty'/exp/mj)
14	osteotomy'/exp or osteotom*:ti,ab
15	pulsed radiofrequency treatment'/exp OR 'pulsed radiofrequency'/exp OR 'radiofrequency ablation'/de OR 'ablation therapy'/de OR 'catheter ablation'/exp OR 'thermal ablation'/exp OR 'thermal ablation therapy'/exp OR 'radiofrequency ablation':ti,ab OR 'radiofrequency neurotomy':ti,ab OR 'radiofrequency denervation':ti,ab OR 'radiofrequency thermocoagulation':ti,ab OR 'pulsed radiofrequency':ti,ab OR 'catheter ablation':ti,ab OR 'thermo-ablation':ti,ab OR 'thermal ablation':ti,ab OR ('nerve':ti,ab AND 'ablation':ti,ab)
16	glucosamine'/exp OR 'chondroitin'/exp OR 'dietary supplement'/exp OR 'ginger extract'/exp OR 'ginger oil'/exp OR 'ginger'/exp OR 'cannabinoid'/exp OR 'curcuma'/exp OR glucosamine:ti,ab OR chondroitin:ti,ab OR supplement:ti,ab OR supplements:ti,ab OR nutraceutical*:ti,ab OR neutraceutical*:ti,ab OR nutriceutical*:ti,ab OR neutriceutical*:ti,ab OR ginger:ti,ab OR cannabidiol:ti,ab OR 'cbd':ti,ab OR curcumin:ti,ab OR curcuma:ti,ab OR turmeric:ti,ab
17	#6 OR #7 OR #8 OR #9 OR #10 OR #11 OR #12 OR #13 OR #14 OR #15 OR #16
18	#5 and #17
19	#5 and #17 and [english]/lim and [2012-2019]/py

Database: Cochrane Central Register of Controlled Trials (CENTRAL)
Interface: Wiley (https://www.cochranelibrary.com/central)
Date Searched: *April 28, 2020*

LINE	SEARCH QUERY
1	[mh "osteoarthritis, knee"] or gonitis:ti,ab or gonarthritis:ti,ab or gonarthros*:ti,ab
2	[mh "knee joint"] or [mh "knee"] or (knee or knees or femorotibial or tibial or patella or patellar):ti,ab

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3	[mh ^osteoarthritis] or [mh ^arthritis] (osteoarthriti* or osteo-arthriti* or osteo-arthros* or osteoarthros*).ti,ab. or ((non-inflamm* or noninflamm* or degenerat* or hypertropic) and (arthriti* or joint* or disease*)):ti,ab
4	#1 or (#2 and #3)
5	[mh ^"Self-Help Devices"] or [mh ^"Orthopedic Equipment"] or [mh ^"Canes"] or (cane or canes):ti,ab or [mh ^"Crutches"] or (crutch or crutches):ti,ab or [mh "Orthotic Devices"] or (orthotic or orthotics or orthoses or orthosis or braces or bracing or shoes or insole or insoles):ti,ab or [mh "Walkers"] or ("assistive device" or "assistive devices" or "walking aids" or walker or walkers or splints or sleeves):ti,ab
6	[mh "Intercellular Signaling Peptides and Proteins"] or ("growth factors" or "growth factor"):ti,ab or ((biological or biologic or cell or cell-based or cellular) AND (therapy or therapies)):ti,ab or ("platelet rich plasma" or "platelet-rich plasma" or "PRP" or "stem cell" or "stem cells"):ti,ab or "biologics":ti,ab or [mh "Biological Therapy"] or [mh "Biological Products"] or ("minimally manipulated" or "minimal manipulation" or "blood product" or "blood products"):ti,ab or [mh "Platelet-Rich Plasma"] or [mh "Stem Cells"] or [mh "Prolotherapy"] or (prolotherapy or prolotherapies):ti,ab or orthobiologics:ti,ab
7	[mh "Injections, Intra-Articular"] or [mh "Viscosupplementation"] or ((intraarticular or "intra articular") and (delivery OR administration OR injection* OR infusion or injectable)):ti,ab or [mh "Hyaluronic Acid"] or (hyaluron* OR "hylan"):ti,ab or [mh "Adrenal Cortex Hormones"] or (corticoid* or cortical or corticostseroid* or "cortico steroid" or corticotherapy):ti,ab or viscosupplement*:ti,ab
8	[mh "Acetaminophen"] or ("paracetamol" or "acetaminophen" or "Tylenol"):ti,ab or [mh "Anti-Inflammatory Agents, Non-Steroidal"] or "NSAIDs":ti,ab or [mh "Cyclooxygenase 2 Inhibitors"] or ((nonsteroidal or non-steroidal or "non steroidal") and (anti-inflammatory or "anti inflammatory" or antiinflammatory)):ti,ab or [mh "Ibuprofen"] or ("ibuprofen" or "ibuprophen" or Advil or flurbiprofen):ti,ab or [mh "Naproxen"] or (naproxen or Aleve):ti,ab or [mh "Celecoxib"] OR (celecoxib or "COX-2 inhibitor" or "COX-2 inhibitors" or "COX2 inhibitor" or "COX2 inhibitors" or Celebrex):ti,ab or [mh "Diclofenac"] or (diclofenac or misoprostol or sulindac or ketoprofen or tolmetin or etodolac or fenoprofen or piroxicam or etodolac or indomethacin or meloxicam or Mobic or ketorolac or Toradol):ti,ab
9	[mh Narcotics] or [mh "Analgesics, Opioid"] or (narcotic* or opioid* or opiate* or papaver* or oxycodone or Oxycontin or OxyER or "Oxy-ER" or "Oxy-CRF" or "OxyIR" or "Oxy-IR" or Percodan or Percocet or Endocet or Roxicet or hydrocodone or dihydrocodeinone or Vicodin or Vicoprofen or Norco or Lortrab or Lorcet or oxymorphone or Opana or morphine or Kadian or Avinza or "MS Contin" or Duramorph or Roxanol or codeine or fentanyl or Duragesic or Actiq or Sublimaze or hydromorphone or Dilaudid or meperidine or Demerol or tramadol or Ultram or buprenorphine or propoxyphene or Darvocet or Omnopon or methadone or Dolopphine or Methadose or suboxone):ti,ab

10	[mh "Weight Loss"] or [mh "Weight Reduction Programs"] or ("weight loss" or "weight reduction" or "body weight" or "lose weight"):ti,ab or [mh "Body Mass Index"]
11	[mh "Therapeutic Irrigation"] or ("lavage"):ti,ab or [mh ^"Arthroscopy"] or (arthroscopy or arthroscopic or arthroendoscopy):ti,ab or [mh "Meniscectomy"] or (meniscectomy or meniscectomies or menisectomy):ti,ab or ((meniscus or meniscal) near/3 (repair or resection or resections or removal or excision)):ti,ab
12	([mh "Acupuncture Therapy"] or (acupuncture or pharmacoacupuncture or acupotomy or auriculotherapy or "dry needling"):ti,ab or [mh "Physical Therapy Modalities"] or [mh "Musculoskeletal Manipulations"] or (physiotherap* or "physical therapy" or "physical therapies" or manipulation or manipulations or massage or "manual therapy" or "manual therapies" or mobilization):ti,ab or [mh "Electromyography"] or [mh "Electric Stimulation Therapy"] or ("transcutaneous electric nerve stimulation" or "TENS" or "NMES" or "electrical stimulation" or electrostimulation or "electric stimulation" or "electronic stimulation" or electrotherapy or "nerve stimulation" or "muscle stimulation" or electromyograph*):ti,ab or [mh "Ultrasonic Therapy"] or (ultrasound or laser or shockwave or "shock wave"):ti,ab or [mh "Laser Therapy"] or [mh "Cryotherapy"] or (cryotherapy or cryotherapies or ice or heat or "cold therapy"):ti,ab or [mh exercise] or [mh "exercise therapy"] or ("strength training" or muscle or force or resistance or resistive or exercise or isometric* or isokinetic* or flexibility or dynamic or stretching):ti,ab) not [mh “Arthroplasty, Replacement, Knee”[mj]]
13	[mh "Osteotomy"] or (osteotom*):ti,ab
14	[mh "Ablation Techniques"] or [mh "Catheter ablation"] or [mh "Pulsed radiofrequency treatment"] or ("radiofrequency ablation" or "radiofrequency neurotomy" or "Radiofrequency denervation" or "radiofrequency thermocoagulation" or "pulsed radiofrequency" or "catheter ablation" or "thermo-ablation" or "thermal ablation" or (nerve) near/2 (ablation)):ti,ab or [mh "Denervation"] or (neurolysis or denervation or denervated or "nerve block" or "nerve blocks" or "nerve blockade" or "nerve blockades" or neurectom* or neurotom*):ti,ab
15	[mh "Glucosamine"] or glucosamine:ti,ab or [mh "Chondroitin"] or chondroitin:ti,ab or [mh "Dietary Supplements"] or (supplement or supplements or nutraceutical* or neutraceutical* or nutriceutical* or neutriceutical*):ti,ab or [mh ^Ginger] or ginger:ti,ab or [mh "Cannabinoids"] or (cannabidiol or CBD):ti,ab or [mh ^Curcumin] or [mh ^Curcuma] or (curcumin or curcuma or turmeric):ti,ab
16	#4 and (#5 or #6 or #7 or #8 or #9 or #10 or #11 or #12 or #13 or #14 or #15)
17	#16 not "conference abstract":pt

View background material via the OAK3 CPG eAppendix 1
View data summaries via the OAK3 CPG eAppendix 2

Appendix IV: Guideline Development Group Disclosures

Gregory Alexander Brown, MD, PhD Submitted on: 11/11/2018
ASTM: Board or committee member ($0) F04.39 Subcommittee Chair, Human Clinical Trials (Self)
HealthTrust Purchasing Group: Other financial or material support ($6,500) Part-time Orthopedic Service Line Director (Self)
Journal of Orthopaedic Trauma: Editorial or governing board ($0) Associate Editor (Self)

Creighton Collins Tubb, MD Submitted on: 10/03/2018
AAOS: Board or committee member ($0) Evidence Based Quality & Value Committee (Self)
American Association of Hip and Knee Surgeons: Board or committee member ($0) Evidence Based Medicine Committee (Self)

Yale Fillingham, MD Submitted on: 10/03/2018
Johnson & Johnson: Paid consultant ($0)

Robert H Brophy, MD Submitted on: 10/05/2018
American Orthopaedic Association: Board or committee member ($0) committee member (Self)
American Orthopaedic Society for Sports Medicine: Board or committee member ($0) Committee member (Self)

Yogesh V Kolwadkar, MD Submitted on: 12/10/2018
American Association of Hip and Knee Surgeons: Board or committee member ($0) Evidence Based Medicine
Committee (Self)
Springer: Editorial or governing board ($0) Journal of Orthopaedic Surgery & Research (Self)

William B Macaulay, MD Submitted on: 10/11/2018
American Association of Hip and Knee Surgeons: Board or committee member ($0) n/a(Self)
Clinical Orthopaedics and Related Research: Editorial or governing board ($0) N/A(Self)
Journal of Arthroplasty: Editorial or governing board ($0) N/A(Self)
ORamaVR: Unpaid consultant Scientific Advisory Board (Self)
OrthAlign: Stock or stock Options Number of Shares: 1,000 N/A(Self)

Nicolas Santiago Piuzzi, MD Submitted on: 01/21/2019
Orthopaedic Research Society: Board or committee member ($0) Clinical Research Committee (Self)

Lynn R Fisher, MD Submitted on: 02/18/2018
Kansas Academy of Family Physicians: Board or committee member ($2,500) current Board Chair until 06/18 (received monthly stipend while President) (Self)
Kansas Healthcare Collaborative: Board or committee member ($0) Secretary/Treasurer (Self)
Kansas Hospital Association: Board or committee member ($0) Board Member (Self)
Kansas Medical Society: Board or committee member ($0) Western KS District Trustee (Self)

G Kelley Fitzgerald, PT, PhD Submitted on: 10/04/2018
Journal of Orthopaedic and Sports Physical Therapy: Editorial or governing board ($0) I am on the Board of
Directors (Self)

Eric C Stiefel, MD Submitted on: 11/16/2018
Arthroscopy Association of North America: Board or committee member ($0)

Jorge A Chahla Jr, MD, PhD Submitted on: 02/01/2019
This individual reported nothing to disclose)

Thomas Trojian, MD Submitted on: 03/21/2018
2018 OARSI GUIDELINES Voting Panel: Board or committee member ($0) Member of the panel(Self)
ACSM - Mid-Atlantic Rehgion: Board or committee member ($0) Board Member(Self)
Osteoarthritis Action Alliance: Board or committee member ($0) Past Chair of steering commitee as of Jan 2018(Self)
Pri-Med: Paid presenter or speaker ($2,000) Number of Presentations: 1 Televised / Streamed Roundtable(Self)
Wolters Kluwer Health - Lippincott Williams & Wilkins: Editorial or governing board ($500) CJSM, Current Sports Medicine Reports(Self)

Mary Kathryn Mulcahey, MD Submitted on: 01/10/2019
AAOS: Board or committee member ($0)
American Orthopaedic Society for Sports Medicine: Board or committee member ($0)
Arthrex, Inc: Paid presenter or speaker ($6,000) Number of Presentations: 6 Women in Sports Medicine Course(Self)
Arthroscopy Association of North America: Board or committee member ($0)
Ruth Jackson Orthopaedic Society: Board or committee member ($0)

Andrew Wilson Ryan, MD Submitted on: 01/17/2019
AAOS (Board of Councilors) Kentucky Orthopaedic Society (Treasurer): Board or committee member ($0)
Johnson & Johnson: Stock or stock Options Number of Shares: 0

Reda M. Tolba, MD Submitted on: 02/04/2019
Astrazeneca, Daiichi sankyo: Paid presenter or speaker ($10,000) Number of Presentations: 4
Astrazeneca,
DSI(Self)

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View data summaries via the OAK3 CPG eAppendix 2