



VA/DoD CLINICAL PRACTICE GUIDELINE FOR THE NON-SURGICAL MANAGEMENT OF HIP & KNEE OSTEOARTHRITIS

**Department of Veterans Affairs
Department of Defense**

QUALIFYING STATEMENTS

The Department of Veterans Affairs and the Department of Defense guidelines are based upon the best information available at the time of publication. They are designed to provide information and assist decision making. They are not intended to define a standard of care and should not be construed as one. Neither should they be interpreted as prescribing an exclusive course of management.

This Clinical Practice Guideline is based on a systematic review of both clinical and epidemiological evidence. Developed by a panel of multidisciplinary experts, it provides a clear explanation of the logical relationships between various care options and health outcomes while rating both the quality of the evidence and the strength of the recommendation.

Variations in practice will inevitably and appropriately occur when clinicians take into account the needs of individual patients, available resources, and limitations unique to an institution or type of practice. Every healthcare professional making use of these guidelines is responsible for evaluating the appropriateness of applying them in the setting of any particular clinical situation.

These guidelines are not intended to represent Department of Veterans Affairs or TRICARE policy. Further, inclusion of recommendations for specific testing and/or therapeutic interventions within these guidelines does not guarantee coverage of civilian sector care. Additional information on current TRICARE benefits may be found at www.tricare.mil or by contacting your regional TRICARE Managed Care Support Contractor.

Version 2.0 - 2020

Prepared by:

The Non-surgical Management of Hip & Knee Osteoarthritis Work Group

With support from:

The Office of Quality and Patient Safety, VA, Washington, DC

&

Office of Evidence Based Practice, U.S. Army Medical Command

Version 2.0 - 2020

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I. Introduction

The Department of Veterans Affairs (VA) and Department of Defense (DoD) Evidence-Based Practice Work Group (EBPWG) was established and first chartered in 2004, with a mission to advise the Health Executive Committee “...on the use of clinical and epidemiological evidence to improve the health of the population...” across the Veterans Health Administration (VHA) and Military Health System, by facilitating the development of clinical practice guidelines (CPGs) for the VA and DoD populations.^[1] This CPG is intended to provide healthcare providers with a framework to evaluate, treat, and manage the individual needs and preferences of adult patients with osteoarthritis (OA), thereby leading to improved clinical outcomes.

In 2014, the VA and DoD published a CPG for the Non-surgical Management of Hip & Knee Osteoarthritis (2014 VA/DoD OA CPG), which was based on evidence reviewed through December 2012. Since the release of that guideline, a growing body of research has expanded the general knowledge and understanding of OA. Consequently, a recommendation to update the 2014 VA/DoD OA CPG was initiated in 2019. The updated CPG includes objective, evidence-based information on the management of OA of the hip and the knee. It is intended to assist healthcare providers in all aspects of patient care and the non-surgical management of OA. The system-wide goal of evidence-based guidelines is to improve the patient’s health and well-being by guiding healthcare providers who are caring for patients with OA along management pathways that are supported by evidence. The expected outcome of the successful implementation of this guideline is to:

- Assess the patient’s condition and determine, in collaboration with the patient, the best treatment method
- Optimize health outcomes and improve quality of life
- Minimize preventable complications and morbidity
- Emphasize the use of patient-centered care (PCC)

II. Background

This guideline, developed under the auspices of the VHA and the DoD pursuant to directives from the VA, is an update to the 2014 VA/DoD OA CPG. It is intended to promote evidence-based management of OA and thereby improve patients’ clinical outcomes. It can assist primary care providers (PCPs) or specialists in the determination of appropriate treatment for OA and delivery of individualized interventions. Although it was developed for a broad range of clinical settings, it should be applied with enough flexibility to accommodate local practice and individual situations.

A. Epidemiology and Cost of Osteoarthritis

Osteoarthritis is one of the most common chronic conditions worldwide and in the United States (U.S.). According to the Centers for Disease Control and Prevention (CDC), OA affects more than 30 million Americans ^[2] with prevalence estimates of 13.9% of adults age 25 years and older, and 33.6% of adults age 65 years and older.^[3] However, the prevalence and incidence rates vary across studies depending on the definition of OA (e.g., radiographic, symptomatic, self-reported, or provider-diagnosed) and study setting (e.g., clinical or population-based).

The epidemiology of OA also differs by sex, age distribution, body weight, and race. Osteoarthritis is more common in women, with worldwide estimates of symptomatic OA of 18% in women and 9.6% in men over 60 years of age.^[4] Osteoarthritis increases after 50 years of age, the knee is the most common site, and studies generally indicated that OA is more common in Blacks compared to Whites.^[5]

It is estimated that, at large, one in two patients may develop symptomatic knee OA in their lifetime,^[6] and one in four may develop symptomatic hip OA in their lifetime.^[7] Obesity increases the lifetime risk of OA significantly; two out of three people with obesity will develop OA.^[8] Given the aging population and obesity epidemic, the number of Americans affected with OA has risen from 21 million in 1990 to 27 million in 2005 to over 30 million in 2019.^[9,10] This upward trend is projected to continue.

Physician-diagnosed OA is more common in military Service Members and Veterans than in the general population. A 2013 CDC study estimated that 25.6% of Veterans have arthritis and incidence rates increase with age.^[11] This study found that OA was more common in Veterans compared to non-Veterans with a prevalence of 25.6% and 23.6%, respectively. In another study, the overall incidence rate for physician-diagnosed OA in active duty Service Members was 7.9 cases per 1,000 person-years (95% confidence interval [CI]: 7.82 – 7.91).^[12] The adjusted incidence rate for OA was approximately 20% higher in women Service Members compared to men (relative risk [RR]: 1.19, 95% CI: 1.17 – 1.21) and age was a significant risk factor. Between 1999 and 2008 there was a 19-fold higher incidence of OA in active duty Service Members greater than 40 years of age compared to those less than 20 years of age.^[12]

Active duty Service Members regularly experience repetitive joint loading during physical activity and military tasks and activities. Research suggests that military-service-related overuse and traumatic and non-traumatic joint injuries may be a contributing factor for the increased risk of developing OA.^[13] Military rank and branch of military service may also correlate with variation in the incidence of OA. For example, junior and senior enlisted Service Members and those serving in the Army experienced the highest incidence rates for OA.^[12]

The large use of healthcare resources to manage OA contributes significantly to healthcare costs.^[14-16] In fact, the medical costs related to OA account for an estimated 1 – 2.5% of the gross domestic product of high-income countries.^[17] Overall, the economic burden of OA and related conditions exceeded an estimated \$340 billion annually in direct healthcare costs. The combination of direct and indirect costs for OA and related disorders is estimated to be \$461 billion.^[18] Hip and knee joint replacements represent a major portion of these costs.^[17] The indirect costs associated with OA greatly surpass healthcare costs and exert significant personal costs for people with OA due to work loss and premature retirement, leading to loss of income and subsequent reductions in personal savings.^[17]

Osteoarthritis also causes substantial disability.^[19,20] Among patients with OA, 80% will have limitations in movement, and 25% will be unable to perform their activities of daily life.^[4] Hip and knee OA are leading causes of disability worldwide accounting for 2.4% of all years lived with disability (YLDs), an overall measure of disease burden.^[21] From 1990 – 2016, OA was in the top 20 contributors to YLDs and ranked second to diabetes as the condition associated with the most rapid increases in disability, with a 46% increase in YLDs.^[22] By 2020, OA is expected to be the fourth leading cause of YLDs globally.^[17] Osteoarthritis is second to back pain as the most common cause of military separation, and it leads to significant disability during peacetime and war.^[23]

In addition to negatively affecting physical health, OA may impact a patient's quality of life and mental well-being.[24] Depression and catastrophizing are common in patients with OA,[25,26] and sleep problems were reported in 72% of adults older than 55 years with OA.[27] Other OA-related sequelae may include muscle weakness, instability, and poor balance leading to falls and other comorbid musculoskeletal conditions, given that musculoskeletal conditions frequently overlap (e.g., fibromyalgia).[28]

B. Disease Course, Clinical Presentation, and Risk Factors for Osteoarthritis

The age of OA onset, sequence, and distribution of joint involvement and disease progression varies. Osteoarthritis is diagnosed at a median of 55 years of age, and patients may live approximately 30 years with the disease. Patients with OA may present to providers with minimal symptoms or have incidental findings on physical examination or radiologic testing. Patients with symptomatic OA typically present with joint pain, aching, stiffness, and limited walking ability.[29] Knee OA is usually bilateral but one knee may be affected more severely; hip OA is frequently unilateral. Osteoarthritis can progress to severe, disabling pain eventually resulting in structural and functional joint failure.

Risk factors for OA may be broadly categorized as patient-level or joint-related factors. Patient-level risk factors include older age, female sex, overweight and obesity, genetics, race, and engagement in certain work or recreational activities. Weight gain can exacerbate symptoms of OA. For Veterans and active duty Service Members with OA, providers should try to avoid prescription medications that promote weight gain and suggest the use of agents that promote weight loss.^a Heavy work activities (e.g., farming, construction work) or work that requires frequent kneeling, heavy lifting, or repetitive use of joints is associated with the development of OA.[30] Studies also show a strong association between high-impact sports (e.g., football, hockey) and the development of OA.[31,32]

Certain joint-related factors may play a role in the development of OA. These factors may include previous injury to the knee or hip, knee malalignment, joint shape, increased bone density, knee extensor muscle weakness, joint laxity, joint deformities (e.g., cam deformity, acetabular dysplasia), and abnormal loading of joints. Less well-defined potential risk factors for OA development include knee extensor muscle weakness and smoking.[33]

The etiology of OA is multifactorial and involves a complex interplay between mechanical, cellular, and biomechanical factors leading to pathology. There is no cure for OA and overall management is aimed at reducing pain and improving function. For patients with refractory, disabling pain, the most effective treatment is total joint replacement. As prevalence continues to rise, the burden OA places on patients and healthcare systems will increase.[17] There will be a greater need for evidence-based, high-quality, and effective OA-related therapies to help reduce the personal and societal burden of OA.

III. About this Clinical Practice Guideline

This updated guideline represents a significant effort toward improving the management of OA among patients eligible to receive care in the VA and/or DoD healthcare systems. As with other CPGs, however, challenges remain. These include evidence gaps, ongoing needs to develop effective strategies for guideline implementation, and evaluation of the effect of guideline adherence on clinical outcomes. This

^a Refer to the current VA/DoD CPG for the Management of Adult Overweight and Obesity for a full list of medications and weight effects to consider. Available at: <https://www.healthquality.va.gov/guidelines/CD/obesity>

guideline is intended for all VA and DoD healthcare practitioners involved in the care of adult patients with hip and knee OA.

As elaborated in the qualifying statement on page one, this CPG is not intended to serve as a standard of care. Standards of care are determined based on all clinical data available for an individual patient and are subject to change as scientific knowledge and technology advance and patterns evolve. This CPG is based on information available through June 3, 2019, and is intended to provide a general guide to best practices. The guideline can assist providers, but the use of a CPG must always be considered as a recommendation within the context of various factors (e.g., providers' clinical judgment, patient values and preferences, state and federal statutes, ethical guidelines, professional standards, and healthcare system policies).

A. Methods

This document is an update to the 2014 VA/DoD OA CPG. The methodology used in developing the 2020 CPG follows the *Guideline for Guidelines*,^b an internal document of the VA and DoD EBPWG that was updated in January 2019.^[34] This document provides information regarding the process of developing guidelines, including the identification and assembly of the Guideline Champions (Champions) and other subject matter experts from the VA and DoD (known as the Work Group) and the development and submission of an updated OA CPG.

This CPG's Work Group was charged with developing evidence-based clinical practice recommendations and publishing a guideline to be used by PCPs within the VA/DoD healthcare systems as well as those within the community who treat patients within the VA and DoD. Specifically, the Work Group was responsible for identifying the key questions (KQs) of the most clinical relevance, importance, and interest for the diagnosis and management of patients with OA. The Work Group also provided direction on inclusion and exclusion criteria for the systematic evidence review and assessed the level and quality of the evidence. The amount of scientific evidence that had accumulated since the 2014 VA/DoD OA CPG was also considered when identifying the KQs. In addition, the Champions assisted in:

- Identifying appropriate disciplines of individuals to be included in the Work Group
- Directing and coordinating the Work Group
- Participating throughout the guideline development and review processes

The VA Office of Quality and Patient Safety, in collaboration with the Office of Evidence Based Practice, U.S. Army Medical Command – the DoD proponents for CPGs – identified three clinical leaders as Champions for the 2020 CPG: Anil Krishnamurthy, MD from the VA and MAJ John Cody, MD and COL Jess Edison, MD, from the DoD.

The Lewin Team, including The Lewin Group, Duty First Consulting, ECRI, Sigma Health Consulting, and Anjali Jain Research & Consulting, was contracted by the VA and DoD to support the development of this CPG and conduct the systematic evidence review. The first conference call was held in February 2019, with participation from the contracting officer's representative (COR), leaders from the VA Office of Quality and Patient Safety and the DoD Office of Evidence Based Practice, and the Champions. During this call,

^b See the *Guideline for Guidelines*. Available at: <http://www.healthquality.va.gov/policy/index.asp>.

participants discussed the guideline's scope, the Champions' roles and responsibilities, the project timeline, and the approach for developing specific research questions on which to base a systematic evidence review. The group also identified a list of clinical specialties and areas of expertise that are important and relevant to the management of OA, from which Work Group members were recruited. The specialties and clinical areas of interest included: primary care, nursing, physical therapy, clinical pharmacology, internal medicine, dietetics, orthopedic surgery, rheumatology, family medicine, sports medicine, physical medicine and rehabilitation, and pain management.

The guideline development process for the 2020 CPG update consisted of:

1. Formulating and prioritizing KQs and defining critical outcomes
2. Convening a patient focus group
3. Conducting the systematic evidence review
4. Convening a face-to-face meeting with the CPG Champions and Work Group members to develop recommendations
5. Drafting and submitting a final CPG on the management of OA to the VA/DoD EBPWG

[Appendix A](#) provides a detailed description of each of these tasks.

a. Grading Recommendations

The Work Group used the Grading of Recommendations Assessment, Development and Evaluation (GRADE) system to assess the quality of the evidence base and assign a strength for each recommendation. The GRADE system uses the following four domains to assess the strength of each recommendation:[\[35\]](#)

- Balance of desirable and undesirable outcomes
- Confidence in the quality of the evidence
- Patient or provider values and preferences
- Other implications, as appropriate, e.g.:
 - ◆ Resource use
 - ◆ Equity
 - ◆ Acceptability
 - ◆ Feasibility
 - ◆ Subgroup considerations

Additional information regarding these domains can be found in [Appendix A](#).

Using these four domains, the Work Group determined the relative strength of each recommendation ("Strong" or "Weak"). Generally, a "Strong" recommendation indicates high confidence in the quality of the available scientific evidence, a clear difference in magnitude between the benefits and harms of an intervention, similar patient or provider values and preferences, and understood influence of other implications (e.g., resource use, feasibility). Generally, if the Work Group has less confidence after the

assessment across these domains and believes that additional evidence may change the recommendation, it assigns a “Weak” recommendation. It is important to note that the GRADE terminology used to indicate the assessment across the four domains (i.e., “Strong” versus “Weak”) should not be confused with the clinical importance of the recommendation. A “Weak” recommendation may still be important to the clinical care of a patient with OA.

Occasionally, instances may occur when the Work Group feels there is insufficient evidence to make a recommendation for or against a therapy or preventive measure. This can occur when there is an absence of studies on a topic that met the systematic evidence review inclusion criteria, studies included in the systematic evidence review report conflicting results, or studies included in the systematic evidence review report inconclusive results regarding the desirable and undesirable outcomes.

Using these elements, the relative strength of each recommendation is presented as part of a continuum:

- Strong for (or “We recommend offering this option ...”)
- Weak for (or “We suggest offering this option ...”)
- No recommendation for or against (or “There is insufficient evidence ...”)
- Weak against (or “We suggest not offering this option ...”)
- Strong against (or “We recommend against offering this option ...”)

The rating of each recommendation made in the 2020 CPG can be found in the section on [Recommendations](#). Additional information regarding the use of the GRADE system can be found in [Appendix A](#).

b. Reconciling 2014 Clinical Practice Guideline Recommendations

Evidence-based CPGs should be current, which typically requires revisions of previous guidelines based on new evidence or as scheduled and subject to time-based expirations.[36] The OA CPG Work Group largely focused on developing new and updated recommendations based on the evidence review conducted for the priority areas addressed by the KQs. In addition to those new and updated recommendations, the Work Group considered, without complete review of the relevant evidence, the current applicability of other recommendations that were included in the 2014 VA/DoD OA CPG, subject to evolving practice in today’s environment. Accordingly, some recommendations found in the 2014 VA/DoD OA CPG do not appear in this updated CPG.

A set of recommendation categories was adapted from those used by England’s National Institute for Health and Care Excellence (NICE).[37,38] These categories, along with their corresponding definitions, were used to account for the various ways in which older recommendations could have been updated. In brief, the categories considered whether the evidence that related to a recommendation was systematically reviewed, the degree to which the recommendation was modified, and the degree to which a recommendation is relevant in the current care environment and within the scope of the CPG. Additional information regarding these categories and their definitions can be found in [Recommendation Categorization](#). The categories for the recommendations included in the 2020 version of the guideline can be found in the [Recommendations](#) section. The categories for the recommendations carried forward from the 2014 VA/DoD OA CPG are noted in [Appendix D](#).

c. Peer Review Process

The CPG was developed through an iterative process in which the Work Group produced multiple drafts of the CPG. The process for developing the initial draft is described in more detail in [Drafting and Submitting the Final Clinical Practice Guideline](#).

Once a near-final draft of the guideline was agreed upon by the Champions and Work Group members, VA and DoD Leadership contacted peer reviewers to solicit their feedback. The peer reviewers were individuals working within the VA and DoD healthcare systems and experts from relevant outside organizations designated by the Work Group. Outside organizations that the Work Group designated to participate in the peer review and that provided feedback are listed in [Drafting and Submitting the Final Clinical Practice Guideline](#). Reviewers were provided a hyperlink to the wiki website where the draft CPG was posted. The review and comment period lasted 14 business days. All feedback from the peer reviewers was discussed and considered by the Work Group. Modifications made throughout the CPG development process were made in accordance with the evidence.

B. Summary of Patient Focus Group Methods and Findings

When forming guideline recommendations, consideration should be given to the values of those most affected by the recommendations: patients. Patients bring perspectives, values, and preferences into their healthcare experience that can vary from those of providers. Focus groups are an efficient method to explore the ideas and perspectives of a group of participants and collect qualitative data on a thoughtfully predetermined set of questions.

Therefore, as part of the effort to update this CPG, VA and DoD Leadership held a patient focus group on April 17, 2019, at the Audie L. Murphy Memorial VA Hospital in San Antonio, TX. The focus group aimed to further understand the perspectives of patients with OA who are covered and/or receiving their care through the VA and/or DoD healthcare systems. The focus group comprised a convenience sample of four participants; two females and two males. All participants were Veterans. The Work Group recognizes the limitations inherent in the small sample size (less than 10 patients were included in the focus group to be consistent with the requirements of the Federal Paperwork Reduction Act, 1980). The Work Group acknowledges the sample included in this focus group is not representative of all patients within the VA and DoD healthcare systems and, thus, findings are not generalizable and did not comprise evidence. For more information on the patient focus group and its key concepts, see [Appendix B](#).

C. Conflicts of Interest

At the start of this guideline development process and other key points throughout, the project team was required to submit disclosure statements to reveal any areas of potential conflict of interest (COI) in the past 24 months. Verbal affirmations of no COI were used as necessary during meetings throughout the guideline development process. The project team was also subject to random web-based surveillance (e.g., Centers for Medicare & Medicaid Services [CMS] open payments or ProPublica).

No conflicts of interest were identified for the Champions or Work Group. If a project team member had reported a COI (actual or potential), then it would have been reported to the VA and DoD program offices. It would have also been discussed with the OA CPG Champions in tandem with their review of the evidence and development of recommendations. The VA and DoD program offices and the OA CPG Champions would have determined the appropriateness of further action (e.g., restricting participation,

removal from the Work Group). If it had been deemed necessary, VA and DoD Leadership and the Champions would have taken action. Disclosure forms are on file with the VA Office of Quality and Patient Safety and available upon request.

D. Scope of this Clinical Practice Guideline

Regardless of the setting, any patient in the VA and DoD healthcare systems should have access to the interventions recommended in this guideline after taking into consideration the patient's specific circumstances.

Guideline recommendations are intended to be patient-centered. Thus, treatment and care should consider a patient's needs and preferences. Effective, open communication between healthcare professionals and the patient is essential and should be supported by evidence-based information tailored to the patient's needs. The use of an empathetic and non-judgmental approach facilitates discussions sensitive to sex, culture, ethnicity, and other considerations. The information that patients are given about treatment and care should be culturally appropriate and available to people with limited literacy skills. Treatment information should also be accessible to people with additional needs such as physical, sensory, or learning disabilities. Family and caregiver involvement should be considered, if appropriate.

This CPG is designed to assist providers in managing or co-managing adult patients with a confirmed diagnosis of OA of the hip and/or knee. Moreover, this CPG's patient population of interest is those with OA who are eligible for care in the VA and DoD healthcare systems and those in the community who receive care from community-based providers. It includes Veterans as well as deployed and non-deployed active duty Service, Guard, and Reserve Members and their dependents.

E. Highlighted Features of this Clinical Practice Guideline

The 2020 edition of the VA/DoD OA CPG is the first update to the original CPG published in 2014. It provides practice recommendations for the care of patients with OA and guidance for treatment. A strength of this CPG is the multidisciplinary stakeholder involvement from its inception, ensuring representation from the broad spectrum of providers engaged in the management of OA.

The framework for recommendations in this CPG included factors beyond the strength of the evidence, including balancing desired outcomes with potential harms of the intervention, the potential for variation in patient values and preferences, and other considerations (e.g., resource use, subgroup considerations) as appropriate. Applicability of the evidence to VA/DoD populations was also considered. An algorithm accompanies the guideline to provide an overview of the recommendations in the context of the flow of patient care and to assist with training providers (see [Algorithm](#) section). The algorithm may be used to help facilitate the translation of guideline recommendations into practice.

F. Patient-centered Care

VA/DoD CPGs encourage providers to use a patient-centered care (PCC) approach that is individualized based on patient needs, characteristics, and preferences. Regardless of the setting, all patients in the healthcare system should be able to access evidence-based care appropriate to their specific needs or condition. When properly executed, PCC may decrease patient anxiety, increase trust in providers, and improve treatment adherence.^[39,40] Improved patient-provider communication and a PCC approach conveys openness and supports disclosure of current and future concerns. As part of the PCC approach,

providers should ask each patient about any concerns he or she has or barriers to high quality care he or she has experienced.

G. Shared Decision Making

Throughout this VA/DoD CPG, the authors encourage providers to focus on shared decision making (SDM). The SDM model was introduced in *Crossing the Quality Chasm*, an Institute of Medicine (now called the National Academy of Medicine) report, in 2001.^[41] It is readily apparent that patients, together with their providers, make decisions regarding their plan of care and management options. Patients with OA require enough information and time to be able to make informed decisions. Providers must be adept at presenting information to their patients regarding treatments, expected outcomes, potential harms, and levels and/or locations of care. Providers are encouraged to use SDM to individualize treatment goals and plans based on patient capabilities, needs, goals, and preferences.

H. Co-occurring Conditions

Co-occurring health conditions are important to recognize because they can modify the degree of risk and trajectory of a patient's lifestyle, impact the diagnosis and management of OA, influence patient or provider treatment priorities and clinical decisions, and affect the overall provider approach to the management of OA. Providers should expect that many Veterans, Service Members, and their families will have co-occurring health conditions. Because of the nature of OA management, which sometimes parallels ongoing care for co-occurring conditions, it is often best to manage OA collaboratively with other providers. Some co-occurring conditions may require early specialist consultation in order to discuss any necessary changes in treatment or to establish a common understanding of how care will be coordinated. There are VA/DoD CPGs for other conditions that may be relevant to the management of OA (e.g., overweight and obesity,^c opioid therapy for chronic pain,^d diabetes mellitus,^e major depressive disorder,^f and posttraumatic stress disorder^g).

I. Implementation

This CPG and algorithm are designed to be adapted by individual healthcare providers with consideration of unique patient circumstances and preferences, local needs, and resources. The algorithm serves as a tool to prompt providers to consider key decision points during an episode of care for their patient with OA of the hip and/or knee. The Work Group submits suggested performance metrics for the VA and DoD to use when assessing the implementation of this guideline. Robust implementation will require wide dissemination through publication in medical literature, online access, educational programs, and ideally electronic medical record programming in the form of clinical decision support tools at the point of care. Moreover, the results of the implementation of this guideline may

^c See the VA/DoD Clinical Practice Guidelines for the Management of Adult Overweight and Obesity. Available at: <https://www.healthquality.va.gov/guidelines/CD/obesity/>

^d See the VA/DoD Clinical Practice Guideline for the Management of Opioid Therapy for Chronic Pain. Available at: <https://www.healthquality.va.gov/guidelines/Pain/cot/>

^e See the VA/DoD Clinical Practice Guideline for the Management of Diabetes Mellitus in Primary Care. Available at: <https://www.healthquality.va.gov/guidelines/CD/diabetes/>

^f See the VA/DoD Clinical Practice Guideline for the Management of Major Depressive Disorder in Primary Care. Available at: <https://www.healthquality.va.gov/guidelines/MH/mdd/>

^g See the VA/DoD Clinical Practice Guideline for the Management of Posttraumatic Stress Disorder and Acute Stress Reaction. Available at: <https://www.healthquality.va.gov/guidelines/MH/ptsd/>

lead to the development of new evidence relevant to clinical practice, such as priority areas for research and optimal allocation of resources.

IV. Guideline Work Group

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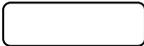
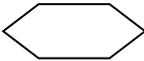
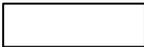
*Additional contributor contact information is available in [Appendix H](#).

V. Algorithm

This CPG includes an algorithm that is designed to facilitate understanding of the clinical pathways and decision-making processes used in managing patients with OA. The use of the algorithm format as a way to represent patient management was chosen based on the understanding that such a format may promote more efficient diagnostic and therapeutic decision-making; it also has the potential to change patterns of resource use. Although the Work Group recognizes that not all clinical practices are linear, the simplified linear approach depicted through the algorithm and its format allows the provider to assess the critical information needed at the major decision points in the clinical process. It includes:

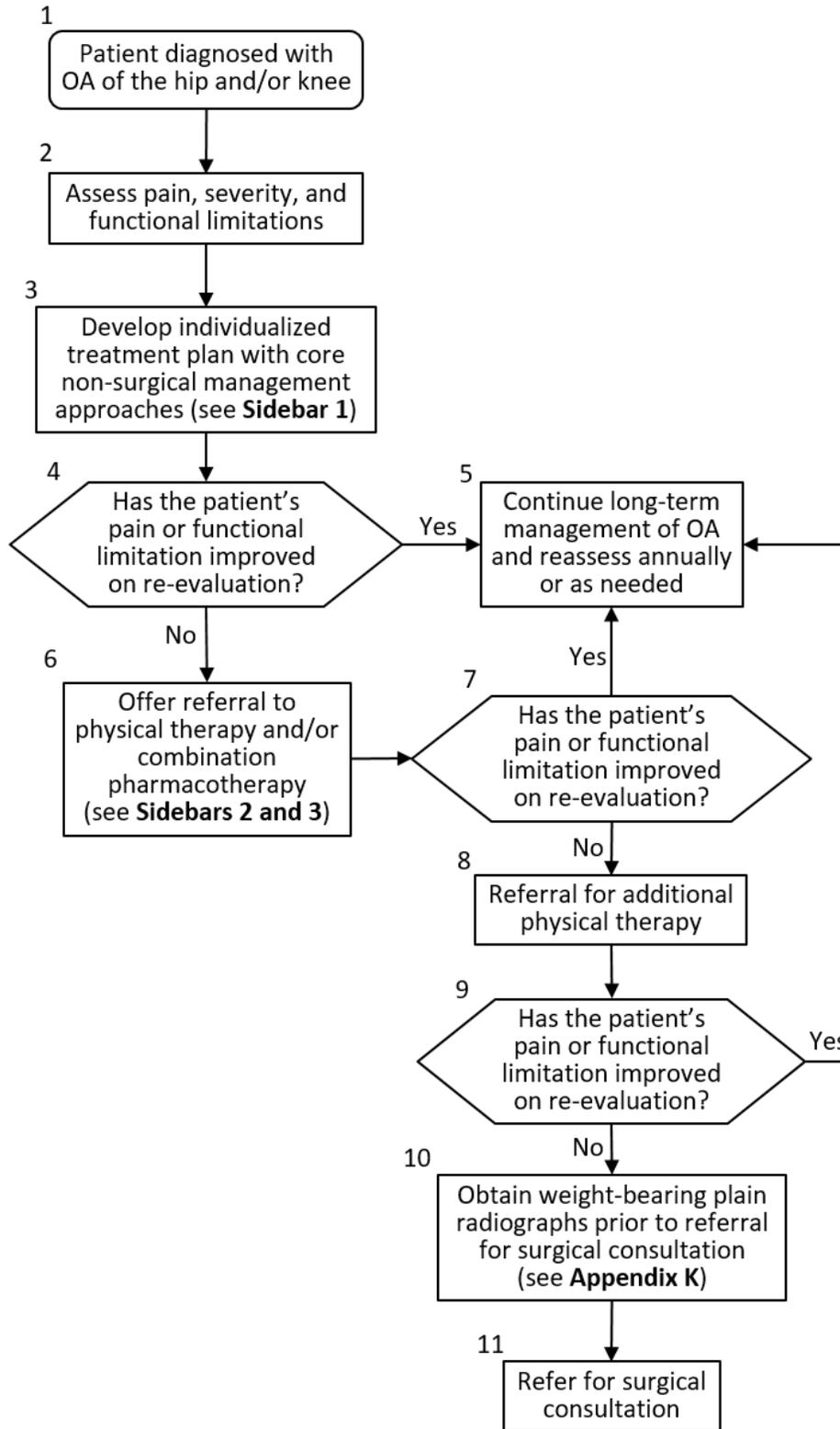
- An ordered sequence of steps of care
- Recommended observations and examinations
- Decisions to be considered
- Actions to be taken

For each VA/DoD CPG, there is a corresponding clinical algorithm that is depicted by a step-by-step decision tree. Standardized symbols are used to display each step in the algorithm, and arrows connect the numbered boxes indicating the order in which the steps should be followed.[\[42\]](#)

Shape	Description
	Rounded rectangles represent a clinical state or condition
	Hexagons represent a decision point in the guideline, formulated as a question that can be answered "Yes" or "No"
	Rectangles represent an action in the process of care
	Ovals represent a link to another section within the guideline

[Appendix J](#) contains alternative text descriptions of the [Algorithm](#).

Algorithm: Management and Treatment of Osteoarthritis of the Hip and/or the Knee



Abbreviations: OA: osteoarthritis

Sidebar 1: Initial Individualized Treatment Plan

Discuss a self-management program:

- Regular self-directed exercise
- Comprehensive lifestyle intervention for weight reduction: refer to the current VA/DoD CPG for the Management of Adult Overweight and Obesity^a
- Bracing for OA of the knee (prescription of adaptive equipment such as a cane and knee braces may also be offered in conjunction with the above to help decrease weight burden/provide stability for knee OA)
- Offer referral for physical therapy^b

Pharmacotherapy:

- Initial treatments:
 - ◆ Topical agents for OA of the knee (e.g., NSAIDs, capsaicin)
 - ◆ Acetaminophen
 - ◆ NSAIDs or COX-2 inhibitors

^a See the VA/DoD Clinical Practice Guidelines for the Management of Adult Overweight and Obesity. Available at: <https://www.healthquality.va.gov/guidelines/CD/obesity>

^b Consider early referral to physical therapy based on pain severity, functional limitations, and adherence

Abbreviations: COX-2: cyclooxygenase-2; CPG: Clinical Practice Guideline; DoD: Department of Defense; NSAIDs: non-steroidal anti-inflammatory drugs; OA: osteoarthritis; VA: Department of Veterans Affairs

Sidebar 2: Second-line and Combination Pharmacotherapy

- Second-line or combination treatments:
- Consider combining two initial treatments (see **Sidebar 1**)
- Consider intra-articular CSI for knee and hip OA:
 - ◆ CSI should be avoided for the three months preceding joint replacement surgery
 - ◆ CSI for the hip should be image-guided
- Duloxetine: consider adding duloxetine as an alternative or adjunct to initial treatments (see **Sidebar 1**)
- Consider intra-articular VSI in patients with inadequately controlled knee pain with core pharmacologic and non-pharmacologic treatments

Abbreviations: CSI: corticosteroid injection; OA: osteoarthritis; VSI: viscosupplementation injections

Sidebar 3: Pharmacotherapy Considerations

- Acetaminophen: because of safety concerns (e.g., hepatotoxicity), the lowest clinically effective dose should be used; in addition, a maximum of 4 g/day should never be exceeded
- NSAIDs or COX-2 inhibitors: should generally be avoided in patients with or at risk for CVD, CKD, and in those patients at risk for serious UGI toxicity
 - ◆ Consider adding a PPI or misoprostol in patients at risk for UGI events who require treatment with NSAIDs or COX-2 inhibitors
 - ◆ Assessment of renal function should occur and NSAIDs and COX-2 inhibitors should be avoided in patients with eGFR <30 ml/min/1.73 m²
- Opioids: in most patients, treatment with an opioid should be avoided; for those already on opioids, refer to the current VA/DoD CPG for the Management of Opioid Therapy for Chronic Pain^a

^a See the VA/DoD Clinical Practice Guideline for the Management of Opioid Therapy for Chronic Pain. Available at: <https://www.healthquality.va.gov/guidelines/Pain/cot/>

Abbreviations: CKD: chronic kidney disease; COX-2: cyclooxygenase-2; CPG: Clinical Practice Guideline; CVD: cardiovascular disease; DoD: Department of Defense; eGFR: estimated glomerular filtration rate; g: grams; m²: square meters; min: minute; ml: milliliters; NSAIDs: non-steroidal anti-inflammatory drugs; OA: osteoarthritis; PPI: proton-pump inhibitor; UGI: upper gastrointestinal tract; VA: Department of Veterans Affairs

VI. Recommendations

Topic	Sub-topic	#	Recommendation	Strength ^a	Category ^b
Diagnosis		1.	We suggest against obtaining magnetic resonance imaging for the diagnosis of osteoarthritis of the hip and knee.	Weak against	Reviewed, New-replaced
Self-management		2.	We suggest a self-management program, including exercise and weight loss for osteoarthritis of the hip and knee, and bracing for osteoarthritis of the knee.	Weak for	Reviewed, New-replaced
Physical Therapy		3.	We suggest offering physical therapy as part of a comprehensive management plan for patients with osteoarthritis of the hip or knee.	Weak for	Reviewed, Amended
Pharmacotherapy	a. Topical Pharmacotherapy	4.	We recommend offering topical non-steroidal anti-inflammatory drugs for patients with pain associated with osteoarthritis of the knee.	Strong for	Reviewed, New-added
		5.	There is insufficient evidence to recommend for or against the use of topical non-steroidal anti-inflammatory drugs for patients with pain associated with osteoarthritis of the hip.	Neither for nor against	Reviewed, New-added
		6.	We suggest offering topical capsaicin for patients with pain associated with osteoarthritis of the knee.	Weak for	Reviewed, Amended
		7.	There is insufficient evidence to recommend for or against the use of topical capsaicin for patients with pain associated with osteoarthritis of the hip.	Neither for nor against	Reviewed, Amended
	b. Oral Pharmacotherapy	8.	We suggest offering acetaminophen and/or oral non-steroidal anti-inflammatory drugs for pain associated with osteoarthritis of the hip and knee.	Weak for	Reviewed, New-replaced
		9.	We suggest offering duloxetine as an alternative or adjunctive therapy for patients with an inadequate response or contraindications to acetaminophen or non-steroidal anti-inflammatory drugs for pain associated with osteoarthritis of the knee.	Weak for	Reviewed, New-replaced
		10.	We suggest against initiating opioids (including tramadol) for pain associated with osteoarthritis of the hip and knee. For patients already on long-term opioid therapy, refer to the current VA/DoD Clinical Practice Guideline for the Management of Opioid Therapy for Chronic Pain. ^c	Weak against	Reviewed, New-replaced
	c. Intra-articular Injections	11.	We suggest offering an intra-articular corticosteroid injection for patients with persistent pain due to osteoarthritis of the knee inadequately relieved by other interventions.	Weak for	Reviewed, New-replaced
		12.	We suggest offering an intra-articular, image-guided corticosteroid injection for patients with persistent pain due to osteoarthritis of the hip inadequately relieved by other interventions.	Weak for	Reviewed, New-replaced
		13.	We suggest offering intra-articular viscosupplementation injection(s) for patients with persistent pain due to osteoarthritis of the knee inadequately relieved by other interventions.	Weak for	Reviewed, New-replaced
		14.	We suggest against the use of intra-articular viscosupplementation injection(s) of the hip.	Weak against	Reviewed, New-replaced

Topic	Sub-topic	#	Recommendation	Strength ^a	Category ^b
Orthobiologics		15.	There is insufficient evidence to recommend for or against platelet-rich plasma injections for the treatment of osteoarthritis of the hip or knee.	Neither for nor against	Reviewed, New-added
		16.	We suggest against stem cell injections (e.g., mesenchymal, adipose-derived, and bone marrow-derived) for the treatment of osteoarthritis of the knee.	Weak against	Reviewed, New-added
Complementary and Integrative Health, Dietary Supplements, and Nutraceuticals		17.	<p>There is insufficient evidence to recommend for or against the use of the following dietary supplements or nutraceuticals for the treatment of osteoarthritis of the hip or knee:</p> <ul style="list-style-type: none"> • Avocado and soybean extract • Boswellia serrata • Cannabidiol (CBD oil) • Chondroitin • Curcumin (active component of turmeric) • Collagen • Glucosamine • Glucosamine plus chondroitin • Methylsulfonylmethane • Omega-3 fatty acid • Pycnogenol (pine bark) • Rosehip • Traditional Chinese medicine • Vitamin D • Vitamin E • Willow bark extract 	Neither for nor against	Reviewed, New-replaced
		18.	<p>There is insufficient evidence to recommend for or against the use of complementary and integrative health interventions for the treatment of osteoarthritis of the hip or knee, including:</p> <ul style="list-style-type: none"> • Acupuncture • Massage • Light touch • Meditation • Tai chi • Yoga 	Neither for nor against	Reviewed, New-replaced
		19.	There is insufficient evidence to recommend for or against the use of transcutaneous electrical nerve stimulation for the treatment of pain in osteoarthritis of the knee.	Neither for nor against	Reviewed, New-added

^a For additional information, please refer to [Grading Recommendations](#).

^b For additional information, please refer to [Recommendation Categorization](#) and [Appendix A](#).

^c See the VA/DoD Clinical Practice Guideline for the Management of Opioid Therapy for Chronic Pain. Available at: <https://www.healthquality.va.gov/guidelines/Pain/cot/>

Abbreviations: DoD: Department of Defense; VA: Department of Veterans Affairs

A. Diagnosis

Recommendation

1. We suggest against obtaining magnetic resonance imaging for the diagnosis of osteoarthritis of the hip and knee.

(Weak against | Reviewed, New-replaced)

Discussion

Radiologic exams are frequently ordered in the primary care setting to make or confirm the diagnosis of OA of the knee and/or hip. The reviewed evidence, consisting of two diagnostic cohort studies by Xu et al. (2013) and Segal et al. (2015), did not show a clear benefit of magnetic resonance imaging (MRI) over plain radiographs for the diagnosis of OA of the knee and/or hip.[\[43,44\]](#) Magnetic resonance imaging can show articular cartilage loss as well as injury to intra- and extra-articular soft tissue structures. However, a study by Menashe et al. (2012) shows benefit only in ruling out OA, rather than diagnosing it.[\[45\]](#) Because Menashe et al. (2012) did not meet the inclusion criteria for this CPG's systematic evidence review, it was not considered in determining the strength of this recommendation. While some surgeons may elect to obtain MRIs occasionally to answer specific clinical or surgical questions on a case-by-case basis, it should not be routinely used in the diagnosis or workup of OA.

There is some variability in patient expectations regarding the use of MRI for hip and knee OA. Some patients inaccurately believe that MRI is better than plain radiographs and, as such, may request an MRI in the clinical setting. They also may feel that MRI is safer due to decreased radiation. The Work Group recognizes this can pose difficult clinical scenarios; however, providers should feel comfortable educating patients on the lack of superiority of MRI over radiographs from a diagnostic standpoint. Additionally, the overall burdens associated with MRI (e.g., increased resource use, cost, time, and logistic difficulty), far outweigh those associated with weight-bearing radiographs. Moreover, while there is minimal physical harm associated with MRI testing, sometimes results can mislead patients and providers as to proper diagnosis and treatment. Some surgeons may request an MRI for surgical planning; however, this applies to a minority of patients and should be left to surgeon discretion following surgical consultation.

As this is a *Reviewed, New-replaced* recommendation, the Work Group systematically reviewed evidence related to this recommendation.[\[43,44\]](#) The Work Group's confidence in the quality of evidence was very low. The body of evidence had some limitations, including small sample sizes. The reviewed literature did not demonstrate the superiority of MRIs to plain, weight-bearing radiographs in the diagnosis of moderate to severe hip and knee OA. There was some variation in patient preference as some patients may demonstrate a preference for MRI. The harms, including increased cost, resource use, and time burdens on the patients and providers, outweighed the lack of evidence-based benefits. Aside from these burdens, there is minimal risk of harm to the patient, and there are some clinical scenarios where MRI can prove useful. Thus, the Work Group decided upon a "Weak against" recommendation.

B. Self-management

Recommendation

2. We suggest a self-management program, including exercise and weight loss for osteoarthritis of the hip and knee, and bracing for osteoarthritis of the knee.

(Weak for | Reviewed, New-replaced)

Discussion

Self-management here is defined as the active engagement of individual patients in daily tasks or activities that aim to improve their quality of life and long-term management of the health condition.^[46] A patient's day to day activities will also impact the loading of joint tissue and potentially the long-term cartilage health.^[47] Therefore, patients need self-management strategies to effectively manage their OA. Any self-management strategy aimed at providing healthy stimulus and/or limiting unhealthy stimulus to the joint's cartilage could be helpful. This may involve the use of exercise, weight loss, and bracing treatments, which the Work Group chose to combine under the larger grouping of self-management strategies.^[47] Patients can implement many of these strategies on their own, though some may require patient education and/or additional support of healthcare providers to be successfully implemented.

Exercise

Exercise is a well-studied intervention for patients with knee and hip OA. Exercise may be able to improve pain, function, muscle strength, neuromuscular control, and joint loading, and improve self-efficacy. Exercise can be performed at home, in group classes, or in a clinic-based setting, and a variety of different types of exercise therapies can be used to fit the needs of an individual patient. Optimal exercise for knee OA likely focuses on aerobic exercise and lower extremity muscle strengthening.^[48]

An SR and meta-analysis by Anwer et al. (2016) suggests home exercise programs with and without supervised clinic-based exercises improve pain and function in patients with OA of the knee.^[49] The review included 15 RCTs and four case-controlled studies, including 4,270 patients with OA of the knee. The interventions included open and closed kinematic chain exercises, stretching exercises, range-of-motion exercises, balance exercises, proprioception, cold compression, neuromuscular electrical stimulation, pedometer-driven walking, and tai chi exercise.

An SR and meta-analysis by Beumer et al. (2016) included comparisons of land exercise versus minimal control in six studies and aquatic exercise versus minimal control in four studies for patients with OA of the hip.^[50] Both forms of exercise were found to be beneficial for pain and function in the short-term but the magnitude of the benefit decreased in medium- and long-term comparisons.

An SR and meta-analysis by Tanaka et al. (2013) compared strengthening exercises and aerobic exercises to control.^[48] The review included eight RCTs (n=505). The authors pooled data from the trials into subgroups of non-weight-bearing strength exercise, weight-bearing strength exercise, and aerobic exercise. All forms of exercise were effective for pain relief in the short-term. There appeared to be a greater reduction in pain relief in the non-weight-bearing strength exercise group. However, the Work Group noted serious study limitations, which impacted some of the subgroup analyses.

An SR and meta-analysis by Tanaka et al. (2016) compared exercise therapy to control interventions.[\[51\]](#) The review included 28 RCTs (n=2,991). The authors reported a greater benefit of exercise therapy on total distance walked at six months and on time spent walking at eight weeks. However, there was significant heterogeneity of exercise type and exercise program among the RCTs.

A key limitation of the SRs is the use of pooled estimated effects.[\[49\]](#) This method provides insight into the overall effects of exercise on pain and function but does not explain potential differences between different types of exercise programs. Thus, there was insufficient evidence to recommend any specific exercise intervention over another. There was no reported harm associated with any specific type of exercise.

Despite general consistency in the evidence supporting exercise for knee and hip OA, patient and provider preferences vary somewhat. The patient focus group expressed support for exercises under the guidance of a physical therapist and stressed the importance of receiving care in convenient settings. Barriers include the time commitment and perception among some patients that exercise will increase pain. From a provider standpoint, there may be uncertainty about making specific recommendations concerning frequency, intensity, duration, resistance, and type of exercise, as there is a wide variety of potentially suitable interventions. Patient adherence to home-based exercise programs is also a concern.[\[49\]](#)

Type of Exercise

The Work Group determined that various exercise therapy approaches are effective for the management of OA of the hip and knee. However, there was insufficient evidence to recommend one specific type of exercise therapy over any other type for the management of hip or knee OA.

Dong et al. (2018) conducted an SR of aquatic versus land-based exercise for knee OA, which included eight RCTs.[\[52\]](#) No statistically significant differences were observed between the two types of therapies in reducing pain or improving physical function, quality of life, or symptoms among adults with knee OA. An SR and meta-analysis by Beumer et al. (2016), which included 19 RCTs, indicated both land-based and water-based exercise programs were superior to a control intervention for pain relief in the short-term (<3 months) but indicated no statistically significant differences between different types of exercise therapy.[\[50\]](#)

Other RCTs compared different types of exercise therapy and found similar results. Gomiero et al. (2018) performed an RCT of 64 patients with knee OA comparing sensory-motor training to resistance training.[\[53\]](#) Both resistance training and sensory-motor training led to statistically significant reductions in pain and improved function. However, there were no statistically significant differences in pain or functional capacity between the two groups.

An RCT by Bennell et al. (2014) compared neuromuscular exercise with quadriceps strengthening among 100 patients with knee OA.[\[54\]](#) Both groups showed significant reductions in pain and improvement in physical function, but no statistically significant difference between groups on pain or physical function. Wang et al. (2016) performed an RCT of 39 patients with knee OA, which compared quadriceps strengthening exercises performed on a vibration platform (whole-body vibration) with quadriceps strengthening alone.[\[55\]](#) This study found no statistically significant differences between the groups in pain or physical function measured at 16 weeks. Another RCT, Vincent et al. (2019), compared eccentric

quadriceps strengthening to concentric quadriceps strengthening in 36 patients with knee OA.[56] Both groups achieved a statistically significant reduction in pain compared to baseline. However, there were no statistically significant differences in pain or function between the two groups.

Osteras et al. (2017) performed an RCT of 33 patients with hip OA where patients received either high-dose or low-dose medical exercise therapy.[57] Both groups showed a statistically significant improvement in pain and function at 12 weeks. However, there were no statistically significant differences in pain or function between groups.

An RCT by Fazaa et al. (2014) compared a combination of thermal treatments (treatments involving hot mineral water [e.g., hydromassage, aquatic exercise]) to a standard exercise therapy program in 233 patients with knee OA.[58] Both groups showed a statistically significant improvement in pain and function at six months compared to baseline values. However, they found superior results from thermal rehabilitation on the Western Ontario and McMaster Universities Osteoarthritis Index (WOMAC) and the Visual Analog Scale (VAS) measured at one year. Additionally, this study had a >20% loss to follow-up in the exercise therapy group, and results at six months favored the exercise therapy group for decreased pain.

Aquatic therapy may be an important consideration for patients who are unable to tolerate land-based therapies. Some exercises may be crucial for knee OA.

All forms of exercise therapy reviewed appear to show significant improvements in pain and function at short-term follow-up; therefore, the Work Group could not recommend a specific type of exercise therapy over another. The magnitude of exercise's effect on pain reduction and improvement in function appears to lessen in long-term comparisons compared to short-term. It is acknowledged that exercise needs to be ongoing for sustained improvements, as strength and function will decline back to baseline if exercise is stopped. The Work Group determined the benefits and harms were balanced because no specific exercise therapy appeared to be more or less beneficial, or more or less harmful, than another. Shared decision making between the provider and patient is an important component to developing an individualized exercise therapy program that is feasible for a patient to implement and perform within their current functional level. The feasibility of implementing certain exercise therapies will also depend on the availability of equipment, space, training, or staff. Providers must also weigh the economic burdens faced by patients attending different types of exercise therapies (e.g., lost wages, transportation costs, co-pays).

Weight Loss

Weight loss may help to reduce cumulative loading to the lower extremity joints.[47] The studies on weight loss evaluated pain, physical function, mobility, and mental quality of life. For overweight and obese patients with OA of the knee, weight loss may improve pain, quality of life (physical domain), physical function, and mobility. However, there are limited studies on the harms and benefits of weight loss in overweight and obese patients with OA of the hip.

Pain

Systematic reviews by Hall et al. (2019) and Chu et al. (2018) report that combined diet and exercise interventions reduce pain in overweight and obese patients with knee OA.[59,60] Chu et al. (2018) reported that combined diet and exercise interventions moderately reduced pain up to 18 months in obese individuals (mean body mass index [BMI] ranged 33.6 – 36.4 kilograms [kg]/square meters [m²]).[59]

Percent weight loss ranged from 4.5 – 11.4% for interventions and 1.3 – 4.3% for any comparator. The weighted effect size was 0.33 (95% CI: 0.17 – 0.48) with four articles assessed (n=676). The authors also noted there were larger effect sizes in the three studies that achieved >10% weight loss.

Evidence from Hall et al. (2019) indicated that diet and exercise interventions reduced pain up to 12 months in overweight and obese patients (mean BMI ranged from 32.8 – 37.9 kg/m²).[\[60\]](#) Mean weight loss was 4.7% with diet and exercise. The authors estimated that at least 6 – 8% weight loss may be required for pain improvement for diet and exercise interventions. These findings are supported by a smaller, multifactorial intervention RCT by Saraboon et al. (2015) that reported an improvement in pain and greater weight loss with the intervention group versus the control.[\[61\]](#)

Hall et al. (2019) reported that diet-only interventions (seven RCTs) in a sample of obese and overweight patients (mean BMI ranged from 32.8 – 37.9 kg/m²) up to 72 weeks were not associated with a statistically significant impact on pain.[\[60\]](#) Mean weight loss was 10.5% with diet. There was no significant association between effect size and change in body mass, adherence to diet and/or exercise, or within-study quality. The authors also noted there was a large degree of heterogeneity across studies. Sadeghi et al. (2019), a second smaller, lower quality RCT (n=62) with a three-month follow-up, reported a statistically significant improvement in pain with the diet versus control group with an average weight loss of 1.7 kg (2%) in the intervention group.[\[62\]](#)

Physical Function, Mobility, and Mental Quality of Life

Interventions were also found to improve physical function. Chu et al. (2018) reported quality of life (physical) and function (6-minute walk test) favored the diet plus exercise intervention versus any comparator, but no differences were reported for quality of life (mental) and function as measured by the timed stair climb test.[\[59\]](#) However, only one of the five studies that assessed physical function achieved >10% weight loss. Although the results were statistically significant, the authors noted more research is needed to determine the effect of weight loss on physical function using a more comprehensive battery of tests.

Hall et al. (2019) reported a statistically significant difference favoring both diet and exercise interventions and diet only interventions for physical function up to 96 weeks.[\[60\]](#) No statistically significant difference was observed for interventions lasting longer than 96 weeks. The authors noted that for interventions lasting longer the 96 weeks, the average weight loss was 7% compared to a weight loss of 11% for interventions lasting less than 96 weeks. The multifactorial RCT by Saraboon et al. (2015) also reported significant differences favoring the diet and exercise interventions compared to the control for mobility, as measured by the timed up and go.[\[61\]](#)

Two SRs and one RCT addressed diet plus exercise interventions, all of which had favorable outcomes for the combined intervention.[\[59-61\]](#) The magnitude of weight loss is an important consideration. Chu et al. (2018) reported that a 5 – 10% weight loss showed positive effects on pain, self-reported disability, and physical quality of life patients with obesity and mild to moderate OA.[\[59\]](#) The SR review by Hall et al. (2019) similarly found the majority of studies included in the SR had an average weight loss of 5 – 10%.[\[60\]](#)

Providers should refer to the current VA/DoD CPG for the Management of Adult Overweight and Obesity for current evidence-based weight reduction recommendations.^h

The Work Group acknowledged that previously published guidelines (which were not considered when determining the strength of this recommendation) have established that weight reduction is a cornerstone of non-pharmacologic therapy for the management of hip and/or knee OA.^[63-65] Furthermore, high-level arthroplasty studies have shown that elevated BMI – in particular BMI >40 kg/m² – is an independent risk factor for developing post-operative peri-prosthetic joint infections.^[66,67] However, some patients and providers believe exercise may exacerbate symptoms of OA despite the longstanding recommendation of exercise as one of the core elements in a comprehensive treatment plan.

Bracing

Bracing with soft braces (defined by study authors as a non-elastic, non-adhesive material) or valgus knee braces may improve pain and self-reported physical function in the knee.^[68,69] Braces are intended to help alter loading patterns at the knee joint with a goal of minimizing joint load.^[47]

An SR by Cudejko et al. (2018) showed a statistically significant difference favoring soft braces in three RCTs.^[69] Soft brace use was associated with a moderate effect ($p < 0.001$) on pain and a small-to-moderate effect ($p = 0.006$) on self-reported physical function in knee OA in both the short- and long-term compared to patients receiving “standard care.” Since the SR included RCTs and non-RCTs (e.g., case-control studies, controlled clinical trials, and crossover studies), the researchers were unable to determine if a soft brace improves performance-based physical function. Also, the included studies did not compare different types of soft braces. There was substantial variability and inconsistency in the usual care comparator arm across the analyzed studies making it difficult to understand and describe “standard or usual care.” The studies lacked evidence related to outcomes of swelling, constraining, and slipping. Harms from the use of a soft brace were not reported.

A meta-analysis by Moyer et al. (2015) found a statistically significant difference favoring valgus knee bracing for pain and function in patients with medial compartment knee OA.^[68] The effect sizes were moderate for pain and function compared to the control group with orthosis use, but only a small, statistically significant effect for pain compared to the control group without orthosis use. While there were no major complications reported with valgus knee braces, 20% of individuals reported poor fit and slipping. Researchers noted there was no consensus in brace wear frequency or duration. Moreover, there is insufficient evidence to recommend one type of soft knee brace over another or one type of valgus knee brace over another.

The Work Group also considered patient preferences, availability of the braces, and minor complications from valgus knee braces. Valgus knee braces are offered predominantly for patients with OA of the medial compartment with a varus deformity. Military profiling may be needed for the use of braces in active duty Service Members. Some patients may want to avoid braces in hot weather. Minor complications of valgus knee braces are common and may affect the usability of the brace. Soft braces are widely available (generally off-the-shelf) and inexpensive. Valgus knee braces can be relatively expensive, are not widely

^h See the VA/DoD Clinical Practice Guidelines for the Management of Adult Overweight and Obesity. Available at: <https://www.healthquality.va.gov/guidelines/CD/obesity>

available, and need custom sizing. Valgus knee braces may be appropriate for patients who are evaluated in orthopedic, physical medicine and rehabilitation, and physical therapy clinics with custom fitting.

Summary

As this is a *Reviewed, New-replaced* recommendation, the Work Group systematically reviewed evidence related to this recommendation.[\[48-62,68,69\]](#) The Work Group’s confidence in the quality of evidence was low. The body of evidence had limitations including unclear reporting of allocation concealment, lack of blinding, randomization, lack of intention-to-treat (ITT) analysis, imprecision of results, heterogeneity of methods and treatments within the studies, limited information on specific components of the exercise therapy, and small sample sizes in some cases. For weight loss and exercise, the benefits of improved pain, quality of life (physical), physical function, and mobility in overweight and obese patients with knee OA outweighed the potential harm of adverse events, which was negligible. In addition, for different types of exercise, feasibility will depend on the availability of equipment and space, as well as the costs of patients attending exercise therapy (e.g., lost wages, transportation costs, co-pays). For bracing, while the studies in our systematic evidence review did not specifically identify harms associated with the use of bracing, the Work Group recognized that bracing can lead to atrophy and functional loss if appropriate exercise is not also undertaken. A small patient pool showed a significant effect related to soft braces for OA. Overall, patient values, preferences, adherence, and self-efficacy regarding participation in weight reduction, exercise programs, bracing, and other forms of self-management may vary. Thus, the Work Group decided upon a “Weak for” recommendation.

More research is needed to determine how long or under what circumstances to wear braces to optimize outcomes. Also, research should compare different types of soft braces.

C. Physical Therapy

Recommendation

3. We suggest offering physical therapy as part of a comprehensive management plan for patients with osteoarthritis of the hip or knee.
(Weak for | Reviewed, Amended)

Discussion

Extensive literature exists to support the use of physical therapy as a core treatment in the comprehensive management of patients with OA of the hip or knee. For example, an RCT by Deyle et al. (2020) compared physical therapy to glucocorticoid injections in a military health system and results favored the physical therapy group on both primary and secondary outcome measures at one year.[\[70\]](#) Since this study was not included in this CPG’s systematic evidence review, it did not impact the strength of this recommendation.

An individualized physical therapy management plan can reduce pain and improve function in patients with hip or knee OA and, therefore, augment medical and pharmacologic approaches.[\[50,71,72\]](#) Physical therapists may utilize both manual physical therapy treatments and prescribed exercises in the treatment of knee and hip OA. Manual therapy treatments utilize hands-on techniques such as soft tissue mobilization, joint manipulation, and joint mobilization. Physical therapists also provide patients with education related to pain, lifestyle, and activity modifications. While physical therapy for knee and hip OA has traditionally been delivered via individual in-person appointments, alternative delivery models of care

such as group visits, internet-based, and telephone-based approaches are increasingly utilized. Therefore, the Work Group reviewed evidence on the comparative effectiveness of different physical therapy approaches and models of care delivery.

Manual Therapy

An SR by Anwer et al. (2018) examined the effects of manual therapy in patients with knee OA.[\[71\]](#) They compared manual therapy alone or manual therapy in combination with exercise to exercise therapy alone or control. The SR consisted of 11 RCTs (n=494). Their review indicated short-term benefit of exercise therapy with manual therapy compared to exercise alone and a stronger effect on pain relief from manual therapy alone compared to exercise alone in short-term follow-up. The Work Group though noted serious limitations in the results due to considerable heterogeneity of the manual interventions and the quality of some of the individual trials. Manual therapy interventions within the trials here included Maitland mobilizations, mobilizations with movement, soft tissue mobilization, myofascial techniques, and high-velocity low amplitude thrust techniques to other lower extremity joints. Only four of the 11 trials were a PEDro grade of six or higher with the remaining scoring below six indicating a low quality of the majority of the trials here.

Beumer et al. (2016) performed an SR and meta-analysis of exercise and manual therapy on pain with hip OA.[\[50\]](#) The SR included 19 RCTs though only four studies compared manual therapy and exercise to exercise or control. The results indicated a short-term benefit for pain relief and function when comparing both aquatic or land-based exercise to control. However, the results failed to indicate a benefit of pain relief from manual therapy with or without exercise compared to exercise therapy alone or a minimal control in hip OA patients in short-term comparisons. There was considerable heterogeneity between the trials in terms of size and methodology, and the authors suggested a need for future well-designed trials exploring manual therapy and exercise in hip OA.

Two RCTs directly compared manual therapy and exercise therapy to exercise alone in patients with knee OA.[\[73,74\]](#) Abbott et al. (2015) performed a four-arm parallel group factorial RCT comparing exercise therapy with booster, exercise therapy alone, exercise therapy and manual therapy, and exercise therapy with manual therapy and booster in 75 patients with knee OA.[\[73\]](#) They found the exercise with booster session and exercise and manual therapy group had the strongest improvements on WOMAC scores and sit to stand tests at one year compared to exercise therapy alone. The exercise and manual therapy also showed favorable results for pain reduction at one year compared to the exercise alone group.

Fitzgerald et al. (2016) also performed a four-arm parallel group factorial RCT comparing exercise therapy with booster, exercise therapy alone, exercise therapy and manual therapy, and exercise therapy with manual therapy and booster in 300 patients with knee OA.[\[74\]](#) There were no differences between groups at one year on WOMAC or performance-based measures. Their secondary analysis did indicate a short-term benefit of manual therapy and booster sessions increase the odds for pain relief at one year.

Physical therapy approaches utilizing manual therapy with or without exercise appear to show positive effects on pain and function in knee OA in both three month and one-year follow-up. The effect of manual therapy on hip OA is less clear, so further study here is warranted. The Work Group's confidence in the quality of evidence was low. The Work Group determined the benefits and harms to be balanced, as manual therapy with or without exercise has shown benefit and both therapies have a similar risk profile.

Shared decision making between the physical therapist and patient is important in utilizing manual therapy interventions. Physical therapists must also weigh the economic burdens faced by patients attending different types of physical therapies (e.g., lost wages, transportation costs, co-pays).

Modes of Physical Therapy Delivery

Modes of physical therapy delivery may include individual or group settings, internet-based, and telephonic coaching. The reviewed evidence did not support one mode of delivery of physical therapy care over traditional face-to-face encounters.[\[75-78\]](#) An RCT by Allen et al. (2016) compared individual physical therapy to group therapy in patients with OA of the knee.[\[78\]](#) The study found no difference in outcomes, specifically the WOMAC pain and function scales. Other smaller studies, such as an RCT by Kloek et al. (2018), did not find outcomes differed when comparing a blended web-based intervention with traditional physical therapy.[\[76\]](#) The researchers combined five face-to-face physical therapy visits along with home web-based applications. This study experienced a high attrition rate (20% at three months; 50% at 12 months) and failed to demonstrate any overall cost savings with the web-based intervention. An RCT comparing physical therapy telephone coaching as an adjunct to a home-based activity plan for knee OA to standard physiotherapy conducted by Bennell et al. (2016) found no difference in pain, WOMAC functioning scale, and quality of life.[\[75\]](#) Kloek et al. (2018) was the only study to include patients with OA of the hip.[\[76\]](#)

The effectiveness of alternative modes of physical therapy delivery may benefit some patients. The reviewed evidence demonstrated no adverse events. Moreover, because of travel, economic, and/or time constraints, some patients may prefer a home web-based program. Indeed, Allen et al. (2016) noted that group visits equate to \$40 less per patient than face-to-face physical therapy.[\[78\]](#)

As this is a *Reviewed, Amended* recommendation, the Work Group systematically reviewed evidence related to this recommendation [\[50,71,73-78\]](#) and considered the assessment of the evidence in the 2014 CPG.[\[79,80\]](#) The Work Group's confidence in the quality of evidence was low. The body of evidence had some limitations (i.e., small sample sizes, confounders in the analysis, and high attrition rates).[\[50,71,73-80\]](#) The benefits of reduced pain and improved physical function outweighed the potential harms, which are similar to engaging in any physical exercise program. There was variation in patient preferences since some prefer and actively seek out physical therapy. Other patients are disinterested in physical therapy because it is perceived as burdensome since frequent visits are required, or there is fear it will increase their pain. Patient preferences also likely vary regarding specific models of physical therapy care delivery. Other considerations include accessibility, as access barriers may limit or prevent patients from using physical therapy. Thus, the Work Group decided upon a "Weak for" recommendation.

While physical therapy is safe and effective for patients with hip and knee OA, research is needed on the long-term effectiveness, changes in healthcare utilization, and comparative effectiveness related to alternative models of physical therapy care delivery such as internet-based and telephone-based for this patient population.

D. Pharmacotherapy

a. Topical Pharmacotherapy

Recommendation

4. We recommend offering topical non-steroidal anti-inflammatory drugs for patients with pain associated with osteoarthritis of the knee.
(Strong for | Reviewed, New-added)
5. There is insufficient evidence to recommend for or against the use of topical non-steroidal anti-inflammatory drugs for patients with pain associated with osteoarthritis of the hip.
(Neither for nor against | Reviewed, New-added)

Discussion

While topical non-steroidal anti-inflammatory drugs (NSAIDs) come in various formulations, diclofenac is the only commercially manufactured topical NSAID currently available in the U.S. Tugwell et al. (2004),[\[81\]](#) an RCT included in the SR by Derry et al. (2016),[\[82\]](#) found topical diclofenac to be superior to placebo and equivalent to oral diclofenac at reducing pain associated with OA of the knee. Additionally, Simon et al. (2009),[\[83\]](#) an RCT included in Derry et al. (2016),[\[82\]](#) found no significant difference between topical and oral diclofenac therapy in providing pain relief. Both Tugwell et al. (2004) and Simon et al. (2009) used the diclofenac solution formulation that includes dimethyl sulfoxide.[\[81,83\]](#) Diclofenac gel also showed statistically significant pain relief over placebo and vehicle control.[\[82\]](#)

Studies involving topical ketoprofen and topical piroxicam compared to oral NSAIDs showed no significant difference in pain reduction.[\[82\]](#) Topical NSAIDs have also shown indirect superiority over oral acetaminophen, opioids, and cyclooxygenase-2 (COX-2) inhibitors; however, these agents have not been compared in head-to-head trials.[\[84\]](#)

Treatment with topical NSAIDs was associated with significantly fewer gastrointestinal (GI) adverse events but significantly more local adverse events compared to oral NSAIDs.[\[82,85\]](#) Safety data is mostly limited to 12-week follow-up. Two open-label studies in Derry et al. (2016) showed the safety profile of topical diclofenac at one year to be consistent with results at 12 weeks.[\[82\]](#)

The systematic evidence review yielded no studies evaluating the effect of topical NSAIDs on pain associated with OA of the hip.

Despite general consistency in the evidence supporting topical NSAIDs, there is variability in patient preferences regarding this treatment. Some patients prefer topical agents given the potential for fewer systemic effects compared to oral agents as there is lower systemic bioavailability with topical NSAIDs compared to oral NSAIDs.[\[82\]](#) However, since these agents may need to be applied up to four times daily, administration may be burdensome. Topical treatments can be difficult to apply because the application site may be covered by clothing. Topical diclofenac should not stain or damage clothing, but it may rub off under tight clothing if an appropriate amount of time for absorption and drying is not allowed. Application can also become an issue when used on larger joints and use can be limited in patients with certain skin conditions. Patients and caregivers should be educated to wash their hands thoroughly after the use of topical NSAIDs and to avoid contact with irritated skin, eyes, or mucous membranes. In addition, some

patients may have less confidence in the efficacy of topical medications compared to oral medications, as well as less confidence in the efficacy of over-the-counter (OTC) medications. Depending on the formulation, topical NSAIDs can be found both OTC or by prescription.

As these are *Reviewed, New-added* recommendations, the Work Group systematically reviewed evidence related to these recommendations.[\[82,84,85\]](#) For Recommendation 4, the Work Group's confidence in the quality of evidence was moderate. However, the systematic evidence review yielded no new evidence related to Recommendation 5. The body of evidence had some limitations including small sample sizes and imprecision resulting from the lack of a placebo comparator.[\[82,84,85\]](#) The benefits of pain reduction outweighed the potential harm of adverse events; however, there is a lack of data on long-term safety outcomes. Patient values and preferences were varied. The strength of evidence along with the safety profile of topical NSAIDs, which appears preferable compared to that of oral NSAIDs, helped determine the strength of the recommendation. Thus, the Work Group decided upon a "Strong for" recommendation for Recommendation 4, and a "Neither for nor against" for Recommendation 5.

Since most trials with topical NSAIDs are ≤ 12 weeks, long-term data on safety and effectiveness is needed. More research is needed on the safety and effectiveness of topical NSAIDs for patients with hip OA.

Recommendation

6. We suggest offering topical capsaicin for patients with pain associated with osteoarthritis of the knee.
(Weak for | Reviewed, Amended)

7. There is insufficient evidence to recommend for or against the use of topical capsaicin for patients with pain associated with osteoarthritis of the hip.
(Neither for nor against | Reviewed, Amended)

Discussion

Topically applied capsaicin has been used for the management of various types of pain, including neuropathic pain syndromes (e.g., postherpetic neuralgia, diabetic neuropathy, post-mastectomy pain) and pain arising from OA. Although topical capsaicin is generally used as adjunctive therapy, it may be used as monotherapy in patients with mild-to-moderate OA pain.

Capsaicin reversibly depletes substance P (SP), an endogenous neuropeptide involved in the pathogenesis and modulation of pain. Capsaicin is derived from chili peppers and its application stimulates the release of SP, initially causing a painful, burning sensation. With prolonged exposure and continued application, SP is depleted from afferent neurons, and transmission of painful stimuli is reduced or absent. Adverse events include temporary burning, stinging, and pain at the application site.

An SR by Laslett et al. (2014) included five RCTs comparing topical capsaicin 0.025 – 0.075% versus placebo and one trial comparing Civamide 0.075% (zucapsaicin, cis-isomer of capsaicin, is not available in the U.S.) to placebo.[\[86\]](#) All five RCTs assessing the benefit of topical capsaicin were relatively small (n=475) and of short duration (<3 months). Four are over a decade old. Among the studies included in Laslett et al. (2014),[\[86\]](#) Deal et al. (1991),[\[87\]](#) Altman et al. (1994),[\[88\]](#) and Kosuwon et al. (2010) [\[89\]](#) enrolled patients with OA of the knee. McCarthy et al. (1992) [\[90\]](#) enrolled patients with OA of the hand and McCleane

(2000) [91] enrolled patients with OA in mixed joints (e.g., knee, shoulder, hand, hip). Evidence from the SR supports at least a moderate effect of capsaicin (standard mean difference [SMD]: 0.44) in reducing moderate pain associated with OA.[86] Studies included in the SR evaluated the benefit of capsaicin as monotherapy, with background acetaminophen or acetaminophen as an adjunctive treatment for improving pain associated with OA.

The benefits of topical capsaicin outweighed the harms as Laslett et al. (2014) supports a moderate benefit of topical capsaicin administered 3 – 4 times daily in reducing pain associated with OA.[86] In the SR, adverse events of capsaicin were local (i.e., burning, stinging, and pain at the application site) and reported in 35 – 100% of patients randomized to capsaicin, which resolved or declined in most patients with continued use. No systematic adverse events were reported with capsaicin. Patients and caregivers should be educated regarding the potential benefits of capsaicin treatment, the limited harms, the importance of adherence to therapy since an adequate trial may take up to 2 – 4 weeks; to wash their hands thoroughly after use; and to avoid contact with irritated skin, eyes, or mucous membranes.

Patient and provider preferences for this treatment may vary. Although capsaicin does not possess systemic adverse events and may be preferred in patients with multiple comorbidities who need to limit the use of oral therapies for OA, some patients may be unable to tolerate the adverse events. However, the local adverse events resolve with continued use. Some patients may have a bias of a perceived lower effectiveness of topical and/or non-prescription treatments. Some may also dislike topical agents given the nuisance of application and application frequency required.

As these are *Reviewed, Amended* recommendations, the Work Group systematically reviewed evidence related to these recommendations.[86] For Recommendations 6 and 7, the Work Group’s confidence in the quality of evidence was low and very low, respectively. In OA of the knee, a favorable response to treatment may not occur for up to two weeks, but the benefit of a moderate reduction in OA pain outweighs the potential temporary local adverse events. There was insufficient evidence to determine the balance of benefits and harms for the use of capsaicin in the hip. Patient values and preferences may vary for both recommendations. Thus, the Work Group decided upon a “Weak for” recommendation for Recommendation 6 and a “Neither for nor against” recommendation for Recommendation 7.

As safe and effective therapies for OA of the hip and knee are limited, well-designed, larger trials of capsaicin for reducing painful OA of the hip and knee are needed to further support the use of therapies with moderate benefits but limited harms.

b. Oral Pharmacotherapy

Recommendation

8. We suggest offering acetaminophen and/or oral non-steroidal anti-inflammatory drugs for pain associated with osteoarthritis of the hip and knee.

(Weak for | Reviewed, New-replaced)

Discussion

Acetaminophen and NSAIDs are both widely available and commonly used by patients seeking pain relief from OA. The initial selection of drug therapy and the dose depends upon various factors including the severity of pain, individual patient factors, comorbid conditions (e.g., cardiovascular disease [CVD],

renal impairment, and history of adverse GI events), previous pharmacologic therapy for OA, and patient preference.

Acetaminophen

Acetaminophen has both analgesic and antipyretic effects but lacks potent anti-inflammatory activity. Acetaminophen in usual doses (2 – 4 grams [g] per day) was previously recognized as the preferred initial choice for the management of OA in most patients. Its use may still be preferred by providers for patients with more mild disease or mild-to-moderate symptoms of OA and in patients at risk for NSAID-induced adverse events (e.g., patients with renal disease, CVD or at risk for CVD, a history of GI ulcers, those receiving oral anticoagulants or corticosteroids [CS], and the elderly [i.e., aged >65 years]).

A network meta-analysis by da Costa et al. (2017) and an SR by Leopoldino et al. (2019) showed clinically insignificant differences for acetaminophen versus placebo in reducing pain and improving function in patients with OA of the hip and/or knee.[\[92,93\]](#) There was not a dose-dependent effect for acetaminophen in the SR by Leopoldino et al. (2019).[\[93\]](#) However, in the network meta-analysis by da Costa et al. (2017), there was a statistical improvement in pain and function with maximal doses of acetaminophen (3,900 – 4,000 milligrams [mg]/day) that was not demonstrated with lower doses.[\[92\]](#) However, differences were not clinically significant regardless of the dose of acetaminophen.[\[92\]](#)

A second SR network meta-analysis in knee OA only, Jung et al. (2018), noted statistically significant benefits of acetaminophen in reducing pain in patients with mild-moderate pain.[\[94\]](#) In Jung et al. (2018), the benefit of acetaminophen ranked higher than some NSAIDs in patients with mild-to-moderate pain associated with knee OA. Jung et al. (2018) did not identify any relevant studies in patients with more severe baseline knee OA pain.[\[94\]](#) In another SR and network meta-analysis by Stewart et al. (2018), the relative reduction in OA pain from baseline was 32.5% for acetaminophen, similar to NSAIDs.[\[84\]](#) Stewart et al. (2018) found that other classes of medications for knee and hip OA reduced pain by a statistically greater degree than acetaminophen (NSAIDs=34.3%, p=0.035; opioids [mostly tramadol]=35.4%, p=0.001; COX-2 inhibitors=36.9%, p<0.001; topical NSAIDs [knee and hand only]=40.9%, p<0.001).[\[84\]](#) The relative benefit of acetaminophen for reducing pain associated with knee and hip OA was greater in Stewart et al. (2018) than da Costa et al. (2017).[\[84,92\]](#)

Although acetaminophen has long been considered a relatively safe analgesic when taken in usual doses (up to 4,000 mg daily), the risk for acute liver injury and liver failure is increased in patients taking doses >4,000 mg daily.[\[95,96\]](#) In the SR by Leopoldino et al. (2019), the incidence of adverse events did not differ between acetaminophen and placebo (RR: 1.01, 95% CI: 0.92 – 1.11).[\[93\]](#) The incidence of serious adverse events and withdrawal because of adverse events between acetaminophen and placebo were not statistically different but the number of events was relatively small and the CIs were wide. Abnormalities in liver function tests (LFTs) were higher with acetaminophen versus placebo (RR: 3.79, 95% CI: 1.94 – 7.39); however, the clinical significance of LFT elevation associated with usual doses of acetaminophen is unclear.

While not included in this CPG's systematic evidence review and, thus, not considered in determining the strength of recommendation, an SR of observational studies by Roberts et al. (2016) explored rates of mortality and cardiovascular (CV), GI, and renal adverse events in patients taking usual doses of acetaminophen.[\[97\]](#) A dose-dependent statistical increase in mortality (n=1 study), CV (n=4 studies), GI (n=1 study), and/or renal events (n=3 studies) was observed with acetaminophen use versus no use.

Although this suggests a potential risk for adverse events, uncontrolled observational studies may represent a channeling bias based on use in selected patients with comorbidities and avoidance of NSAIDs.

Because of the potential for unintentional overdose from taking acetaminophen from multiple sources (e.g., prescription and OTC single and combination products >4,000 mg/day), suggested maximum doses have been reduced to <4,000 mg daily (e.g., 3,000 mg, 3,250 mg, ≤3,900). However, professional discretion can be used if doses up to 4,000 mg daily are deemed necessary for individual patients. Maximum doses of acetaminophen should be limited to the shortest possible duration.

Non-steroidal Anti-inflammatory Drugs

Oral NSAIDs are commonly prescribed for OA of the hip or knee and are generally well tolerated. The long-term use of NSAIDs is limited by adverse events (e.g., increased CV events, gastric and duodenal ulceration and perforation, bleeding, renal impairment). The risks of these complications increase with age, drug-drug and drug-disease interactions, and duration and quantity of use.[\[98\]](#) These risks are especially concerning in the patient population typically affected by OA, who tend to be older, often struggle with other chronic comorbidities, and may be vulnerable to the effects of polypharmacy. Alternative therapies to reduce these risks are limited.

The suggestion to consider NSAIDs for managing pain associated with hip and knee OA is supported by three SRs with network meta-analyses for effectiveness and two SRs with meta-analyses focusing on safety.[\[84,92,94,99,100\]](#) The SR by Osani et al. (2019) focused on NSAID safety and also examined the durability of symptom relief.[\[99\]](#) Additionally, the Puljak et al. (2017) SR compared the effectiveness and safety of celecoxib versus placebo and other NSAIDs.[\[101\]](#) The SR by da Costa et al. (2017) (n=58,451) included 76 trials studying the use of NSAIDs or acetaminophen and found that all active treatments improved pain associated with OA of the hip or knee versus placebo.[\[92\]](#) However, not all treatments met the predefined criteria for a minimally important difference (MID) to be considered clinically significant.[\[92\]](#) Of the interventions meeting the criteria for MID (i.e., rofecoxib 25 – 50 mg, etoricoxib 30 – 90 mg, and diclofenac 150 mg), only diclofenac is available in the U.S. Comparatively, maximum daily doses of naproxen and ibuprofen had an estimated 80% probability of meeting the MID for pain reduction.

The SR by Stewart et al. (2018) evaluated 29 studies of commonly prescribed analgesics (e.g., NSAIDs [n=9 studies], COX-2 inhibitors [n=9 studies]).[\[84\]](#) The relative reduction in pain from baseline was 34.3% for oral nonselective NSAIDs and 36.9% for COX-2 inhibitors. Both nonselective NSAIDs and COX-2 inhibitors performed statistically better than acetaminophen, which reduced pain by 32.5% (p<0.001). An SR by Jung et al. (2018) (n=44 studies) evaluated the comparative effectiveness of oral analgesics for knee OA.[\[94\]](#) For improving WOMAC pain, etoricoxib ranked the highest, followed by naproxen, acetaminophen, and celecoxib. In a subgroup analysis stratified by baseline severity of pain and radiologic severity of OA, etoricoxib, celecoxib, aceclofenac, and meloxicam or aceclofenac were the highest ranked therapies in the more severe pain group. In the group with mild-to-moderate pain, tramadol, celecoxib, diclofenac, and acetaminophen ranked highest. In Jung et al. (2018), ibuprofen was not included in any of the studies.[\[94\]](#) Rofecoxib, etoricoxib, and aceclofenac are not commercially available in the U.S.

In an SR by Puljak et al. (2017) studying celecoxib for the treatment of OA, celecoxib was slightly superior to placebo and various alternative NSAIDs in improving pain and function.[\[101\]](#) However, because of limited and missing data from several studies and industry sponsorship, the authors expressed strong

reservations about their findings.[\[101\]](#) In an SR and meta-analysis by Osani et al. (2019), the durability of pain relief from NSAIDs (measured over 2 – 26 weeks) in patients with knee OA was systematically examined from data collected in 72 clinical trials (n=26,424).[\[99\]](#) Osani et al. (2019) noted a moderate effect of NSAIDs in reducing pain (SMD: 0.43) and improving function in patients with knee OA, peaking at two weeks with the magnitude of benefit lessening after approximately eight weeks of treatment.[\[99\]](#) In the same SR, the incidence of GI adverse events was statistically higher in the NSAID versus placebo groups at four weeks (RR: 1.38, 95% CI: 1.21 – 1.57).[\[99\]](#) Cardiovascular adverse events were not different between NSAIDs and placebo. Most of the adverse events were temporary and minor in severity.

An SR by Curtis et al. (2019) (n=40 trials) examined the safety of COX-2 inhibitors.[\[100\]](#) Overall, drug-related adverse events were increased in the COX-2 group versus placebo (RR: 1.21, 95% CI: 1.09 – 1.46). Upper GI adverse events, including dyspepsia, gastritis, and heartburn, were also statistically higher versus placebo (RR: 1.19, 95% CI: 1.03 – 1.38). The risk for hypertension, heart failure, and edema was statistically higher for COX-2 inhibitors versus placebo. However, the risk for hypertension was not statistically significant when rofecoxib was removed from the analysis. Further detail on considerations for selecting oral NSAIDs as well as information on NSAIDs and the risks of adverse upper GI events, CV events, and renal disease can be found in [Appendix F](#).

Summary

The evidence supports a clinically significant reduction in pain with NSAIDs and a lesser overall effect of reducing pain with acetaminophen in patients with OA of the hip or knee.[\[84,92-94\]](#) The superiority of NSAIDs over acetaminophen for treating OA pain was more apparent in patients with moderate-to-severe levels of pain at baseline, while differences were negligible in patients with milder disease or milder symptoms.[\[94\]](#) The risk for and type of adverse events from NSAIDs or COX-2 inhibitors are well established. Therefore, providers should carefully consider the medical history of patients being considered for such therapy. Moreover, providers should avoid offering this treatment to patients with comorbidities that increase their risk for adverse events (e.g., CKD [chronic kidney disease], especially severe CKD, at risk for or known CVD, at risk for NSAID-related upper GI events). Adverse events associated with the use of acetaminophen appear to be dose-related (e.g., elevated LFTs, unintentional overdose) but no large prospective trials evaluate the risk for CV, GI, or renal events.

As this is a *Reviewed, New-replaced* recommendation, the Work Group systematically reviewed evidence related to this recommendation.[\[84,92-94,99-101\]](#) The Work Group's confidence in the quality of evidence was low. The benefit of these agents outweighed the risks in most patients, and patient preferences likely vary. Indeed, focus group participants expressed they may perceive non-prescription medications as less effective since acetaminophen and NSAIDs are commonly used for the management of pain in patients with OA and are widely available as prescription and/or OTC. However, avoidance of NSAIDs or COX-2 inhibitors is suggested in patients with certain comorbidities. Thus, the Work Group decided upon a "Weak for" recommendation.

Recommendation

9. We suggest offering duloxetine as an alternative or adjunctive therapy for patients with an inadequate response or contraindications to acetaminophen or non-steroidal anti-inflammatory drugs for pain associated with osteoarthritis of the knee.

(Weak for | Reviewed, New-replaced)

Discussion

Six RCTs evaluated in an SR by Chen et al. (2019) (n=2,059) demonstrated that duloxetine achieved significant reductions in pain outcomes, including 24-hour pain scores, weekly 24-hour average pain scores, and a $\geq 50\%$ reduction in weekly mean pain scores when compared to placebo at 10 – 16 weeks follow-up.[\[102\]](#) The same SR found a statistically significant improvement in physical function for patients in the duloxetine treatment arm at 10 – 16 weeks when compared to placebo. Five of the RCTs suggested that duloxetine increases the incidence of mild treatment-emergent adverse events (e.g., GI toxicity, sexual dysfunction, mild insomnia).[\[102\]](#)

An RCT (n=150) by Enteshari-Moghaddam et al. (2019) showed that duloxetine significantly reduced pain severity compared to acetaminophen and gabapentin in patients aged 45 – 75 years with moderate-to-severe knee OA at three months.[\[103\]](#) Duloxetine led to reductions in both mean VAS and mean WOMAC pain subscale index scores. At three months, patients treated with duloxetine noted a respective 61.45% and 78.29% mean reduction in VAS and WOMAC pain subscale scores compared to 31.20% and 50.25% in the group treated with acetaminophen. This RCT demonstrated that duloxetine also significantly improved physical function (WOMAC physical activity subscale) compared to acetaminophen. Eight patients in the duloxetine group experienced treatment-related side effects (i.e., drowsiness, fatigue, dry mouth), which were mild. No side effects were reported in the acetaminophen group. Of note, the Enteshari-Moghaddam et al. (2019) RCT excluded patients with a concomitant mood disorder diagnosis.[\[103\]](#)

Chen et al. (2019) and Enteshari-Moghaddam et al. (2019) only included short-term studies (≤ 16 weeks) of duloxetine's safety and efficacy in managing pain associated with OA; as such, one must consider the risk of discontinuation syndrome after long-term use.[\[102,103\]](#) Patients should be educated that the medication is to be taken daily (not as needed) and discontinued only after close consultation with their prescribing provider. Slow tapering will almost always be required. Duloxetine prescriptions should start at doses ≤ 30 mg daily and be increased to a goal of 60 mg daily. If a patient is taking another class of antidepressant medication (e.g., selective serotonin reuptake inhibitor) for a comorbid mood disorder, providers should consider transitioning to an equivalent dose of duloxetine using a cross-tapering strategy to avoid the risk of serotonin syndrome. As an initial consideration for providers, duloxetine therapy should *not* be initiated if a patient's estimated glomerular filtration rate (eGFR) is determined to be < 30 milliliters (ml)/minute (min)/ 1.73 m^2 . Of note, no other literature was reviewed looking at the use of different serotonin-norepinephrine reuptake inhibitors for the treatment of OA of the hip or the knee.

As this is a *Reviewed, New-replaced* recommendation, the Work Group systematically reviewed evidence related to this recommendation.[\[102,103\]](#) The Work Group's confidence in the quality of evidence was low. The body of evidence had a few limitations, including that most RCTs were short-term (≤ 16 weeks). This intervention's benefits, including improvement in pain and function, outweighed the small potential

for harm. Some variation in patient values and preferences is likely given this medication's development for and primary use as an antidepressant. Thus, the Work Group provided a "Weak for" recommendation.

Recommendation

10. We suggest against initiating opioids (including tramadol) for pain associated with osteoarthritis of the hip and knee. For patients already on long-term opioid therapy, refer to the current VA/DoD Clinical Practice Guideline for the Management of Opioid Therapy for Chronic Pain.
(Weak against | Reviewed, New-replaced)

Discussion

Systematic reviews by da Costa et al. (2014), Fuggle et al. (2019), Toupin et al. (2019), and RCTs by Banerjee et al. (2016), Rauck et al. (2013), and Spierings et al. (2013) compared various opioids (i.e., codeine, transdermal fentanyl, hydromorphone, morphine, oxycodone, tramadol, tapentadol) to no treatment, placebo, or active control for the treatment of hip or knee OA.[\[104-109\]](#) The evidence showed that most opioids consistently reduced pain intensity more than placebo in patients with hip and knee OA. The effect sizes were relatively small for patients with knee OA (SMD: -0.22, 95% CI: -0.41 – -0.04), hip OA (SMD: -0.33, 95% CI: -0.93 – 0.28), and knee and hip OA combined (SMD: -0.29, 95% CI: -0.38 – -0.20).

While opioid treatment led to a statistically significant reduction in pain intensity, the reduction did not reach the benchmark for clinical significance set by da Costa et al. (2014) (SMD: 0.37, corresponding to 0.9 centimeters [cm] reduction on a 10 cm VAS).[\[109\]](#) Treatment with all opioids, except for tapentadol, also improved physical function more than placebo, but these improvements were relatively small.[\[104-109\]](#)

Codeine, transdermal fentanyl, hydromorphone, morphine, oxycodone, oxymorphone, tramadol, and tapentadol all led to a higher risk for adverse events compared to placebo (RR: 1.28 – 1.69).[\[104-109\]](#) Studies also assessed other safety outcomes, including withdrawal symptoms, study withdrawal due to adverse events, and serious adverse events that were significantly worse in the opioid treatment groups compared to placebo. Withdrawal symptoms from opioids were frequent and the risks for study withdrawal due to adverse events were large. In an SR and meta-analysis of seven RCTs by Fuggle et al. (2019), tramadol was associated with a significantly higher risk of serious adverse events compared to placebo (RR: 1.78, 95% CI: 1.11 – 2.84) at 1 week – 3 months.[\[107\]](#) Details of what constituted serious adverse events were not reported.

An RCT by Bianchi et al. (2003) [\[110\]](#) included in the SR by Toupin et al. (2019) [\[104\]](#) compared tramadol to acetaminophen and showed no statistically significant differences in pain reduction or study withdrawal due to adverse events at seven days. Randomized controlled trials by Pavelka et al. (1998),[\[111\]](#) Beaulieu et al. (2008),[\[112\]](#) and DeLemos et al. (2011) [\[113\]](#) included in the SR by Toupin et al. (2019) [\[104\]](#) compared NSAIDs (i.e., diclofenac, celecoxib) to tramadol at four and 12 weeks. The NSAIDs reduced pain (SMD: 0.21, 95% CI: 0.07 – 0.36) and improved function (SMD: 0.23, 95% CI: 0.09 – 0.37) over tramadol. Tramadol was associated with more adverse events and more study withdrawals than NSAIDs, although there was no difference in serious adverse events. Fuji et al. (2014) [\[114\]](#) and Park et al. (2012),[\[115\]](#) RCTs included in the SR by Toupin et al. (2019),[\[104\]](#) compared the combination of tramadol and acetaminophen versus NSAIDs alone and found no statistically significant difference in pain reduction between groups at 8 – 12 weeks. Park et al. (2012) found no difference in physical function or adverse

events at eight weeks, suggesting there was no advantage to adding acetaminophen to tramadol relative to NSAIDs for patients with OA pain.[115]

An RCT by Banerjee et al. (2016) compared the COX-2 inhibitor etoricoxib to tapentadol and found no significant differences in pain reduction or physical function (WOMAC stiffness and function) at 12 weeks.[108] Adverse events were common in both treatment groups (49% versus 37%, $p=0.048$, favoring tapentadol).

Providers should note that the current VA/DoD CPG for Opioid Therapy for Chronic Pain recommends against initiating long-term opioid therapy for chronic pain.ⁱ Alternatives to opioid therapy (e.g., self-management strategies, other non-pharmacologic treatments) are the mainstay of management. When pharmacologic therapies are used, non-opioids are recommended over opioids.

However, patients who do not have an adequate response to several non-pharmacologic and non-opioid therapies and continue to have persistent, severe OA pain are particularly challenging to manage. In this situation, a cautious, patient-centered opioid therapy approach that prioritizes safety may be considered for carefully selected patients in which the benefits are anticipated to outweigh the risks. If opioids are prescribed for OA pain, it should be for the shortest duration and at the lowest effective dose. Furthermore, appropriate monitoring as per the VA/DoD CPG for Opioid Therapy is suggested.

As this is a *Reviewed, New-replaced* recommendation, the Work Group systematically reviewed evidence related to this recommendation.[104-109] The Work Group's confidence in the quality of evidence was very low. The Work Group found few active-control, comparative effectiveness, or head-to-head trials comparing the relative efficacy of opioids to other analgesics, which are more clinically relevant and informative for treatment decision-making. The evidence was limited by short-term trials (i.e., 1 – 17 weeks). Also, because of the serious risks of opioids, which include withdrawal, misuse, abuse, overdose, and opioid use disorder, and emerging evidence of endocrine dysfunction, sleep-disordered breathing, falls, fractures, and infections, the Work Group concluded that the risks associated with opioid treatment outweighed potential benefits. The evidence consistently showed the benefits of opioids include a modest reduction in pain intensity and improved function compared to placebo in patients with OA of the knee and hip, but these small benefits have not been studied over the long-term and are likely not clinically significant. However, the Work Group acknowledged that opioids may be considered for certain patients. Thus, the Work Group decided upon a “Weak against” recommendation.

Osteoarthritis is a chronic condition, yet existing studies of pharmacologic options for OA of the knee and hip are relatively short-term. Researchers should conduct longer duration studies to better assess the long-term effectiveness and safety of pharmacologic options and better reflect the chronic disease management required for OA. Also, more research is needed to assess the effectiveness and safety of the combination of pharmacologic treatments and the combination of pharmacologic, especially non-opioid, and non-pharmacologic treatments. Decision aids that assist providers in calculating the risk-benefit ratio would help with the selection of pharmacologic treatments, especially when opioids are considered.

ⁱ See the current VA/DoD Clinical Practice Guideline for the Management of Opioid Therapy for Chronic Pain. Available at: <https://www.healthquality.va.gov/guidelines/Pain/cot/>

c. Intra-articular Injections

Recommendation

11. We suggest offering an intra-articular corticosteroid injection for patients with persistent pain due to osteoarthritis of the knee inadequately relieved by other interventions.
(Weak for | Reviewed, New-replaced)

12. We suggest offering an intra-articular, image-guided corticosteroid injection for patients with persistent pain due to osteoarthritis of the hip inadequately relieved by other interventions.
(Weak for | Reviewed, New-replaced)

Discussion

An SR by Tian et al. (2018) with four RCTs found intra-articular methylprednisolone reduced pain and improved function in OA-related knee pain when compared to saline injection at four and 24 weeks.[\[116\]](#) Similarly, intra-articular triamcinolone reduced knee pain and increased function compared to placebo at six weeks but not 12 weeks.[\[117\]](#) A large SR by Juni et al. (2015) found corticosteroid injection (CSI) significantly reduced knee pain and improved knee function at 4 – 6 weeks when compared with placebo or no treatment; however, the benefits were marginal or not clinically significant at three months and equivalent at six months between controls and CSI.[\[118\]](#) Further, an RCT by Conaghan et al. (2018) found FX006, an extended-release intra-articular CSI, significantly reduced knee pain and improved function at 1 – 3 months when compared to saline in patients with knee OA.[\[119\]](#) Nevertheless, one long-term RCT by McAlindon et al. (2017) found no significant difference in knee pain or function for intra-articular triamcinolone versus saline at two-years follow-up.[\[120\]](#)

When comparing adverse events of intra-articular CSI, SRs by Tian et al. (2018) and Juni et al. (2015) and an RCT by Conaghan et al. (2018) found no significant differences between groups in total adverse events at six months.[\[116,118,119\]](#) Another study by McAlindon et al. (2017) demonstrated a significantly higher rate of total adverse events in the saline group compared to the triamcinolone group at two years, but no significant difference between groups in serious adverse events.[\[120\]](#)

For quality of life measures, the data for intra-articular knee CSI was mixed. An RCT by Conaghan et al. (2018) for FX006 extended-release CSI demonstrated improved quality of life at one and three months,[\[119\]](#) despite an SR by Juni et al. (2015) containing two relevant RCTs finding no significant difference in quality of life between groups for CSI versus placebo.[\[118\]](#) This study also suggested no differences between groups in joint space narrowing,[\[118\]](#) though a separate RCT demonstrated greater change (i.e., worsening) in some radiographic measures (e.g., cartilage thickness, index compartment, and total mean cartilage loss, cartilage damage index, index compartment) in patients receiving triamcinolone given every three months versus saline at two-years follow-up.[\[120\]](#)

This CPG’s systematic evidence review did not identify any new SRs or RCTs examining whether CSI should be avoided in the three months before joint replacement surgery of the knee. Although infection is a known complication arising from both joint injection and arthroplasty, limited data shows an increased risk of deep joint infection in patients who have undergone intra-articular CSI before joint (e.g., knee, hip) arthroplasty. Patient factors that may increase this risk include prior open surgical procedure,

immunosuppressive therapy, poor nutrition, hypokalemia, diabetes, obesity, and a history of smoking.[\[121\]](#)

There are, however, retrospective or case-control studies on the risk of deep joint infection after joint arthroplasty. An SR by McMahon et al. (2013) included 12 studies assessing the rates of superficial and deep joint infections (n=2,068) in cohorts of patients who did or did not receive a CSI and who underwent hip or knee arthroplasty.[\[122\]](#) The SR concluded that steroid injection prior to joint replacement (either hip or knee) did not statistically increase the risk for superficial or deep joint infection. Whether steroid injections performed elsewhere in the body increase the risk for deep joint infection in the three months before surgery was not reviewed. McMahon et al. (2013) was not included in this CPG's systematic evidence review and, thus, was not considered in determining the strength of this recommendation.[\[122\]](#)

Similar to CSIs, dextrose prolotherapy has been used to relieve OA-related knee pain. The Work Group reviewed the available literature and found one SR by Hung et al. (2016), which investigated the effect of dextrose prolotherapy on the treatment of OA.[\[123\]](#) Dextrose prolotherapy significantly reduced knee pain versus exercise, but not more versus other injections, at six months. No significant safety concerns were identified with prolotherapy, except for one patient that developed diffuse edema of both legs at weeks 24 and 28. Limitations of the Hung et al. (2016) review included inappropriate blinding.[\[123\]](#)

Despite general consistency in the evidence supporting CSIs for knee pain associated with OA, patient preferences vary somewhat. The patient focus group noted this treatment is burdensome because it is invasive and requires frequent in-office visits. Also, CSIs of the knee may increase resource use and some providers may not have adequate training or confidence to administer these injections. Further, patients may require additional follow-up visits if complications or adverse events occur.

For OA of the hip, three of the five RCTs in an SR by McCabe et al. (2016) found no significant between-group differences in pain between CSI and placebo at 3 – 12 weeks follow-up.[\[124\]](#) The remaining RCTs did not independently evaluate pain as an outcome. However, there was substantial heterogeneity among individual study effect sizes ranging from no effect to a very large effect favoring CSI. Regarding the safety of CSI in the hip, McCabe et al. (2016) reviewed four RCTs that included 310 patients and found only one serious adverse event (i.e., deep vein thrombosis three months post-CSI).[\[124\]](#) Two trials reported on adverse events in the CSI group, while a third found similar rates of adverse events between CSI and placebo groups (i.e., 51% in the CSI group versus 52% in the placebo group). Most events were either mild or deemed unrelated to the treatment. Further, McCabe et al. (2016) found clinically significant between-group differences in the number of OMERACT-OARSI (Outcome Measures in Rheumatology Clinical Trials – Osteoarthritis Research Society) responders (i.e., patients with a substantial improvement in pain and/or function) favoring CSI over placebo at eight weeks.[\[124\]](#)

As these are *Reviewed, New-replaced* recommendations, the Work Group systematically reviewed evidence related to these recommendations.[\[116-120,123-125\]](#) The Work Group's confidence in the quality of evidence for both recommendations was low. The body of evidence had limitations including small sample sizes and confounders in the analysis. The benefits of these recommendations (i.e., improved outcomes for pain, function, and quality of life) slightly outweighed the potential small harm from adverse events. Patient values and preferences vary somewhat and this treatment may increase resource use, especially for CSI of the hip because image guidance is required. The availability of ultrasound or

fluoroscopy may not be readily available, along with the clinical expertise to perform the injection. Thus, the Work Group decided upon “Weak for” recommendations.

More research is needed on the timing, safety, and effectiveness of CSIs for patients with OA-related knee pain. Also, the use of anesthetics, long-acting formulations, and a combination of agents needs to be assessed. Finally, researchers should explore whether there is an optimal time interval (e.g., three months) to avoid CSI before joint replacement surgery to reduce the risk for deep joint infection.

Recommendation

13. We suggest offering intra-articular viscosupplementation injection(s) for patients with persistent pain due to osteoarthritis of the knee inadequately relieved by other interventions.

(Weak for | Reviewed, New-replaced)

14. We suggest against the use of intra-articular viscosupplementation injection(s) of the hip.

(Weak against | Reviewed, New-replaced)

Discussion

Viscosupplementation injections (VSIs) (which refers to all synthetic hyaluronic acid [HA] preparations) are designed to provide lubrication in the setting of OA. For patients with pain related to OA of the knee, the use of VSIs may improve pain and function.[\[126-129\]](#) Recent evidence comparing VSIs to CSIs found that CSIs improved the short-term (one month) VAS pain scores better than VSIs, but that they are equivalent at three months, and VSIs provided statistically significant improvement in VAS pain scores compared to CSIs at 6, 9, and 12 months.[\[127\]](#) Further, they shared similar functional improvements in range of motion at three and six months and similar risk profiles.[\[127\]](#) This pattern was also demonstrated in an RCT by Trueba Davalillo et al. (2015).[\[130\]](#) However, two other RCTs, Campos et al. (2017) and Siddharth et al. (2017), showed no difference for pain relief or function at one and six months comparing VSI to CSI.[\[131,132\]](#)

For patients with pain related to symptomatic OA of the hip, we suggest against the use of VSIs. Overall, we found a paucity of literature on injections (i.e., VSI and CSI) in the hip. An SR by Leite et al. (2017) evaluated four RCTs comparing VSI to placebo and found no difference in pain relief at all-time points.[\[133\]](#) Additionally, this SR included three RCTs comparing VSI to CSI in the hip, which also showed no difference in pain relief or adverse events. For hip OA specifically, VSIs have a higher risk profile (e.g., proximity to the neurovascular bundle), and there is a lack of literature on the subject.

The 2014 VA/DoD OA CPG Work Group found insufficient evidence to recommend for or against the use of VSI in the treatment of knee OA. Since 2014, several large SRs have shown some benefit of VSI compared to placebo and some benefit at later time points compared to CSI.[\[126-129\]](#) Some included studies were downgraded in quality because of bias; however, there were large sample sizes and the outcomes were fairly consistent across study groups, particularly regarding reduction in pain at longer time intervals and with safety.[\[126-129\]](#) The articles did not provide guidance on the severity of OA which may or may not benefit.

As these are *Reviewed, New-replaced* recommendations, the Work Group systematically reviewed evidence related to these recommendations.[\[126-133\]](#) The Work Group’s confidence in the quality of

evidence was low. While literature supports the use of VSIs in the management of knee OA, patient preferences regarding this intervention may vary. Additionally, different formulations of VSIs have weekly dosing schedules, which some patients may find burdensome. Viscosupplementation injections are also associated with high resource use given their higher cost compared to other injections. Given the potential benefits, acceptable small number of adverse events, and patient preferences and resource use, the Work Group decided upon a “Weak for” recommendation for Recommendation 13. Conversely, given the increased burden of hip injections requiring image guidance and increased specialization to administer, the risk of local injury to neurovascular structures, and the lack of demonstrated benefit, the Work Group decided upon a “Weak against” recommendation for Recommendation 14.

The research gaps regarding VSIs include a relative lack of long-term adverse event studies beyond one year. Additionally, further studies are needed to determine optimized dosing schedules. Lastly, there is insufficient evidence on efficacy and safety in VSI use for hip OA, even in the short-term.

E. Orthobiologics

Recommendation

15. There is insufficient evidence to recommend for or against platelet-rich plasma injections for the treatment of osteoarthritis of the hip or knee.

(Neither for nor against | Reviewed, New-added)

Discussion

Platelet-rich plasma (PRP) is a novel regenerative medicine treatment option whose physiologic mechanism of action is hypothesized to involve direct delivery of multiple growth factors proposed to be implicated in soft tissue repair. The systematic evidence review produced one SR comparing PRP to HA for hip OA.[\[140\]](#) For knee OA, the systematic evidence review found studies comparing PRP to HA, sham saline injection, CSI, and rehabilitation modalities. The systematic evidence review did not yield studies comparing PRP to prolotherapy.

There is limited research on the use of PRP in hip OA. An SR by Ye et al. (2018) included four trials comparing PRP to HA.[\[134\]](#) Ye et al. (2018) found that PRP leads to statistically significant reductions in pain compared to HA at two months but not at six and 12 months.[\[134\]](#) The clinical relevance of this statistically significant difference is unclear. Alternatively, the SR found no difference in function between PRP and HA at all follow-up periods. Finally, there was no difference in safety between PRP and HA for nausea and infection. However, the Work Group’s confidence in the quality of evidence was downgraded given problems with blinding and ITT analyses. The Work Group agreed that the benefits and harms/burden of PRP were generally balanced.

Regarding PRP in knee OA, the systematic evidence review produced one SR of 15 trials and seven additional RCTs comparing PRP to HA. The same outcomes were evaluated, including pain reduction, functional improvement, and safety. Evidence from four RCTs in the SR conducted by Han et al. (2019) and two additional RCTs suggest that PRP leads to no difference in pain reduction relative to HA at three months.[\[135-137\]](#) Evidence from five RCTs in the SR by Han et al. (2019) and three additional RCTs suggest statistically significant pain reduction favoring PRP at six and 12 months.[\[135,138-140\]](#) Additionally, evidence from five RCTs in Han et al. (2019) suggests that PRP leads to improved function relative to HA at

3, 6, and 12 months.[\[135\]](#) Furthermore, four RCTs suggest PRP leads to improved function at six and 12 months.[\[138-141\]](#) Finally, evidence from nine RCTs in Han et al. (2019) and five additional RCTs suggest there were no serious adverse events reported and no differences between PRP and HA.[\[135,138-142\]](#) Mild adverse events associated with the injection site (i.e., swelling, pain) were noted 3 – 5 days post-procedure for both PRP and HA, suggesting no differences in safety.

An RCT by Buendia-Lopez et al. (2018) suggests that PRP leads to no difference in MRI-evaluated progression of cartilage degeneration-cartilage thickness compared to HA at 12 months.[\[138\]](#) Also, an RCT by Lisi et al. (2018) suggests a significant difference between the proportion of each group improving >1 grade on the Kellgren and Lawrence Grading Scale (KLGs) as evaluated by MRI, favoring PRP at six months.[\[136\]](#) Lastly, an RCT by Ahmad et al. (2018) suggests that PRP leads to significantly more ultrasound-detected improvements in synovial vascularity, hypertrophy, and effusion compared to HA at both three and six months.[\[139\]](#)

Regarding PRP versus sham saline injection in knee OA, the systematic evidence review produced three relevant RCTs.[\[148-150\]](#) In particular, evidence from RCTs by Smith (2016) and Patel et al. (2013) suggests that PRP leads to a significant difference in pain reduction relative to sham saline at 3, 6, and 12 months.[\[149,150\]](#) Furthermore, all three RCTs suggest that PRP leads to a significant difference in improved function relative to sham saline at 3, 6, and 12 months.[\[148-150\]](#) There were no serious adverse events reported in these RCTs.

The systematic evidence review produced five relevant RCTs regarding PRP versus CSI in knee OA.[\[151-155\]](#) Evidence from these RCTs was inconsistent regarding whether PRP leads to a significant difference in pain reduction, as well as improved function, relative to CSI at 2, 3, and 6 months. Similarly, these RCTs suggest there were no serious or minor adverse events reported.

The last area reviewed was PRP versus rehabilitation interventions (e.g., exercise, transcutaneous electrical nerve stimulation [TENS], general rehabilitation) in knee OA. The evidence from RCTs by Angoorani et al. (2015) and Gaballa et al. (2019) was inconsistent regarding whether PRP leads to a significant difference in pain reduction relative to rehabilitation (e.g., electrotherapy, exercises) at two and three months.[\[143,144\]](#) Additionally, these RCTs suggest PRP does not lead to functional differences relative to rehabilitation at two and three months. Finally, both RCTs reported no serious adverse events but increased minor adverse events in the PRP group.[\[143,144\]](#)

The use of PRP to manage patients with hip or knee OA is promising, as the mechanism of action of these injections is believed to use the body's mechanisms to reduce inflammation, promote restoration of cartilage, and affect disease progression. All studies used validated and disease-specific outcomes (e.g., WOMAC, the Knee Injury and Osteoarthritis Outcome Score [KOOS], VAS) for the outcomes of interest. Most of the studies were conducted in Europe (i.e., Spain, Italy, and Turkey), the Middle East (i.e., Iran and Egypt), and China. This may suggest these therapies are more aligned with cultural values that promote autologous healing or are more focused on preventing disease progression or generating new cartilage.

Across the studies, there was significant heterogeneity in the preparation, dose, and frequency of injection administration for both PRP and the comparators of HA, CSI, and rehabilitation. The relative

benefits of leukocyte-rich or leukocyte-poor PRP and the concentration of different cells within the blood was heterogeneous and not standardized across studies. As such, the influence of these variations on efficacy is not clear at present. In the studies reviewed, ultrasound was used consistently in hip OA to guide injections but rarely in knee OA. The impact of imaging-guidance for joint injection on outcomes is not clear; however, it is generally recommended that, when possible, ultrasound or fluoroscopy be used to most accurately deliver the PRP solution. Platelet-rich plasma compared to CSI and rehabilitation were the most problematic (i.e., allocation, blinding, ITT analysis) and comparison to sham saline was the least problematic.

Despite this heterogeneity, overall the evidence evaluating PRP to HA, which had the largest number of RCTs, suggested consistent benefit in both pain reduction and function at six months and 12 months, and benefit in function only at three months.[\[135\]](#) When PRP is compared to sham saline injections, there was a consistent benefit in pain and function. Inconsistent findings from five RCTs do not clarify whether PRP is more effective than CSI, and the evidence from these studies was limited given their small sample sizes. Similarly, the evidence from two RCTs comparing PRP to rehabilitation interventions (i.e., TENS, exercise) was also limited given small sample sizes.

As this is a *Reviewed, New-added* recommendation, the Work Group systematically reviewed evidence related to this recommendation.[\[134-148\]](#) The Work Group's confidence in the quality of evidence reviewed was very low given the serious inconsistency and imprecision with study designs, lack of standardization (e.g., dose, frequency, preparation technique), and outcome measures. The benefits and harms were balanced with this novel treatment. The benefits include pain reduction, improved function/quality of life, and the potential for some minor change in disease progression. The risks were low and rare, being limited to minor adverse events involving the injection site (e.g., soreness, redness, infection). Given the novelty of this treatment option, there is some variation in patient preference. Some patients will likely request this treatment option earlier in the disease process, whereas many patients will prefer exhausting all non-interventional options. Of note, PRP is a relatively expensive treatment option currently excluded from coverage by insurers. The Work Group also acknowledged the treatment cost and additional resources required (i.e., centrifuge, PRP and intravenous kits, technician training, and increased procedural time). Thus, the Work Group decided upon a "Neither for nor against" recommendation.

While PRP research is in its infancy, specifically regarding hip and knee OA, many well-designed studies evaluate the effectiveness of PRP with various musculoskeletal tendinopathies. Future research directions need to involve standardized PRP concentrations, frequency of injections, optimal method for processing blood sample, as well as comparative efficacy studies exploring the relationship between leukocyte-rich versus leukocyte-poor PRP. Additional research directions should also take a closer look at the evaluation of soft tissue changes in various imaging modalities to include ultrasound and/or MRI. A single RCT by Louis et al. (2018) [\[149\]](#) that was included in the SR by Han et al. (2019) [\[135\]](#) attempted to evaluate safety and establish a minimum tolerable dose and toxicity levels of PRP and HA. This would suggest that more research is needed to evaluate these safety thresholds.

Recommendation

16. We suggest against stem cell injections (e.g., mesenchymal, adipose-derived, and bone marrow-derived) for the treatment of osteoarthritis of the knee.

(Weak against | Reviewed, New-added)

Discussion

Stem cell therapy is an area of growing interest in the field of regenerative medicine. Unlike blood-derived therapies, stem cell therapies may produce their regenerative effect primarily via cellular engraftment with their direct incorporation into injured and adjacent tissue. However, cytokines released by these stem cells can also contribute to tissue regeneration by promoting growth and differentiation of local cells.

It is important to distinguish between the major types of stem cell therapies. The mesenchymal stem or stromal cells (MSC) are the body's repair cells. They are undifferentiated multipotent stem cells that are relatively mature with less capacity for differentiation and proliferation compared with pluripotent stem cells. Bone marrow aspirate has been the traditional source for MSCs, although they comprise only 0.01 – 0.001% of nucleated marrow cells. Adipose tissue tends to be a richer source of MSCs and harvesting is considered to be less invasive.[\[150\]](#) Importantly, regardless of tissue source, the number of MSCs declines with age. Some biotech companies will offer alternative methods of stem cell manufacturing that is less costly and less regulated but considered to be non-quantitative. As such, the concentration of MSCs is unknown but considerably lower than traditional, culture-expanded MSCs. These cells have also been termed “adipose stromal vascular fraction,” but are often referred to as MSCs when described in marketing materials.[\[151\]](#) The expanded MSCs are most often used in research, while the non-expanded heterogeneous stem cell therapies are offered by most stem cell providers. Providers should be aware of this difference and further investigation into comparative efficacy is needed.

Research in this area is in its infancy. This CPG's systematic evidence review identified two SRs and eight RCTs that addressed the benefits and harms of stem cell intra-articular injections in patients with knee OA; however, it did not identify relevant evidence on stem cell therapy in patients with hip OA.

The Kim et al. (2019) SR examined intra-articular injections of bone-marrow-derived MSCs and adipose-derived stromal vascular fraction containing adipose-derived MSCs (ADMSCs).[\[125\]](#) Kim et al. (2019) favored MSC injections over control for all pain- and function-related outcomes up to 24 months for knee OA. However, although the outcomes were considered statistically significant, the clinical significance was questionable and the control group was heterogeneous. Kim et al. (2019) also did not find a significant difference in MRI evaluations (n=96) between MSC injections versus control.[\[125\]](#) The limitations of Kim et al. (2019) include incomplete outcome data, selective reporting, inappropriate blinding, and other bias reported.

Limitations of the eight additional RCTs included unclear methods for randomization and allocation concealment. Three RCTs addressed adipose-derived stem cell injections.[\[151-153\]](#) Freitag et al. (2019) reported one or two injections of ADMSC were significantly favored (versus control groups) for pain (Numeric Pain Rating Scale and KOOS) with no safety concerns at 12 months in patients with moderate knee OA.[\[152\]](#) The Lee et al. (2019) RCT indicated that high-dose ADMSC provided significant pain relief (VAS) at six months over baseline with no safety concerns in patients with knee OA (KLGs 2 and 3).[\[151\]](#)

Finally, the RCT by Lu et al. (2019) indicated that intra-articular injections of human adipose-derived mesenchymal progenitor cells at zero and three weeks provided no safety concerns and significantly more pain relief at 12 months versus HA in patients with knee OA (mostly KGLS 2 and 3).[\[153\]](#)

Two RCTs addressed bone marrow-derived stem cell injections.[\[154,155\]](#) Emadedin et al. (2018) showed significant differences favoring autologous bone marrow-derived MSCs versus control for WOMAC pain and function subscales at six months with no safety concerns in patients with knee OA (KGLS 2 – 4).[\[154\]](#) An RCT by Goncars et al. (2017) indicated significant differences favoring a single injection of bone marrow-derived mononuclear cells versus three injections of HA for pain (KOOS) and function (Knee Society Score) at 12 months with no safety concerns (KGLS 2 – 3).[\[155\]](#) However, the study lacked clear randomization, allocation, concealment methods, and blinding, and did not report attrition.

An RCT by Schwappach et al. (2017) compared three biweekly injections of low-molecular-weight-fraction of 5% human serum albumin (LMWF-5A) versus control and found LMWF-5A was significantly favored for WOMAC pain but not function at 20 weeks in patients with moderate-to-severe knee OA.[\[156\]](#) No serious treatment-related adverse events were reported in the trial. Also, an RCT by Kim et al. (2018) indicated that TissueGene-C was significantly favored versus placebo for all pain- and function-related outcomes at 52 weeks in patients with KGLS 3 knee OA.[\[157\]](#) An RCT by Kon et al. (2018) found mixed results for autologous protein solution versus saline for pain reports at 12 months in patients with KGLS 2 and 3 knee OA.[\[158\]](#) Arthralgia was reported in patients in both treatment arms.

The body of evidence had limitations, including serious inconsistency and imprecision with study designs and outcome measures. In particular, the Work Group expressed concerns about blinding, incomplete outcome data collection, selective reporting, other biases, and unclear randomization and allocation concealment methods. Limitations of the evidence base also included a lack of studies in patients with hip OA, limited evidence for interventions in patients with severe knee OA, lack of reporting on radiographic-related outcomes, and no studies comparing interventions with CSI.

Given the novelty of this treatment, some variation in patient preference is likely. Some patients may request this treatment option earlier in the disease process, but many patients still prefer exhausting all non-invasive options. Stem cell therapy is also a relatively expensive treatment option that is currently not covered by insurers. The Work Group also acknowledged the treatment's cost and the additional resources required (e.g., centrifuge, technician training, increased procedural time). For example, bone-marrow-derived stem cells require an additional, moderately invasive iliac crest harvesting procedure to obtain the stem cells used for the injection. The harvesting is relatively innocuous but does require additional resources typically including some form of image guidance (i.e., ultrasound or fluoroscopy), time, and support staff. There is also some minor procedural discomfort from the harvesting site. While currently not well studied, stem cell therapy may not be a recommended treatment option among older adult patients who have severe and/or advanced OA.

As this is a *Reviewed, New-added* recommendation, the Work Group systematically reviewed evidence related to this recommendation.[\[125,151-158\]](#) The Work Group's confidence in the quality of evidence was low. The body of evidence had limitations, including serious inconsistency, imprecision, and a lack of studies in patients with hip OA. The benefits (i.e., pain reduction, improved function, quality of life) and the potential for some minor change in disease progression were balanced with the risks, which were rare and

limited to minor adverse events involving the injection site. Although not included in the systematic evidence review and, thus, not affecting the strength of the recommendation, limited studies find MSCs to be a safe therapy and published clinical trials involving local implantation to treat orthopedic conditions have not shown a significant risk of tumor formation, unintended differentiation, or other serious adverse events.^[150,159] Patient values and preferences likely vary. Thus, the Work Group decided upon a “Weak against” recommendation.

There is limited research on stem cell therapy for the treatment of knee and hip OA. While there appear to be some promising areas, much is still unknown. There are numerous types of stem cell therapy; thus, researchers will need to further evaluate efficacy over the current standard of care and the comparative efficacy of the various stem cell derivations. Analysis of interval timing of injections, concentrations, and type of cells utilized, as well as post-procedure rehabilitation protocols, need investigation. Lastly, research should evaluate the soft tissue changes occurring post-stem cell injection with various imaging modalities, including ultrasound and MRI.

F. Complementary and Integrative Health, Dietary Supplements, and Nutraceuticals

Recommendation

17. There is insufficient evidence to recommend for or against the use of the following dietary supplements or nutraceuticals for the treatment of osteoarthritis of the hip or knee:

- Avocado and soybean extract
- Boswellia serrata
- Cannabidiol (CBD oil)
- Chondroitin
- Curcumin (active component of turmeric)
- Collagen
- Glucosamine
- Glucosamine plus chondroitin
- Methylsulfonylmethane
- Omega-3 fatty acid
- Pycnogenol (pine bark)
- Rosehip
- Traditional Chinese medicine
- Vitamin D
- Vitamin E
- Willow bark extract

(Neither for nor against | Reviewed, New-replaced)

Discussion

This recommendation examined 16 dietary supplements: avocado and soybean extract, Boswellia serrata, cannabidiol, chondroitin, curcumin, collagen, glucosamine, glucosamine plus chondroitin, methylsulfonylmethane (MSM), omega-3 fatty acids, pycnogenol (pine bark), rosehip, traditional Chinese medicine, vitamin D, vitamin E, and willow bark extract.^[160-173] Further discussion on the supporting

literature for these dietary supplements can be found in [Appendix G](#). Cannabidiol and omega-3 fatty acids were included in the search strategy but did not return any literature meeting the inclusion criteria.

The acceptability of and familiarity with dietary supplements likely vary across patients and providers. These supplements are widely marketed and available OTC. Furthermore, most dietary supplements included in this CPG's systematic evidence review are not on TRICARE formulary or VA's One National Formulary and, thus, would be an out-of-pocket expense for patients.

Also, the products used in the trials may differ from what is found on a formulary, store shelves, or online (i.e., the consumer version). Dietary supplements are not as strictly regulated as pharmaceuticals and do not require U.S. Food and Drug Administration (FDA) approval to be marketed to consumers. Furthermore, the FDA does not review supplements for safety and effectiveness before they are marketed. Patients who choose to take dietary supplements should be provided education on third-party testing and supplement safety. Further information for patients and providers can be found at Operation Supplement Safety.^j

It is also important to note that several of these dietary supplements have the potential for drug-supplement interactions. Providers should ask about and be aware of the dietary supplements their patients may be taking so that potential drug-supplement interactions can be mitigated, and when appropriate report adverse events as indicated. Providers can assess drug-supplement interactions at the Natural Medicines comprehensive database.^k

Many of these dietary supplements demonstrated a small benefit in pain and function in the short-term, but equivalence with placebo long-term. Additionally, the short follow-up times are insufficient to determine the risk of long-term adverse events. Evidence from an SR by Zhu et al. (2018) suggests the risk of adverse GI events was higher in the chondroitin group compared to placebo.^[167] Other studies did not indicate a significant difference between groups for adverse events.^[169]

As this is a *Reviewed, New-replaced* recommendation, the Work Group systematically reviewed evidence related to this recommendation.^[160-173] The Work Group's confidence in the quality of evidence was very low. The body of evidence had significant limitations including small study sizes and heterogeneity of dosing and follow-up times. Of note, some studies were industry-funded. Given the low potential for adverse events with most supplements (see [Appendix G](#)) and that many studies reported an improvement in pain and function, the Work Group determined the benefits slightly outweighed the harms. The risk of adverse events or outcomes from potential drug-supplement interactions needs to be considered in individual patients. Thus, the Work Group decided upon a "Neither for nor against" recommendation.

The currently available research on dietary supplements and nutraceutical agents is lacking in methodological rigor and clear protocol implementation. For these products to be viable, consistent, and trusted therapeutic options that can be measured and evaluated, clarity is needed in product content and dosage, and assurance is needed in purity and quality. Nationally, more rigorous regulation of dietary supplements and nutraceuticals is required. Additionally, further research is also needed into related long-term side effect profiles of these supplements for patients with knee and hip OA.

^j Operation Supplement Safety is available at: <https://www.opss.org/>

^k *Natural Medicines* is available at: <http://info.therapeuticresearch.com/dod>

Recommendation

18. There is insufficient evidence to recommend for or against the use of complementary and integrative health interventions for the treatment of osteoarthritis of the hip or knee, including:

- Acupuncture
- Massage
- Light touch
- Meditation
- Tai chi
- Yoga

(Neither for nor against | Reviewed, New-replaced)

Discussion

This recommendation includes six forms of complementary and integrative health (CIH) interventions: acupuncture, massage, light touch, meditation, tai chi, and yoga. There was insufficient evidence to recommend for or against the use of these CIH interventions for the treatment of OA of the hip or knee.

Acupuncture

Acupuncture is a treatment modality described from ancient texts through the modern medical era as potentially having pain reduction effects and resulting in some functional improvements. Many practitioners perform acupuncture, ranging from traditional acupuncturists to medical physician acupuncturists. The methods by which acupuncture is studied is highly variable, which creates a body of evidence that is challenging to analyze in a systematic fashion.

Fire needle (a specific technique of acupuncture using super-heated needles) and electro-acupuncture may improve pain and function in patients with OA of the knee. A network meta-analysis by Li et al. (2018) found the fire needle and electro-acupuncture techniques produced statistically significant improvements in pain and function measures, while warm needle technique (applying a mild heat source to needle handle after it is in place in the acupuncture point) did not demonstrate similar improvement.[\[174\]](#) In a meta-analysis of individual patient data, Vickers et al. (2018) concluded acupuncture has a clinically-relevant, persistent effect on chronic pain, but these conclusions are tempered by the fact that the acupuncture studies in patients with OA made up less than a third of the 39 studies and patients included in the overall meta-analysis.[\[175\]](#) Neither Vickers et al. (2018) nor Li et al. (2018) assessed adverse events related to acupuncture.[\[174,175\]](#)

An SR by Manheimer et al. (2018) found acupuncture has little to no effect in reducing pain or improving function in patients with OA of the hip.[\[176\]](#) Manheimer et al. (2018) was the only SR that specifically considered acupuncture in the treatment of OA of the hip and found only minor possible side effects of acupuncture treatment.[\[176\]](#)

Patient preferences likely vary because based on preferences regarding the use of needles. Likewise, providers' preferences may differ on whether to recommend or deliver acupuncture. Also, patients may experience the burden of multiple visits or out-of-pocket costs associated with acupuncture.

Massage and Light Touch

Massage was considered in this CPG primarily as that performed by massage therapists practicing Swedish massage technique. Many techniques can be encompassed in this category of intervention, but Swedish versus a “light touch” method was reviewed to determine the strength of evidence on which to base our recommendation.

In an RCT by Perlman et al. (2019), Swedish massage improved WOMAC global scores (pain and function) of patients with knee OA compared to light touch and usual care.[\[177\]](#) The findings are tempered by the relatively small sample size (n=200) and patient population limitations. Enrolled individuals were 80% female and 85% white, which may limit generalizability. In this limited study, massage had a very low risk of harm and a potential short-term benefit of pain relief. The favorable effect was seen at eight weeks in the massage group compared to light touch and usual care and was sustained but not increased between eight and 52 weeks with continued weekly sessions. Providers and patients may consider massage as a short-term symptom control modality and, if individual patient financial resources permit, patients who undergo weekly treatments may experience a long-term benefit.

The availability of this treatment modality may vary by location. This treatment may also pose financial challenges to patients since the massage treatments generally are not covered by insurers.

Meditation

The only literature on meditation was an RCT by Kuntz et al. (2018) (see the [Yoga](#) section).[\[178\]](#) In this RCT, meditation was evaluated as a control.

Tai Chi

Tai chi is a common name for a spectrum of traditional movement and exercise practices that have been associated with improved pain and function in some patient populations. Zhu et al. (2016) and Lu et al. (2017) each studied a small group of older women in China and found Tai Ji Quan sessions (tai chi practice) three times per week for 24 weeks improved pain, function, sleep, and quality of life compared to an educational control (biweekly wellness education classes).[\[179,180\]](#) Another RCT by Wang et al. (2016) found a tai chi program for 12 weeks produced similar improvement to a standard knee OA physical therapy program (i.e., six weeks of weekly sessions in a physical therapy clinic, then six weeks of a self-directed home program).[\[181\]](#) Both interventions showed improvements in pain and function scores. No serious adverse outcomes occurred in the tai chi arm. In an SR by Hall et al. (2017), tai chi intervention groups demonstrated improvements in pain and disability measures over control (no treatment) groups (SMD: -0.66).[\[182\]](#)

Yoga

Yoga exercises broadly encompass a spectrum of physical exercises traditionally practiced with a meditation component. There are various subsets of yoga practice methods and, thus, wide variability in which methods are studied and how they are studied. This creates a body of evidence that is challenging to analyze in a systematic fashion.

An RCT by Kuntz et al. (2018) (n=31) comparing yoga to traditional exercise to control (non-exercise meditation) showed no adverse outcomes and demonstrated clinically important differences in pain and

self-reported function between control and both the yoga and traditional exercise groups.[178] Also, an RCT by Cheung et al. (2017) (n=83) found that Hatha Yoga (defined as the physical form of yoga) versus low impact aerobics and strengthening exercises versus control (education only) improved scores on a functional index and pain scale over eight weeks of the intervention and follow-up.[183] Another RCT by Park et al. (2017) (n=112) evaluated the specific “Sit N Fit Chair Yoga” program over eight weeks.[184] Individuals in the intervention group had statistically significant improvements in pain, function, and fatigue, compared to the control group (home exercise program) at three months follow-up.

Summary

As this is a *Reviewed, New-replaced* recommendation, the Work Group systematically reviewed evidence related to this recommendation.[174-184] The Work Group’s confidence in the quality of evidence was very low. The body of evidence had limitations, including overall small effect sizes, small sample sizes, and short duration of the studies. Other limitations include the wide variety of available methods or types of acupuncture, tai chi, and yoga. However, low risk of adverse events makes these modalities reasonable for treating pain if a patient chooses to pursue these programs. Thus, the benefits slightly outweighed the harms. The Work Group also considered the potential financial challenges to patients since medical plans may not cover trained instructors or these interventions. The availability of these treatment modalities may also vary by geographic locale. Thus, the Work Group decided upon a “Neither for nor against” recommendation.

Recommendation

19. There is insufficient evidence to recommend for or against the use of transcutaneous electrical nerve stimulation for the treatment of pain in osteoarthritis of the knee.

(Neither for nor against | Reviewed, New-added)

Discussion

An SR by Chen et al. (2016) found that TENS use in OA of the knee had a statistically significant but not clinically meaningful difference in pain compared to control.[185] Chen et al. (2016) noted that for small studies, the largest effects of TENS occurred at a two-week follow-up, while larger studies indicated no difference between TENS and control, especially in long-term follow-up.[185] The included studies also failed to show any improvement in range of motion or timed up-and-go test compared to control. Included RCTs had small sample sizes with considerable heterogeneity and inconsistencies in their findings, which makes it difficult to reach definitive conclusions.

Cherian et al. (2015) compared 40 patients with TENS to a control standard group and found statistically significant improvement in pain (VAS) at three months but no significant difference in functional measures between groups.[186] An RCT by Inal et al. (2015) compared sham, high-frequency TENS, and low-frequency TENS for patients with knee OA.[187] Inal et al. (2015) found similar reductions in pain at rest and pain with movement but no differences between groups at two or six weeks. Cherian et al. (2016) found, among 30 patients randomized into a TENS group and a control group, the improvement in the timed up-and-go test, timed stair-climb test, and 20-time step test at three months favored the TENS group.[188] However, there was no significant difference between groups for pain (VAS) at three months. Another RCT by Cherian et al. (2016) compared standard care and TENS for OA of the knee and found no difference in pain (VAS) or functional outcomes measured at one year.[189] All four RCTs were small and

had significant study limitations including limited description of randomization methods, allocation concealment, and blinding of outcome assessors.

Concerning harms, Chen et al. (2016) found no significant difference in all-cause discontinuation of TENS compared to control.[\[185\]](#) The uncommon, mild potential harms of TENS included increased pain, skin breakdown, redness, and skin irritation.[\[186,189\]](#) The benefits of TENS appear to be small, short-term effects, which are unlikely to be clinically significant. Within the SR by Chen et al. (2016), there was insufficient evidence to demonstrate clear effectiveness of a particular type of TENS application or stimulation frequency in comparison to interferential stimulation.[\[185\]](#) The systematic evidence review also did not yield any evidence examining the use of TENS for hip OA.

The Work Group also considered patient preferences, feasibility, and subgroup considerations. Patients with comorbidities may not be able to participate in an exercise program. This intervention may benefit these patients if other non-surgical treatments are not feasible. The focus group noted that patients view exercise programs, including physical therapy, as helpful, but pain can impede successful adherence to an exercise program. Transcutaneous electrical nerve stimulation may offer short-term pain relief. In patients who had prior success with using TENS therapy for pain relief, a provider could consider TENS as an adjunct therapy for short-term pain relief.

The systematic evidence review specifically searched but was unable to find studies meeting the inclusion criteria for other types of specialty electrotherapeutic devices (e.g., H-Wave, Alpha-Stim, Biowave). Considering the resource use and lack of clear effectiveness demonstrated for these devices, there is a lack of evidence to recommend these devices over TENS for use in clinical practice in knee or hip OA.

As this is a *Reviewed, New-added* recommendation, the Work Group systematically reviewed evidence related to this recommendation.[\[185-189\]](#) The Work Group's confidence in the quality of evidence was very low. There were significant limitations in the evidence given the heterogeneity of methods, application of devices, size of the studies, risk of bias, and inconsistent results on pain and function. The benefits of TENS for OA of the knee slightly outweighed the harms. Patient preferences and subgroup considerations also impacted this recommendation. Thus, the Work Group decided upon a "Neither for nor against" recommendation.

Future research should evaluate whether patients with comorbidities that prevent participation in an exercise program would benefit from the use of TENS or other electrotherapeutic devices for pain relief.

VII. Research Priorities

During the development of the 2020 VA/DoD OA CPG, the Work Group identified numerous areas for future research, including areas requiring stronger evidence to support current recommendations as well as research exploring new areas to guide future CPGs.

A. Long-term Studies and Comparative Effectiveness Research

- Osteoarthritis is a chronic condition; therefore, studies of a longer duration (>12 weeks) should be conducted to determine long-term effectiveness and safety.
- There is a paucity of research on the comparative effectiveness of different treatment options for OA of the knee and hip. Additional studies are needed to examine the comparative effectiveness of pharmacologic and non-pharmacologic options.

B. Evidence to Support the Safe and Effective Use of Orthobiologic Therapies and Other Emerging Biologic Treatments for Osteoarthritis

- Researchers indicate that clinical trials are necessary to standardize the optimal concentration or tissue, injection timing, and frequency and processing procedure for PRP and stem cell therapies in OA. Once standardized methods for preparing and administering these therapies have been determined, RCTs evaluating the effectiveness, safety, and comparative effectiveness of orthobiologic therapies (e.g., PRP, stem cells, amniotic fluid/tissue) to existing treatments for reducing pain and improving function in OA are needed.
- Additionally, trials designed to determine whether orthobiologics may have regenerative effects in OA are needed.

C. Physical Therapy

- While physical therapy is a safe and effective intervention for patients with hip and knee OA, research is needed on the long-term effectiveness and impact on healthcare cost and utilization related to physical therapy in the treatment of this patient population.
- Additional research is recommended to help determine when the optimal timing for the delivery of physical therapy services would be within the disease progression of hip and knee OA.
- Manual physical therapy interventions appear to have benefit for knee OA patients, but have had mixed results in studies on hip OA. Future high quality trials are recommended to elucidate the effects of manual physical therapy interventions in targeted subgroups of patients with hip OA.
- Further studies are also recommended on how to more effectively engage patients in physical therapy interventions. Given changes in demand and healthcare utilization, studies comparing alternate modes of treatment delivery for physical therapy should be performed comparing telemedicine, internet-based, group, and in-person treatment for both utilization and treatment effectiveness.

D. Exercise

- Exercise is a key component of a self-management program for the management of OA of the hip and/or knee. Further research is needed on the comparative effectiveness of different exercise interventions. Specific areas of focus should include non-weight-bearing strength exercises, weight-bearing strength exercises, and aerobic exercise.
- Considerable heterogeneity in exercise parameters exists across trials and future research should aim to control for loading and other dosing parameters when comparing exercise regimes.

E. Complementary and Integrative Health Interventions to Reduce Reliance on Pharmacologic Treatments

- Further research is needed on the effectiveness of CIH for the management of knee and/or hip OA. Questions regarding the timing of interventions and whether combination therapies work better than in isolation also persist. Also, where CIH treatments fit into current management paradigms for OA of the knee and hip is not clear. Lastly, the cost-effectiveness of CIH therapies in comparison to standard medical treatments is unknown and needs further research.

F. Dietary Supplements and Nutraceuticals in Osteoarthritis

- The use of OTC dietary supplements and nutraceuticals is common among patients with OA. Further research is needed to determine the dose, dose frequency, effectiveness, and safety of supplements. There is also a need for more robust, large-scale, non-industry funded studies to improve the quality of evidence.

G. Non-surgical Interventions for the Management of Hip Osteoarthritis

- Overall, limited studies address the treatment of hip OA. Future studies should focus specifically on the management of hip OA to better inform clinical decision making.

Appendix A: Evidence Review Methodology

A. Developing the Key Questions

The CPG Champions, along with the Work Group, were tasked with identifying KQs to guide the systematic evidence review on the non-surgical management of hip and knee OA. These questions, which were developed in consultation with the Lewin Team, addressed clinical topics of the highest priority for the VA and DoD populations. The KQs follow the population, intervention, comparison, outcome, timing, and setting (PICOTS) framework for evidence questions, as established by the Agency for Healthcare Research and Quality (AHRQ). [Table A-1](#) provides a brief overview of the PICOTS typology.

Table A-1. PICOTS [190]

PICOTS Elements	Description
Patients, Population, or Problem	Describes the patients of interest. It includes the condition(s), populations or sub-populations, disease severity or stage, co-occurring conditions, and other patient characteristics or demographics.
Intervention or Exposure	Refers to the specific treatments or approaches used with the patient or population. It includes doses, frequency, methods of administering treatments, etc.
Comparison	Describes the interventions or care that is being compared with the intervention(s) of interest described above. It includes alternatives such as placebo, drugs, surgery, lifestyle changes, standard of care, etc.
Outcome	Describes the specific results of interest. Outcomes can include short, intermediate, and long-term outcomes, or specific results such as quality of life, complications, mortality, morbidity, etc.
Timing, if applicable	Describes the duration of time that is of interest for the particular patient intervention and outcome, benefit, or harm to occur (or not occur).
Setting, if applicable	Describes the setting or context of interest. Setting can be a location (such as primary, specialty, or inpatient care).

The Champions, Work Group, and evidence review team carried out several iterations of this process, each time narrowing the CPG’s scope and literature review by prioritizing topics of interest. As a result of resource constraints, all developed KQs were not able to be included in the systematic evidence review. Thus, the Champions and Work Group determined which questions were of highest priority and those were included in the review. [Table A-2](#) contains the final set of KQs used to guide this CPG’s systematic evidence review.

Once the KQs were finalized, the Work Group prioritized the outcomes they had defined for each KQ based on how important the Work Group judged each outcome to be. Ranking outcomes by their relative importance can help focus attention on those outcomes that are considered most important for clinical decision making when making judgments regarding the overall quality of the evidence to support a recommendation.^[191]

Using GRADE methodology, the Work Group rated each outcome on a 1 – 9 scale (7 – 9, critical for decision making; 4 – 6, important, but not critical, for decision making; and 1 – 3, of limited importance for decision making). Critical and important outcomes were included in the evidence review (see [Outcomes](#)); however, only critical outcomes were used to determine the overall quality of evidence (see [Grading Recommendations](#)).

a. Population(s)

- Key Questions 1 – 12: Adults (≥ 18 years of age) with OA of the hip and/or knee
- Key Question 10: Patients with a body mass index (BMI) >25 kilograms (kg)/square meter (m^2)
- Key Questions 11 – 12: Adults with signs or symptoms of OA of the hip and/or knee

b. Interventions

- Key Question 1 – Alone or in combination:
 - ◆ COX-2 versus non-selective NSAIDs
 - ◆ Acetaminophen
 - ◆ Duloxetine
- Key Question 2:
 - ◆ Intra-articular
 - CS
 - CS/anesthetic combinations
 - Long-acting CS (e.g., ZILRETTA®)
 - Hyaluronate/hylan/hyaluronic acid
 - ◆ Viscosupplementation
- Key Question 3:
 - ◆ Stem cells
 - ◆ PRP or other orthobiologics (e.g., amniotic fluid, amniotic membrane); Lipogems (liposuction and injection near the knee for OA of the knee)
 - ◆ Dextrose prolotherapy
 - ◆ Exosome therapy
- Key Question 4 – Topical agents:
 - ◆ Diclofenac gel
 - ◆ Capsaicin
 - ◆ Methyl salicylate/menthol cream (Biofreeze); trolamine salicylate
 - ◆ Lidocaine ointment or patch
- Key Question 5:
 - ◆ Tramadol
 - ◆ Non-tramadol opioids (e.g., immediate-release morphine, tapentadol, codeine, hydrocodone)
 - ◆ Opioids in combination with NSAIDs, acetaminophen, duloxetine

- Key Question 6:
 - ◆ Curcumin-free turmeric
 - ◆ Glucosamine
 - ◆ Chondroitin
 - ◆ Omega-3 fatty acids
 - ◆ Vitamins D and E
 - ◆ Collagen
 - ◆ Willow bark extract
 - ◆ MSM
 - ◆ Avocado and soybean extract
 - ◆ Boswellia serrata
 - ◆ Pycnogenol
 - ◆ Rosehip
 - ◆ Cannabidiol oil
 - ◆ Traditional Chinese medication
- Key Question 7:
 - ◆ Acupuncture
 - ◆ Manual therapy
 - ◆ Massage
 - ◆ Tai chi
 - ◆ Mindfulness
 - ◆ Meditation
 - ◆ Yoga
 - ◆ Chiropractic
- Key Question 8:
 - ◆ Weight-bearing radiographs
- Key Question 9:
 - ◆ TENS
 - ◆ H Wave
 - ◆ BioWave
 - ◆ Alpha-stim

- Key Question 10:
 - ◆ Diet therapy
 - ◆ Exercise
 - ◆ Diet and exercise
- Key Question 11:
 - ◆ Physical therapy, generally
 - ◆ Non-impact activity (e.g., aquatic physical therapy, cycling)
- Key Question 12 – Self-management strategies:
 - ◆ Activity guidelines
 - ◆ Self-directed exercise
 - ◆ Braces
 - ◆ Walking aids
 - ◆ Taping
 - ◆ Thermal modalities
 - ◆ Better Choices, Better Health

c. Comparators

- Key Question 1:
 - ◆ Placebo
 - ◆ Different drug
- Key Question 2:
 - ◆ CS to placebo or sham injection
 - ◆ Hyaluronic acid/hylan/hyaluronate to placebo or sham injection
 - ◆ CSI to hyaluronic acid/hylan/hyaluronate injection
 - ◆ Preoperative intra-articular injection or joint injection or hip or knee injection versus no injection
- Key Question 3:
 - ◆ Treatment as usual
 - ◆ CS/other injectables
 - ◆ Placebo/sham
- Key Question 4:
 - ◆ Oral pharmacotherapy
 - ◆ COX-2 versus non-selective NSAIDs

- ◆ Acetaminophen
- ◆ Duloxetine
- Key Question 5:
 - ◆ Placebo
 - ◆ NSAIDs
 - ◆ Acetaminophen
 - ◆ Duloxetine
 - ◆ Diclofenac gel
 - ◆ Capsaicin
 - ◆ Methyl salicylate/menthol cream (Biofreeze)
 - ◆ Lidocaine ointment or patch
- Key Question 6:
 - ◆ Alone or in combination with other dietary supplements and pharmacotherapy
 - ◆ Placebo
- Key Question 7:
 - ◆ Standard of care (do not compare to medications, nor placebo)
 - ◆ Combination therapy
- Key Question 8:
 - ◆ Non-weight-bearing radiographs of the knee or supine x-rays of the hip
 - ◆ MRI
- Key Question 9:
 - ◆ NSAIDs versus other pain modalities
- Key Question 10:
 - ◆ Healthy lifestyle (control)
 - ◆ No intervention
 - ◆ Exercise
- Key Question 11:
 - ◆ Manual versus non-impact physical therapy (e.g., manual, aquatic, gait training)
 - ◆ Timing
 - ◆ Modalities of delivery
 - ◆ Dose/intensity of physical therapy
- Key Question 12:
 - ◆ Usual care

d. Outcomes

- Key Questions 1, 4, 5, 7, 9 – 11:
 - ◆ Critical outcomes
 - Pain
 - Safety
 - ◆ Important outcomes
 - Function
 - Quality of life
- Key Question 2:
 - ◆ Critical outcomes
 - Pain
 - Safety
 - ◆ Important outcomes
 - Function
 - Quality of life
 - Radiographic change
- Key Question 3:
 - ◆ Critical outcomes
 - Pain
 - Function
 - Safety
 - ◆ Important outcomes
 - Quality of life
 - Radiographic change
- Key Question 6:
 - ◆ Critical outcomes
 - Pain
 - Safety
 - ◆ Important outcomes
 - Function
 - Quality of life
 - No worsening labs (all adverse outcomes)

- Key Question 8:
 - ◆ Critical outcomes
 - Accuracy of diagnosis
 - Assessment of severity of arthritis in the affected hip/knee(s)
- Key Question 12:
 - ◆ Critical outcomes
 - Safety
 - ◆ Important outcomes
 - Activity level (e.g., pedometer)
 - Function
 - Quality of life
 - Pain

e. Timing

- Key Questions 1, 2, 4 – 6, 10: no minimum follow-up
- Key Question 3: minimum follow-up three months (prolotherapy), four months (PRP/stem cell therapy)
- Key Questions 7, 9: minimum follow-up one month
- Key Question 8: at the time of consultation with the surgeon
- Key Questions 11, 12: minimum follow-up three months

f. Setting

- Key Questions 1 – 12: Outpatient primary care
- Key Question 9: Inpatient setting

B. Conducting the Systematic Evidence Review

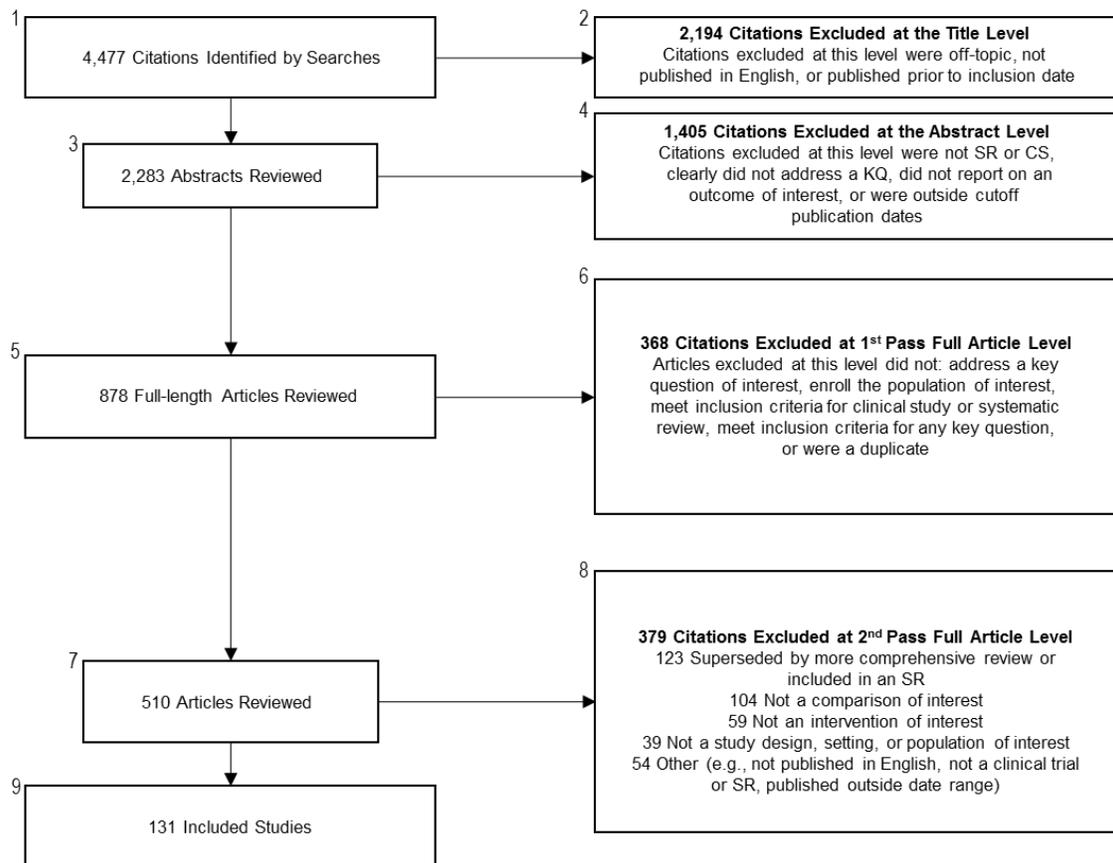
Based on the Work Group’s decisions regarding the scope, the KQs, and the PICOTS statements, the Lewin Team produced a systematic evidence review protocol before conducting the review. The protocol was reviewed and approved by the Champions and Work Group members. The protocol described in detail the final set of KQs, the methodology to be used during the systematic evidence review process, and the inclusion/exclusion criteria to be applied to each potential study, including study type, sample size, and PICOTS criteria.

Extensive literature searches identified 4,477 citations potentially addressing the KQs of interest to this evidence review. Of those, 2,194 were excluded upon title review for clearly not meeting inclusion criteria (e.g., not pertinent to the topic, not published in English, published prior to study inclusion publication date, or not a full-length article). Overall, 2,283 abstracts were reviewed with 1,405 of those being

excluded for the following reasons: not an SR or accepted study design (see the [General Criteria for Inclusion in Systematic Review](#) and [Key Question Specific Criteria](#)), did not address a KQ of interest to this review, did not report on an outcome of interest, or published outside cutoff publication dates. A total of 878 full-length articles were reviewed. Of those, 368 were excluded at a first pass review for the following reasons: not addressing a KQ of interest, not enrolling the population of interest, not meeting inclusion criteria for study design, not meeting inclusion criteria for any KQ, or being a duplicate. A total of 510 full-length articles were thought to address one or more KQs and were further reviewed. Of these, 379 were ultimately excluded. Reasons for their exclusion are presented in [Figure A-1](#) Study Flow Diagram below.

Overall, 131 studies addressed one or more of the KQs and were considered as evidence in this review. [Table A-2](#) indicates the number of studies that addressed each of the questions.

Figure A-1. Study Flow Diagram



Abbreviations: CS: clinical study; KQ: key question; SR: systematic review

Alternative Text Description of Study Flow Diagram

[Figure A-1](#) Study Flow Diagram is a flow chart with nine labeled boxes linked by arrows that describe the literature review inclusion/exclusion process. Arrows point down to boxes that describe the next literature review step and arrows point right to boxes that describe the excluded citations at each step (including the reasons for exclusion and the numbers of excluded citations).

1. Box 1: 4,477 citations identified by searches
 - a. Right to Box 2: 2,194 citations excluded at the title level
 - i. Citations excluded at this level were off-topic, not published in English, or published prior to inclusion date
 - b. Down to Box 3
2. Box 3: 2,283 abstracts reviewed
 - a. Right to Box 4: 1,405 citations excluded at the abstract level
 - i. Citations excluded at this level were not an SR or clinical study, clearly did not address a KQ, did not report on an outcome of interest, or were outside cutoff publication dates
 - b. Down to Box 5
3. Box 5: 878 full-length articles reviewed
 - a. Right to Box 6: 368 citations excluded at 1st pass full article level
 - i. Articles excluded at this level did not: address a key question of interest, enroll the population of interest, meet inclusion criteria for clinical study or SR, meet inclusion criteria for any key question, or were a duplicate
 - b. Down to Box 7
4. Box 7: 510 articles reviewed
 - a. Right to Box 8: 379 citations excluded at 2nd pass KQ level
 - i. 123 superseded by more comprehensive review or included in an SR
 - ii. 104 not a comparison of interest
 - iii. 59 not an intervention of interest
 - iv. 39 not a study design, setting, or population of interest
 - v. 54 other (e.g., not published in English, not a clinical trial or SR, published outside date range)
 - b. Down to Box 9
5. Box 9: 131 included studies

Table A-2. Evidence Base for KQs

Question Number	Question	Number of Studies & Type of Studies
1	What are the benefits and harms of FDA approved oral pharmacotherapy for treatment of OA of the hip and knee?	7 SRs and 2 RCTs
2	What are the benefits and harms and comparative effectiveness of FDA approved intra-articular injections of pharmacotherapy agents for treatment of moderate – severe OA of the hip and knee?	7 SRs and 8 RCTs
3	What are the benefits and harms of intra-articular orthobiologics regenerative medicine [stem cell injections or others (e.g., Platelet-rich plasma, amniotic fluid, amniotic membrane)] for treatment of OA of the hip and knee?	4 SRs and 25 RCTs
4	What are the comparative benefits and harms of topical pharmacotherapy agents versus oral pharmacotherapy for treatment of OA of the hip and knee?	6 SRs
5	What are the benefits and harms of tramadol and other opioids as an alternative to or adjunct to non-opioid pharmacotherapies for managing moderately severe to severe OA of the hip and knee?	3 SRs and 3 RCTs
6	What are the benefits and harms of dietary supplements and nutraceuticals for treatment of OA of the hip and knee?	9 SRs and 8 RCTs
7	What are the benefits and harms of CIH treatments of OA of the hip and knee as either monotherapy or adjunctive therapy?	6 SRs and 9 RCTs
8	What diagnostic testing is needed to confirm the diagnosis of OA?	2 diagnostic cohort studies
9	What are the benefits and harms of electrostimulation devices on hip and knee OA?	1 SR and 4 RCTs
10	What are the benefits and harms of weight loss on short-term and long-term complications and outcomes of hip and knee OA?	2 SRs and 2 RCTs
11	What is the comparative effectiveness of physical therapy for OA of the hip and knee?	3 SRs and 13 RCTs
12	What are the benefits and harms of various self-management interventions for OA of the hip and knee?	6 SRs and 1 RCT
Total Evidence Base		131 studies

Abbreviations: CIH: complementary and integrative health; FDA: Food and Drug Administration; OA: osteoarthritis; RCT: randomized controlled trial; SR: systematic review

a. General Criteria for Inclusion in Systematic Review

- Clinical studies or SRs published on or after December 1, 2012, to June 3, 2019. If multiple SRs addressed a KQ, we selected the most recent and/or comprehensive review. SRs were supplemented with clinical studies published after the SR.
- Studies must be published in English.
- Publication must have been a full clinical study or SR; abstracts alone were not included. Similarly, letters, editorials, and other publications that are not full-length clinical studies were not accepted as evidence.

- SRs must have searched MEDLINE or EMBASE for eligible publications, performed a risk of bias assessment of included studies, and assessed the quality of evidence using a recognizable rating system, such as GRADE or something compatible (e.g., the one used by the AHRQ Evidence-based Practice Centers). If an existing review did not assess the overall quality of the evidence, evidence from the review must be reported in a manner that allowed us to judge the overall risk of bias, consistency, directness, and precision of evidence. We did not use an existing review as evidence if we were not able to assess the overall quality of the evidence in the review.
- Studies assessed diagnostic testing or a pharmacologic or non-pharmacologic intervention for management of OA. Appropriate study designs are noted under [Key Question Specific Criteria](#).
- Study must have enrolled at least 20 patients (10 per study group) unless otherwise noted (see [Key Question Specific Criteria](#) below).
- Study must have enrolled at least 85% of patients who meet the study population criteria: adults aged 18 years or older with OA of the hip and/or knee.
- Study must have reported on at least one outcome of interest.

b. Key Question Specific Criteria

- For KQs 1 – 7, 9 – 12, SRs of RCTs and individual RCTs not included in SRs were required.
- For KQ 8, SRs of diagnostic cohort studies and individual diagnostic cohort studies not included in SRs were required.

Information regarding the bibliographic databases, date limits, and platform/provider can be found in [Table A-3](#) below. Additional information on the search strategies, including topic-specific search terms and search strategies, can be found in [Appendix I](#).

Table A-3. Bibliographic Database Information

	Name	Date Limits	Platform/Provider
Bibliographic Databases	Cochrane Database of Systematic Reviews (Cochrane Reviews)	December 1, 2012, to June 3, 2019	Wiley
	EMBASE (Excerpta Medica)	December 1, 2012, to June 3, 2019	Elsevier
	MEDLINE PreMEDLINE (National Library of Medicine)	December 1, 2012, to June 3, 2019	Elsevier
	PubMed (Inprocess, Publisher, and PubMedNotMedline records)	December 1, 2012, to June 3, 2019	National Library of Medicine
Grey Literature	Agency for Healthcare Research and Quality (AHRQ) website	December 1, 2012, to June 3, 2019	AHRQ

C. Convening the Face-to-face Meeting

In consultation with the COR, the Champions, and the Work Group, the Lewin Team convened a three- and one-half-day face-to-face meeting of the CPG Champions and Work Group members on October 22 – 25, 2019. These experts were gathered to develop and draft the clinical recommendations for an update to the 2014 VA/DoD OA CPG. Lewin presented findings from the systematic evidence review to facilitate and inform the process.

Under the direction of the Champions, the Work Group members were charged with interpreting the results of the systematic evidence review and were asked to categorize and carry forward recommendations from the 2014 VA/DoD OA CPG, modifying the recommendations as necessary. The members also developed new clinical practice recommendations not presented in the 2014 VA/DoD OA CPG based on the 2019 systematic evidence review. The subject matter experts were divided into three smaller subgroups at this meeting.

As the Work Group members drafted clinical practice recommendations, they also assigned a rating for each recommendation based on a modified GRADE and USPSTF methodology. Each recommendation was rated by assessing the quality of the overall evidence base, the associated benefits and harms, the variation in values and preferences, and other implications of the recommendation.

In addition to developing recommendations during the face-to-face meeting, the Work Group members also revised the 2014 VA/DoD OA CPG algorithm to reflect the new and amended recommendations. They discussed the available evidence as well as changes in clinical practice since 2014, as necessary, to update the algorithm.

D. Grading Recommendations

This CPG uses the GRADE methodology to assess the quality of the evidence base and assign a strength for each recommendation. The GRADE system uses the following four domains to assess the strength of each recommendation:[\[35\]](#)

- Balance of desirable and undesirable outcomes
- Confidence in the quality of the evidence
- Values and preferences
- Other implications, as appropriate, e.g.:
 - ◆ Resource use
 - ◆ Equity
 - ◆ Acceptability
 - ◆ Feasibility
 - ◆ Subgroup considerations

The following sections further describe each domain.

Balance of desirable and undesirable outcomes refers to the size of anticipated benefits (e.g., increased longevity, reduction in morbid event, resolution of symptoms, improved quality of life, decreased resource use) and harms (e.g., decreased longevity, immediate serious complications, adverse event, impaired quality of life, increased resource use, inconvenience/hassle) relative to each other. This domain is based on the understanding that most providers will offer patients therapeutic or preventive measures as long as the advantages of the intervention exceed the risks and adverse effects. The certainty or uncertainty of the provider about the risk-benefit balance will greatly influence the strength of the recommendation.

Some of the discussion questions that fall under this domain include:

- Given the best estimate of typical values and preferences, are you confident that the benefits outweigh the harms and burden or vice versa?
- Are the desirable anticipated effects large?
- Are the undesirable anticipated effects small?
- Are the desirable effects large relative to undesirable effects?

Confidence in the quality of the evidence reflects the quality of the evidence base and the certainty in that evidence. This second domain reflects the methodological quality of the studies for each outcome variable. In general, the strength of a recommendation follows the level of evidence, but not always, as other domains may increase or decrease the strength. The systematic evidence review for this CPG, which was conducted by ECRI, assessed the confidence in the quality of the evidence base using GRADE methodology and assigned a rating of “High,” “Moderate,” “Low,” or “Very Low.” The outcomes judged to be critical were used to determine the overall quality of evidence. Per GRADE, if the quality of evidence differs across the critical outcomes, the lowest quality of evidence for any of the relevant critical outcomes determines the overall quality of the evidence for a recommendation; the overall confidence cannot be higher than the lowest confidence in effect estimates for any outcome that is determined to be critical for clinical decision making.[\[191,192\]](#)

The elements that go into the confidence in the quality of the evidence include:

- Is there high- or moderate-quality evidence that answers this question?
- What is the overall certainty of this evidence?

Values and preferences is an overarching term that includes patients’ perspectives, beliefs, expectations, and goals for health and life. More precisely, it refers to the processes that individuals use in considering the potential benefits, harms, costs, limitations, and inconvenience of the therapeutic or preventive measures in relation to one another. For some, the term “values” has the closest connotation to these processes. For others, the connotation of “preferences” best captures the notion of choice. In general, values and preferences increase the strength of the recommendation when there is high concordance and decrease it when there is great variability. In a situation in which the balance of benefits and risks are uncertain, eliciting the values and preferences of patients and empowering them and their surrogates to make decisions consistent with their goals of care becomes even more important. A recommendation can be described as having “similar values”, “some variation”, or “large variation” in typical values and preferences between patients and the larger populations of interest.

Some of the discussion questions that fall under the purview of values and preferences include:

- Are you confident about the typical values and preferences and are they similar across the target population?
- What are the patient’s values and preferences?
- Are the assumed or identified relative values similar across the target population?

Other implications consider the practicality of the recommendation, including resource use, equity, acceptability, feasibility, and subgroup considerations. Resource use is related to the uncertainty around the cost-effectiveness of a therapeutic or preventive measure. For example, statin use in the frail elderly and others with multiple co-occurring conditions may not be effective and, depending on the societal benchmark for willingness to pay, may not be a good use of resources. Equity, acceptability, feasibility, and subgroup considerations require similar judgments around the practicality of the recommendation.

The framework below ([Table A-4](#)) was used by the Work Group to guide discussions on each domain.

Table A-4. GRADE Evidence to Recommendation Framework

Decision Domain	Questions to Consider	Judgment
Balance of desirable and undesirable outcomes	<ul style="list-style-type: none"> • Given the best estimate of typical values and preferences, are you confident that the benefits outweigh the harms and burden or vice versa? • Are the desirable anticipated effects large? • Are the undesirable anticipated effects small? • Are the desirable effects large relative to undesirable effects? 	<ul style="list-style-type: none"> • Benefits outweigh harms/burden • Benefits slightly outweigh harms/burden • Benefits and harms/burden are balanced • Harms/burden slightly outweigh benefits • Harms/burden outweigh benefits
Confidence in the quality of the evidence	<ul style="list-style-type: none"> • Is there high- or moderate-quality evidence that answers this question? • What is the overall certainty of this evidence? 	<ul style="list-style-type: none"> • High • Moderate • Low • Very low
Values and preferences	<ul style="list-style-type: none"> • Are you confident about the typical values and preferences and are they similar across the target population? • What are the patient’s values and preferences? • Are the assumed or identified relative values similar across the target population? 	<ul style="list-style-type: none"> • Similar values • Some variation • Large variation
Other implications (e.g., resource use, equity, acceptability, feasibility, subgroup considerations)	<ul style="list-style-type: none"> • Are the resources worth the expected net benefit from the recommendation? • What are the costs per resource unit? • Is this intervention generally available? • Is this intervention and its effects worth withdrawing or not allocating resources from other interventions? • Is there lots of variability in resource requirements across settings? 	<ul style="list-style-type: none"> • Various considerations

The strength of a recommendation is defined as the extent to which one can be confident that the desirable effects of an intervention outweigh its undesirable effects and is based on the framework above,

which combines the four domains.^[193] GRADE methodology does not allow for recommendations to be made based on expert opinion alone. While strong recommendations are usually based on high or moderate confidence in the estimates of effect (quality of the evidence) there may be instances where strong recommendations are warranted even when the quality of evidence is low.^[35] In these types of instances where the balance of desirable and undesirable outcomes and values and preferences played large roles in determining the strength of a recommendation, this is explained in the discussion section for the recommendation.

The GRADE of a recommendation is based on the following elements:

- Four decision domains used to determine the strength and direction (described above)
- Relative strength (Strong or Weak)
- Direction (For or Against)

The relative strength of the recommendation is based on a binary scale, “Strong” or “Weak.” A strong recommendation indicates that the Work Group is highly confident that desirable outcomes outweigh undesirable outcomes. If the Work Group is less confident in the balance between desirable and undesirable outcomes, they present a weak recommendation.

Similarly, a recommendation for a therapy or preventive measure indicates that the desirable consequences outweigh the undesirable consequences. A recommendation against a therapy or preventive measure indicates that the undesirable consequences outweigh the desirable consequences.

Occasionally, instances may occur when the Work Group feels there is insufficient evidence to make a recommendation for or against a particular therapy or preventive measure. This can occur when there is an absence of studies on a particular topic that met evidence review inclusion criteria, studies included in the evidence review report conflicting results, or studies included in the evidence review report inconclusive results regarding the desirable and undesirable outcomes.

Using these elements, the grade of each recommendation is presented as part of a continuum:

- Strong for (or “We recommend offering this option ...”)
- Weak for (or “We suggest offering this option ...”)
- No recommendation for or against (or “There is insufficient evidence ...”)
- Weak against (or “We suggest not offering this option ...”)
- Strong against (or “We recommend against offering this option ...”)

Note that weak (For or Against) recommendations may also be termed “Conditional”, “Discretionary”, or “Qualified.” Recommendations may be conditional based upon patient values and preferences, the resources available, or the setting in which the intervention will be implemented. Recommendations may be at the discretion of the patient and provider or they may be qualified with an explanation about the issues that would lead decisions to vary.

E. Recommendation Categorization

a. Recommendation Categories and Definitions

A set of recommendation categories was adapted from those used by NICE.[37,38] These categories, along with their corresponding definitions, were used to account for the various ways in which recommendations could have been updated from the 2014 VA/DoD OA CPG. The categories and definitions can be found in [Table A-5](#).

Table A-5. Recommendation Categories and Definitions*

Evidence Reviewed	Recommendation Category	Definition
Reviewed	New-added	New recommendation following review of the evidence
	New-replaced	Recommendation from the previous CPG that has been carried over to the updated CPG that has been changed following review of the evidence
	Not changed	Recommendation from the previous CPG that has been carried forward to the updated CPG where the evidence has been reviewed but the recommendation is not changed
	Amended	Recommendation from the previous CPG that has been carried forward to the updated CPG where the evidence has been reviewed and a minor amendment has been made
	Deleted	Recommendation from the previous CPG that has been removed based on review of the evidence
Not reviewed	Not changed	Recommendation from previous CPG that has been carried forward to the updated CPG, but for which the evidence has not been reviewed
	Amended	Recommendation from the previous CPG that has been carried forward to the updated CPG where the evidence has not been reviewed and a minor amendment has been made
	Deleted	Recommendation from the previous CPG that has been removed because it was deemed out of scope for the updated CPG

*Adapted from the NICE guideline manual (2012) [38] and Garcia et al. (2014) [37]

Abbreviation: CPG: clinical practice guideline

b. Categorizing Recommendations with an Updated Review of the Evidence

Recommendations were first categorized by whether or not they were based on an updated review of the evidence. If evidence had been reviewed, recommendations were categorized as “New-added,” “New-replaced,” “Not changed,” “Amended,” or “Deleted.”

“Reviewed, New-added” recommendations were original, new recommendations that were not in the 2014 VA/DoD OA CPG. “Reviewed, New-replaced” recommendations were in the previous version of the guideline but were modified to align with the updated review of the evidence. These recommendations could have also included clinically significant changes to the previous version. Recommendations categorized as “Reviewed, Not changed” were carried forward from the previous version of the CPG unchanged.

To maintain consistency between 2014 recommendations, which were developed using the USPSTF methodology, and 2020 recommendations, which were developed using the GRADE methodology, it was necessary to modify the 2014 recommendations to include verbiage to signify the strength of the

recommendation (e.g., “We recommend,” “We suggest”). Because the 2014 recommendations inherently needed to be modified at least slightly to include this language, the “Not changed” category was not used. For recommendations carried forward to the updated CPG with a review of the evidence and slightly modified wording, the “Reviewed, Amended” recommendation category was used. This allowed for the wording of the recommendation to reflect GRADE methodology as well as for any other non-substantive (i.e., not clinically meaningful) language changes deemed necessary. The evidence used to support these recommendations was carried forward from the previous version of the CPG and/or was identified in the evidence review for the update.

Recommendations could have also been designated “Reviewed, Deleted.” These were recommendations from the previous version of the CPG that were not brought forward to the updated guideline after review of the evidence. This occurred if the evidence supporting the recommendations was out of date, to the extent that there was no longer any basis to recommend a particular course of care and/or new evidence suggests a shift in care, rendering recommendations in the previous version of the guideline obsolete.

c. Categorizing Recommendations without an Updated Review of the Evidence

There were also cases in which it was necessary to carry forward recommendations from the previous version of the CPG without an updated SR of the evidence. Because of time and budget constraints, the update of the OA CPG could not review all available evidence on the management of OA but instead focused its KQs on areas of new or updated scientific research or areas that were not previously covered in the CPG.

For areas of research that have not changed, and for which recommendations made in the previous version of the guideline were still relevant, recommendations could have been carried forward to the updated guideline without an updated SR of the evidence. The support for these recommendations in the updated CPG was thus also carried forward from the previous version of the CPG. These recommendations were categorized as “Not reviewed.” If evidence had not been reviewed, recommendations could have been categorized as “Not changed,” “Amended,” or “Deleted.”

“Not reviewed, Not changed” recommendations refer to recommendations from the previous version of the OA CPG that were carried forward unchanged to the updated version. The category of “Not reviewed, Amended” was used to designate recommendations which were modified from the 2014 VA/DoD OA CPG with the updated GRADE language, as explained above.

Recommendations could also have been categorized as “Not reviewed, Deleted” if they were determined to be out of scope. A recommendation was out of scope if it pertained to a topic (e.g., population, care setting, treatment, and condition) outside of the scope for the updated CPG as defined by the Work Group.

The categories for the recommendations included in the 2020 version of the guideline are noted in the [Recommendations](#). The categories for the recommendations from the 2014 VA/DoD OA CPG are noted in [Appendix D](#).

F. Drafting and Submitting the Final Clinical Practice Guideline

Following the face-to-face meeting, the Champions and Work Group members were given writing assignments to craft discussion sections to support each of the new recommendations and/or to update discussion sections from the 2014 VA/DoD OA CPG to support the amended “carried forward” recommendations. The Work Group also considered tables, appendices, and other sections from the 2014 VA/DoD OA CPG for inclusion in the update. During this time, the Champions and Work Group also made additional revisions to the algorithm, as necessary.

After developing the initial draft of the updated CPG, an iterative review process was used to solicit feedback on and make revisions to the CPG. Once they were developed, the first two drafts of the CPG were posted on a wiki website for a period of 14 – 20 business days for internal review and comment by the Work Group. All feedback submitted during each review period was reviewed and discussed by the Work Group and appropriate revisions were made to the CPG.

Draft 3 of the CPG was made available for outside peer review and comment. This process is described in the section titled [Peer Review Process](#). Organizations outside of the VA or DoD that the Work Group designated to participate in the peer review and that provided feedback included:

- Johns Hopkins University
- American Medical Society for Sports Medicine (AMSSM)
- OrthoKansas LMH Health
- Operation Supplement Safety
- University of Utah Department of Orthopaedics
- University of North Carolina Department of Medicine

The Work Group notes that peer review by the organizations listed above does not indicate approval or endorsement of this CPG.

After revisions were made based on the feedback received during the peer review and comment period, the Champions presented the CPG to the EBPWG for their approval. Changes were made based on feedback from the EBPWG and the guideline was finalized.

The Work Group also produced a set of guideline toolkit materials which included a provider summary, pocket card, and patient summary. The final 2020 OA CPG was submitted to the EBPWG in July 2020.

Appendix B: Patient Focus Group Methods and Findings

A. Methods

As part of the effort to update this CPG, the VA and DoD Leadership held a patient focus group on April 17, 2019, at the Audie L. Murphy Memorial VA Hospital in San Antonio, TX. The focus group aimed to further understand and incorporate the perspective of patients with OA and who are covered and/or receiving their care through the VA and/or DoD healthcare systems, as these patients are most affected by the recommendations put forth in the CPG. The focus group elicited the perspective of patients that receive treatment for OA within the VA and/or DoD healthcare systems, on topics related to the management of OA in the VA and DoD healthcare systems, their treatment plan history, care delivery setting, medications and treatment, non-pharmacologic therapies, and the impact of therapy.

VA and DoD Leadership and the OA CPG Champions recruited participants for the focus group along with assistance from local providers at the patient focus group site. There were four focus group participants. Patient focus group participants were not designed to be a representative sample of VA and DoD patients. However, recruitment focused on eliciting a range of perspectives likely to be relevant and informative in the guideline development process. Patients were not incentivized for their participation or reimbursed for travel expenses.

The OA CPG Champions and Work Group, with support from Lewin, developed a set of questions to help guide the focus group. The focus group facilitator led the discussion using the previously prepared questions as a general guide to elicit the most important information from the patients regarding their experiences and views about their treatment and overall care. Given the limited time and the range of interests of the focus group participants, not all of the listed questions were addressed.

B. Patient Focus Group Findings

a. Participants stressed the importance of individualized care and being treated with dignity.

- Two participants had early-onset symptoms or diagnosis. Two participants were diagnosed while still active duty.
- Participants with early-onset OA noted that providers sometimes did not treat them with respect because they were “too young” for OA. They felt their OA was stigmatized or not treated seriously.
- Participants’ reactions upon learning about their OA varied. One participant thought their knee pain was a result of natural aging, while others expected it because of the nature of their military duties.
- Two participants felt their military service caused or accelerated OA.

b. Participants’ experience with and preferences for treatment varied. However, all expressed a preference for physical therapy and tried to avoid injections and pharmacotherapy.

- All participants had tried a variety of treatments for pain relief, including pharmacotherapy, physical therapy, injections, topical medications, TENS, and CIH interventions.

- Participants sometimes viewed treatments as a trial and error process and would generally use a treatment until it stopped being effective.
- Two participants felt that while they were active duty, providers gave them OTC pain medications, such as ibuprofen 800 mg, too often. This caused side effects.
- Three participants had been prescribed opioids, but all hoped to avoid opioids and did not support their chronic use.
- In terms of treatment preferences, all participants preferred physical therapy and generally disliked receiving injections and using walking aids.

c. Osteoarthritis has impacted the quality of life of all participants – both physically and mentally – and significantly impacted their life decisions.

- All participants indicated they try to stay active – pain permitting – and all enjoy water exercise. Also, all participants shared the long-term goal of remaining active and performing basic life functions.
- All participants reported that OA prevents them from doing activities they enjoy.
- All participants experienced insomnia because of pain. Providers should recognize this effect of OA and provide treatment for sleep problems.
- Participants reported embarrassment or regret because OA has prevented them from performing basic life functions. Also, they felt their youth and the invisible nature of joint pain contributes to the stigma.

d. Participants reported moderate exposure to, and understanding of, complementary and integrative health.

- All participants have tried one or more forms of CIH interventions (e.g., massage, yoga, meditation) and some have considered trying other forms.
- Two participants were not aware of the VA's full range of CIH offerings and see private providers for CIH interventions.
- Three participants had tried supplements or nutraceuticals but reported limited to no benefits.
- Two participants have heard that cannabidiol oil and marijuana are useful in managing pain and wanted to understand whether it is a safe and effective treatment for OA.

e. Participants stressed the importance of access to care. While preferences for in-person or virtual healthcare varied, participants stressed the importance of receiving care in convenient settings.

- Three participants preferred the option of having virtual care/communication with providers (e.g., telehealth, telephone care, physical therapy with home exercises, secure messaging).
- Participants reported care is sometimes inaccessible based on lack of personal time, distance to providers, or appointment wait times.
- All participants enjoyed at-home physical therapy, particularly after having in-person training and receiving take-home sheets explaining recommended exercises.

Appendix C: Evidence Table

Table C-1. Evidence Table^{a,b,c,d}

2020 Recommendation	2014 Strength of Recommendation	Evidence	2020 Strength of Recommendation	Recommendation Category
1. We suggest against obtaining magnetic resonance imaging for the diagnosis of osteoarthritis of the hip and knee.	D	[43,44] Additional references: [45]	Weak against	Reviewed, New-replaced
2. We suggest a self-management program, including exercise and weight loss for osteoarthritis of the hip and knee, and bracing for osteoarthritis of the knee.	C, EO, C	[48-62,68,69] Additional references: [46,47,63-67]	Weak for	Reviewed, New-replaced
3. We suggest offering physical therapy as part of a comprehensive management plan for patients with osteoarthritis of the hip or knee.	B	[50,71,73-80] Additional references: [70,72]	Weak for	Reviewed, Amended
4. We recommend offering topical non-steroidal anti-inflammatory drugs for patients with pain associated with osteoarthritis of the knee.	Not applicable	[82,84,85] Additional references: [81,83]	Strong for	Reviewed, New-added
5. There is insufficient evidence to recommend for or against the use of topical non-steroidal anti-inflammatory drugs for patients with pain associated with osteoarthritis of the hip.	Not applicable	N/A	Neither for nor against	Reviewed, New-added

^a The 2014 VA/DoD OA CPG used the USPSTF evidence grading system. Inclusion of more than one 2014 Grade indicates that more than one 2014 CPG recommendation is covered under the 2020 recommendation. The strength of recommendations were rated as follows: Grade A indicates that the certainty of evidence is high that the magnitude of net benefits is substantial; Grade B indicates that the certainty of evidence is moderate and that the magnitude of net benefits is either moderate or substantial, or that the certainty of evidence is high that the magnitude of net benefits is moderate; Grade C indicates that the certainty of the evidence is either high or moderate and that the magnitude of net benefits is small; Grade D indicates that the certainty of the evidence is high or moderate and that the magnitude of net benefits is either zero or negative; Grade I indicates that the evidence is insufficient to determine the relationship between benefits and harms (i.e., net benefit); Grade EO for Expert Opinion indicates that the magnitude of net benefit (substantial or moderate) is of sufficient clinical importance to make a recommendation, even if it is based on low certainty (weak evidence). “Not applicable” indicates that the 2020 OA CPG recommendation was a new recommendation and, therefore, does not have an associated 2014 Grade.

^b The first set of references listed in each row in the evidence column constitutes the evidence base for the recommendation. To be included in the evidence base for a recommendation, a reference needed to be identified through the 2019 evidence review or included in the evidence base for the 2014 VA/DoD OA CPG. The second set of references in the evidence column (called “Additional References”) includes references that provide additional information related to the recommendation, but which were not systematically identified through a literature review. These references were not included in the evidence base for the recommendation and, therefore, did not influence the strength and direction of the recommendation.

^c Refer to the Grading Recommendations section for more information on how the strength of the recommendation was determined using GRADE methodology.

^d Refer to the Recommendation Categorization section for more information on the description of the categorization process and the definition of each category.

2020 Recommendation	2014 Strength of Recommendation	Evidence	2020 Strength of Recommendation	Recommendation Category
6. We suggest offering topical capsaicin for patients with pain associated with osteoarthritis of the knee.	C	[86] Additional references: [87-91]	Weak for	Reviewed, Amended
7. There is insufficient evidence to recommend for or against the use of topical capsaicin for patients with pain associated with osteoarthritis of the hip.	I	[86] Additional references: [87-91]	Neither for nor against	Reviewed, Amended
8. We suggest offering acetaminophen and/or oral non-steroidal anti-inflammatory drugs for pain associated with osteoarthritis of the hip and knee.	B, B	[84,92-94,99-101] Additional references: [95-98]	Weak for	Reviewed, New-replaced
9. We suggest offering duloxetine as an alternative or adjunctive therapy for patients with an inadequate response or contraindications to acetaminophen or non-steroidal anti-inflammatory drugs for pain associated with osteoarthritis of the knee.	B	[102,103]	Weak for	Reviewed, New-replaced
10. We suggest against initiating opioids (including tramadol) for pain associated with osteoarthritis of the hip and knee. For patients already on long-term opioid therapy, refer to the current VA/DoD Clinical Practice Guideline for the Management of Opioid Therapy for Chronic Pain.	C	[104-109] Additional references: [110-115]	Weak against	Reviewed, New-replaced
11. We suggest offering an intra-articular corticosteroid injection for patients with persistent pain due to osteoarthritis of the knee inadequately relieved by other interventions.	C	[116-120,123-125] Additional references: [121,122]	Weak for	Reviewed, New-replaced
12. We suggest offering an intra-articular, image-guided corticosteroid injection for patients with persistent pain due to osteoarthritis of the hip inadequately relieved by other interventions.	C	[116-120,123-125] Additional references: [121,122]	Weak for	Reviewed, New-replaced
13. We suggest offering intra-articular viscosupplementation injection(s) for patients with persistent pain due to osteoarthritis of the knee inadequately relieved by other interventions.	I	[126-133]	Weak for	Reviewed, New-replaced
14. We suggest against the use of intra-articular viscosupplementation injection(s) of the hip.	EO	[126-133]	Weak against	Reviewed, New-replaced
15. There is insufficient evidence to recommend for or against platelet-rich plasma injections for the treatment of osteoarthritis of the hip or knee.	Not applicable	[134-148] Additional references: [149]	Neither for nor against	Reviewed, New-added

2020 Recommendation	2014 Strength of Recommendation	Evidence	2020 Strength of Recommendation	Recommendation Category
16. We suggest against stem cell injections (e.g., mesenchymal, adipose-derived, and bone marrow-derived) for the treatment of osteoarthritis of the knee.	Not applicable	[125,151-158] Additional references: [150,159]	Weak against	Reviewed, New-added
17. There is insufficient evidence to recommend for or against the use of the following dietary supplements or nutraceuticals for the treatment of osteoarthritis of the hip or knee: <ul style="list-style-type: none"> • Avocado and soybean extract • Boswellia serrata • Cannabidiol (CBD oil) • Chondroitin • Curcumin (active component of turmeric) • Collagen • Glucosamine • Glucosamine plus chondroitin • Methylsulfonylmethane • Omega-3 fatty acid • Pycnogenol (pine bark) • Rosehip • Traditional Chinese medicine • Vitamin D • Vitamin E • Willow bark extract 	I, D	[160-173]	Neither for nor against	Reviewed, New-replaced
18. There is insufficient evidence to recommend for or against the use of complementary and integrative health interventions for the treatment of osteoarthritis of the hip or knee, including: <ul style="list-style-type: none"> • Acupuncture • Massage • Light touch • Meditation • Tai chi • Yoga 	I	[174-184]	Neither for nor against	Reviewed, New-replaced
19. There is insufficient evidence to recommend for or against the use of transcutaneous electrical nerve stimulation for the treatment of pain in osteoarthritis of the knee.	Not applicable	[185-189]	Neither for nor against	Reviewed, New-added

Appendix D: 2014 Recommendation Categorization Table

Table D-1. 2014 Recommendation Categorization Table^{a,b,c,d,e,f}

Recommendation Number	Page	2014 Recommendation Text	2014 Grade	Recommendation Category	2020 Recommendation
1	18	Clinicians should conduct a history and physical examination for all patients, with an emphasis on the musculoskeletal examination.	EO	Reviewed, Deleted	--
2	19	Clinicians may use plain radiography to confirm the clinical diagnosis of hip and knee osteoarthritis.	C	Reviewed, Deleted	--
3	20	Clinicians should not use magnetic resonance imaging (MRI) as an evaluative tool to diagnose, confirm, or manage the treatment of osteoarthritis.	D	Reviewed, New-replaced	Recommendation 1
4	21	Clinicians should avoid routine use of laboratory examinations or synovial fluid analysis to diagnose osteoarthritis of the hip and/or knee.	EO	Reviewed, Deleted	--
5	22	The decision to prescribe any intervention should be based on consideration of assessment findings, risk vs. benefit analysis, pain severity, functional status, patient preference, and resource utilization.	EO	Not reviewed, Deleted	--
6	23	For patients with osteoarthritis of the hip and/or knee, clinicians should attempt the core non-surgical therapies prior to referral to surgery.	C	Not reviewed, Deleted	--
7	23	For patients with osteoarthritis of the hip and/or knee, clinicians should refer for physical therapist services early on, as part of a comprehensive management plan.	B	Reviewed, Amended	Recommendation 3
8	24	Clinicians should refer overweight or obese patients (defined by a BMI > 25 kg/m ²) with osteoarthritis of the knee to a weight management program to lose a minimum of five percent body weight and maintain this new level of weight.	C	Reviewed, New-replaced	Recommendation 2

^a The first column indicates the recommendation number of each recommendation within the 2014 VA/DoD OA CPG.

^b The second column indicates the page number of each recommendation within the 2014 VA/DoD OA CPG.

^c The 2014 Recommendation Text column contains the wording of each recommendation from the 2014 VA/DoD OA CPG.

^d The 2014 VA/DoD OA CPG used the USPSTF evidence grading system (<http://www.uspreventiveservicestaskforce.org>). The recommendation strengths were: A, B, C, D, I, or EO.

^e The Recommendation Category column indicates the way in which each 2014 VA/DoD OA CPG recommendation was updated.

^f For recommendations that were carried forward to the 2020 VA/DoD OA CPG, this column indicates the new recommendation(s) to which they correspond.

Recommendation Number	Page	2014 Recommendation Text	2014 Grade	Recommendation Category	2020 Recommendation
9	24	Clinicians should refer overweight or obese patients (defined by a BMI > 25 kg/m ²) with osteoarthritis of the hip to a weight management program to lose a minimum of five percent body weight and maintain this new level of weight.	EO	Reviewed, New-replaced	Recommendation 2
10	26	For patients with osteoarthritis of the knee, the addition of manual physical therapy as an adjunct to traditional physical therapy and supervised exercise can improve pain, function, and walking distance.	B	Reviewed, Deleted	--
11	26	For patients with osteoarthritis of the hip, the addition of manual physical therapy as an adjunct to traditional physical therapy and supervised exercise can improve pain, function, and range of motion.	B	Reviewed, Deleted	--
12	27	For adults with osteoarthritis of the knee who do not tolerate land-based therapeutic exercise, clinicians should consider adjunctive aquatic physical therapy.	C	Reviewed, New-replaced	Recommendation 2
13	28	For patients with osteoarthritis of the knee or hip, the prescription and training of ambulation or walking aids should be carried out by a physical therapist or the referring provider.	EO	Reviewed, Deleted	--
14	30	In patients with no contraindications to pharmacologic therapy, clinicians should consider acetaminophen or oral non-steroidal anti-inflammatory drugs (NSAIDs) as first line treatment.	B	Reviewed, New-replaced	Recommendation 8
15	30	Clinicians should ensure that patients receive no more than four grams of acetaminophen daily from all sources of prescribed and non-prescribed medications.	A	Not reviewed, Deleted	--
16	30	In patients requiring treatment with oral NSAIDs and who are at risk for serious upper gastrointestinal (GI) adverse events, clinicians should consider the addition of a proton-pump inhibitor (PPI) or misoprostol.	A	Not reviewed, Deleted	--
17	30	Clinicians should consider the balance of benefit and potential harm in prescribing oral NSAIDs in patients at risk for or with known cardiovascular disease or renal injury/disease.	B	Reviewed, New-replaced	Recommendation 8
18	36	In patients with mild to moderate pain associated with osteoarthritis of the knee, topical capsaicin can be considered as first line or adjunctive therapy.	C	Reviewed, Amended	Recommendation 6
19	36	There is insufficient evidence to recommend for or against the use of topical capsaicin for the hip as first line or adjunctive therapy.	I	Reviewed, Amended	Recommendation 7

Recommendation Number	Page	2014 Recommendation Text	2014 Grade	Recommendation Category	2020 Recommendation
20	38	For patients with persistent moderate or moderately severe osteoarthritis pain, clinicians may offer duloxetine or tramadol as an alternative or adjunct to oral NSAIDs.	B	Reviewed, New-replaced	Recommendation 9
21	38	For patients with persistent severe osteoarthritis pain who have contraindications, inadequate response, or intolerable adverse effects with non-opioid therapies and tramadol, clinicians may consider prescribing non-tramadol opioids.	C	Reviewed, New-replaced	Recommendation 10
22	40	For patients with symptomatic osteoarthritis of the knee, clinicians may consider intra-articular corticosteroid injection.	C	Reviewed, New-replaced	Recommendation 11
23	40	There is insufficient evidence to recommend for or against the use of intra-articular hyaluronate/hylan injection in patients with osteoarthritis of the knee; however, it may be considered for patients who have not responded adequately to nonpharmacologic measures and who have an inadequate response, intolerable adverse events, or contraindications to other pharmacologic therapies.	I	Reviewed, New-replaced	Recommendation 13
24	40	For patients with moderate to severe osteoarthritis of the hip, clinicians may consider imaging/ultrasound directed corticosteroid injection to reduce pain.	C	Reviewed, New-replaced	Recommendation 12
25	40	Intra-articular injection of hyaluronate/hylan is not recommended for patients with osteoarthritis of the hip.	EO	Reviewed, New-replaced	Recommendation 14
26	43	In patients with hip and/or knee osteoarthritis, there is insufficient evidence to recommend for or against the use of dietary supplements for relief of pain and improved function.	I	Reviewed, New-replaced	Recommendation 17
27	43	In patients with hip and/or knee osteoarthritis, clinicians should not prescribe chondroitin sulfate, glucosamine, and/or any combination of the two, to treat joint pain or improve function.	D	Reviewed, New-replaced	Recommendation 17
28	45	In adults with hip and/or knee osteoarthritis, there is insufficient evidence to recommend for or against referral for short term trial needle acupuncture or chiropractic therapy for relief of pain and improved function.	I	Reviewed, New-replaced	Recommendation 18
29	47	For patients with osteoarthritis of the hip and/or knee, who experience joint symptoms (such as pain, stiffness, and reduced function) with substantial impact on their quality of life (individualized based upon patient assessment), and who have not benefited from the core non-surgical therapies, clinicians may offer referral for joint replacement surgery.	B	Not reviewed, Deleted	--

Recommendation Number	Page	2014 Recommendation Text	2014 Grade	Recommendation Category	2020 Recommendation
30	47	In patients with osteoarthritis of the hip and/or knee considered for surgical consultations, clinicians should obtain weight-bearing plain radiographs within 6 months prior to the referral to surgical consultation.	B	Not reviewed, Deleted	--
31	47	In candidates for joint replacement of the hip and/or knee, joint injections should not be given into the involved joint if surgery is anticipated within three months.	EO	Reviewed, Deleted	--

Appendix E: Patient History and Physical Examination

A. Knee and Hip Osteoarthritis Risk Factors

Evidence shows older age, elevated BMI, and history of joint injury increase the risk of both knee and hip OA.[\[194-197\]](#) However, not all patients who sustain joint trauma will develop symptomatic OA, nor will all patients develop OA as they age.[\[47\]](#) The genetic contribution to OA has been reported to be on average 50%.[\[198,199\]](#) Females are generally thought to be at higher risk for the development of OA, though the prevalence is greater in knee OA.[\[194,200\]](#) Knee misalignment is thought to be associated with the progression of knee OA, though the precise nature of biomechanical stresses that lead to the development of OA is complex.[\[194,201,202\]](#) Hip OA has been associated with anatomic abnormalities of the joint, such as various types of hip dysplasia, slipped capital femoral epiphyses, and femoral acetabular impingement.[\[201-203\]](#) Knee OA has been associated with prior knee injury, in particular, meniscus and ligament injuries.[\[204-206\]](#)

The relationship between recreational sport and the development of OA is also complex. Studies have found a correlation between heavy physical activity and the development of OA, but it appears moderate daily recreational activity is not a consistent risk factor for clinical or radiographic knee/hip OA.[\[207-209\]](#)

Occupational risk factors for knee OA include frequent heavy physical load on the joint, frequent exposure to bending, kneeling, squatting, prolonged standing on rigid surfaces, excessive walking, regular stair climbing, jumping, unnatural body position, heavy lifting, and vibration.[\[210-217\]](#) Occupational risk factors for hip OA include occupations that involve standing for >2 hours per day and occupations that involve frequent heavy lifting.[\[218-220\]](#) There may be an association with occupational tasks involved in farming and heavy construction. Rates of OA have been reported to be significantly higher in military populations than in comparable age groups in the general population.[\[12\]](#)

Recognizing the limited number of effective modalities for the non-surgical management of patients suffering from hip and knee OA, the prevalence of chronic comorbid cardiac and renal disease in this patient population, and the well-established adverse effects of NSAIDs available as prescription and OTC products, early surgical consultation for arthroplasty should be encouraged in patients with known coronary disease and/or an eGFR <30 ml/min.

B. Knee Osteoarthritis Patient History

Patients with knee OA typically present with symptoms of activity-related knee pain, often relieved by rest, and joint stiffness of limited duration notably after periods of inactivity.[\[221\]](#) The pain is often described as a deep, aching pain that can be both localized or diffuse. Patients may also complain of crepitus, bony tenderness, reduced range of motion, swelling, and/or joint instability, buckling, or giving way.[\[221\]](#) They may report exacerbation of pain or difficulty with performing activities of daily living that stress the joint such as standing, squatting, kneeling, walking, and stair climbing.[\[221\]](#)

C. Knee Osteoarthritis Patient Physical Examination

In the physical examination of symptomatic knee OA, it can be helpful to include an assessment of BMI, the presence of palpable crepitus in any knee compartment, the presence of joint line tenderness, the frontal plane alignment of the lower limb, the passive range of motion of the knee, lower limb muscle strength (especially the knee flexors and knee extensors), joint proprioception, palpation of tenderness or

effusion, and varus or valgus laxity of the knee.[\[222,223\]](#) Patients with knee OA may also present with various gait impairments, which can be observed in the clinic. Gait impairments are thought to lead to abnormal joint loading during gait. For example, patients with medial knee OA are more likely to present with a higher knee adduction moment during gait.[\[222\]](#) Patients with knee OA may be at increased risk for future falls compared to age-matched control because of pain during gait, impairments in proprioception, and balance and lower limb muscle control during gait.[\[224-226\]](#) Therefore, an assessment of balance and fall risk should be considered in patients with knee OA.

D. Hip Osteoarthritis Patient History

Patients with hip OA present most often with complaints of groin or anterior thigh pain with activity or weight-bearing but can progress eventually to pain at rest.[\[202,227\]](#) Providers should be aware that hip pain can produce referred pain to the buttock, the knee, and even below the knee.[\[228,229\]](#) Providers should inquire about occupational history, prior hip injuries, history of OA at other sites, family history of OA, activity participation, and pain history. Patients may complain of pain with squatting and stair climbing. Sitting may be uncomfortable, especially if the hip is placed in excessive flexion. Patients will often lean away from the involved hip while in a seated position and attempt to slightly decrease the degree of required hip flexion.[\[230\]](#) Although the classic complaint of patients with hip OA is groin pain, the patients may localize their pain by placing their ipsilateral thumb in their groin with their hand and fingers cupping their greater trochanter and buttocks forming the “C sign.”[\[230\]](#) The pain experienced by the patient can be stabbing, sharp, or dull. Similar to OA of the knee, the hip becomes increasingly stiff as the disease progresses and patients frequently report stiffness in the hip following a period of inactivity.

E. Hip Osteoarthritis Patient Physical Examination

Examination of the patient with hip OA should assess BMI, passive range of motion (particularly internal rotation, flexion, and abduction), gait, balance, and lower limb muscle strength (particularly the hip abductors and hip flexors). An assessment of the lumbar spine or sacroiliac joint may be warranted. With hip OA, the motion of the hip can become progressively restricted secondary to synovitis, soft tissue contractures, and loss of joint congruency. Examination may reveal a flexion contracture or reduced internal rotation, flexion, and abduction.[\[227\]](#) Restricted internal rotation may predict the presence of hip OA in patients presenting to a primary care provider with hip pain.[\[231\]](#) Patients with a painful hip will often stand with a slightly flexed hip and knee to relax the hip joint capsule.[\[202\]](#) Abnormal gait patterns can include a winking gait with excessive pelvic rotation in the axial plane, an abductor deficient gait, an antalgic gait with a shortened stance phase on the painful side, or a short leg gait with dropping of the shoulder in the direction of the short leg.[\[232\]](#) Special testing of the hip can be helpful in the differential diagnosis process, but evidence is lacking for the use of any special test in the context of predicting early hip OA.[\[233\]](#)

Appendix F: Pharmacologic Therapies

Table F-1. Pharmacologic Agents for the Treatment of OA^{a,b} and their Selected Characteristics

Type	Generic Name	Brand	Formulations	Usual Starting Dose	Max Single Dose	Frequency	Notes
COX-2 Selective NSAIDs ^c	Celecoxib	Celebrex [®] , Elyxyb [™] / Generics	C, Soln	100 – 200 mg	200 mg	Once or twice daily	Max 200 mg/day for OA
Partially Selective NSAIDs	Etodolac	Generics/XR	C, T, T (XR)	200 mg (IR) 400 mg (XR)	IR 400 mg XR 1,000 mg	IR 2 – 4 times daily XR once daily	IR up to 1,000 mg daily XR up to 1,200 mg daily
	Meloxicam	Mobic [®] , Vivlodex [®] , Qmiiz [®] ODT/ Generics	C, T, ODT	Mobic, ODT 7.5 mg Vivlodex 5 – 10 mg	15 mg Vivlodex 10 mg	Once daily	Max dose is 15 mg daily Max dose is 10 mg (Vivlodex)
	Nabumetone	Generics	T	1,000 mg	2,000 mg	Once daily	May divide twice daily; max dose is 2,000 mg daily
Non-aspirin, Non-selective NSAIDs	Diclofenac potassium/sodium	Generics	T, C, Soln	50 mg	75 mg	2 – 3 times daily	Max total daily dose is 150 mg; may divide up to 3 times daily
	Diclofenac sodium (XR)	Generics	T (XR)	100 mg	100 mg	Once daily	Max dose is 100 mg daily
	Fenoprofen	Nalfon [®] / Generics	C, T	200 – 400 mg	600 mg	3 – 4 times daily	Higher renal risk; total daily dose should not exceed 3,200 mg
	Flurbiprofen	Ansaid [®] / Generics	T	50 – 100 mg	100 mg	Twice daily	Max daily dose is 300 mg
	Ibuprofen	Generics	T, C, Susp	400 mg	800 mg	3 – 4 times daily	Max dose in chronic pain is 2,400 mg daily

^a Refer to VA or DoD formularies for availability of agents or comparable agents. The list of available formulations may not be all-inclusive or may change with time as will generic availability. Combination products are not included in Table F-1.

^b For additional details on warnings and precautions, drug-drug interactions, adverse events, dosing considerations and use in special populations, etc., refer to the prescribing information for the individual agents of interest.

^c All NSAIDs have the potential to increase the risk for cardiovascular events and therefore should be used at the lowest effective dose for the shortest possible duration. Use with caution or avoid use of NSAIDs in patients with renal impairment, history of gastrointestinal bleeding, uncontrolled hypertension, congestive heart failure, advanced liver diseases, at high risk for or with known CVD, patients receiving anticoagulants or systemic corticosteroids, etc.

Type	Generic Name	Brand	Formulations	Usual Starting Dose	Max Single Dose	Frequency	Notes
Non-aspirin, Non-selective NSAIDs	Indomethacin	Indocin® SR/ Tivorbex®/ Generics	C, C (XR), Supp, Susp	25 – 50 mg (IR) 75 mg (SR)	50 mg 75 mg	2 – 3 times daily 1 – 2 times daily	May divide up to 4 times daily (IR); max dose is 150 mg daily
	Ketoprofen IR	Generics	C, OTC T	50 mg	75 mg	3 – 4 times daily	Max dose is 300 mg daily
	Ketoprofen ER	Generics	C	200 mg	200 mg	Once daily	Max dose is 200 mg daily
	Meclofenamate sodium	Generics	C	50 mg	100 mg	4 times daily	May give 3 times daily; max dose is 400 mg daily
	Naproxen	Naprosyn®/ Generics	T, Susp	500 mg	500 mg	Twice daily	Max dose in chronic pain is 1,000 mg daily
			T–EC (XR)	375 – 500 mg (EC)	500 mg	Twice daily	Max dose in chronic pain is 1,000 mg daily
	Naproxen sodium	Anaprox® DS/ Generics	T	550 mg	550 mg	Twice daily	Max dose in chronic pain is 1,100 mg daily
	Oxaprozin	Daypro®/ Generics	T	1,200 mg	1,200 mg	Once daily	Max dose is 1,200 mg daily
	Piroxicam	Feldene®/ Generics	C	20 mg	20 mg	Once daily	Max dose is 20 mg daily; may divide twice daily
	Sulindac	Generics	T	150 – 200 mg	200 mg	Twice daily	Max dose is 400 mg daily
Tolmetin	Generics	T, C	400 – 600 mg	600 mg	3 times daily	Max dose is 1,800 mg daily	
Non-acetylated Salicylates	Diflunisal	Generics only	T	250 – 500 mg	1,000 mg	2 – 3 times daily	Max dose is 1,500 mg daily
	Choline magnesium trisalicylate	Generics	T, Liquid	750 mg	1,500 mg	2 – 3 times daily	Max dose is 3,000 mg daily
	Salsalate	Generics	T	500 – 750 mg	1,000 mg	2 – 3 times daily	May increase to 3 times daily; max dose is 3,000 mg daily

Type	Generic Name	Brand	Formulations	Usual Starting Dose	Max Single Dose	Frequency	Notes
Acetaminophen	Acetaminophen	Generics	C, T, T (XR), Supp, Susp	650 mg	1,300 mg	3 – 4 times daily (max dose 2 – 4 g daily, depending upon the patient)	Max 3,000 mg/day in most patients. Consider lower total daily doses (e.g., 2 – 3 g) in elderly patients or those with heavy use of alcohol. In carefully selected patients, the max dose can be increased to no more than 4,000 mg/day. The total daily dose of acetaminophen from all sources (single and multiple ingredient products) must not exceed 4,000 mg/day
Topical Therapies	Capsaicin	Generics	Cream, Gel, Liquid, Lotion Varied concentrations: 0.025 – 0.075%	–	–	Apply 3 – 4 times daily	Patients may experience burning/tingling sensation in the first few days of use; instruct patients to wash their hands with soap and water after application
	Diclofenac	Voltaren®	Gel 1%	2 – 4 g	4 g	Four times daily	Max dose is 32 g daily. Max of 16 g per lower extremity joint and 8 g per upper extremity joint daily. Single dose of 4 g applied to a lower extremity joint while 2 g applied to an upper extremity joint
		Pennsaid®	Soln 2%	2 pumps (40 mg)	2 pumps (40 mg)	Twice daily	Spread the solution evenly around the front, back, and sides of the knee; local skin irritation
		Flector®	Patch 1.3%	1 patch (180 mg)	1 patch (180 mg)	Twice daily	Not FDA approved for OA; local skin irritation
	Solaraze®	Gel 3%	–	–	Twice daily	Not FDA approved for OA; local skin irritation	

Type	Generic Name	Brand	Formulations	Usual Starting Dose	Max Single Dose	Frequency	Notes
Other Therapies	Duloxetine	Cymbalta®/ Generics	Delayed release C	30 mg for 1 week, increase to 60 mg once daily	60 mg	Once daily	Max dose is 60 mg daily; higher doses are not associated with improved outcomes, but a higher rate of adverse events is reported Avoid in end-stage renal disease or CrCl <30 ml/min or in patients with substantial alcohol intake Refer to prescribing information for other details including contraindications, drug-drug interactions, gradually reducing dose if withdrawing treatment, warnings and precautions, and adverse events

Abbreviations: C: capsule; COX-2: cyclooxygenase-2; CrCl: creatinine clearance; CVD: cardiovascular disease; EC: enteric-coated; ER: extended release; FDA: Food and Drug Administration; g: grams; IR: immediate release; mg: milligrams; min: minute; ml: milliliters; NSAIDs: non-steroidal anti-inflammatory drugs; OA: osteoarthritis; ODT: oral disintegrating tablet; OTC: over-the-counter; Soln: solution; SR: sustained release; Supp: suppository; Susp: suspension; T: tablet; XR: extended release

Table F-2. Treatment Course for Hyaluronate/Hylan Injections

Hyaluronate/ Hylan	Treatment Course-frequency (each injection is given at weekly intervals)	Volume	Notes
Durolane	Single injection	3.0 ml	–
Euflexxa	3 weekly	2.0 ml	–
Gel-One	Single injection	3.0 ml	Caution in those with avian allergy
Gelsyn-3	3 weekly	2.0 ml	–
GenVisc 850	5 weekly	2.5 ml	–
Hyalgan	3 or 5 weekly	2.0 ml	Caution in those with avian allergy
Hymovis	2 weekly	3.0 ml	–
Monovisc	Single injection	4.0 ml	–
Orthovisc	3 – 4 weekly	2.0 ml	–
Supartz FX	3 or 5 weekly	2.5 ml	Caution in those with avian allergy
Synjoynt	3 weekly	2.0 ml	–
Synvisc	3 weekly	2.0 ml	Caution in those with avian allergy
Synvisc-One	Single injection	6.0 ml	Caution in those with avian allergy
Trivisc	3 weekly	2.5 ml	–

Abbreviations: ml: milliliters

A. Considerations for Selecting Oral Non-steroidal Anti-inflammatory Drugs

Non-steroidal anti-inflammatory drugs are a heterogeneous class of drugs that differ in their relative potencies of COX-1 and COX-2 inhibition and, consequently, in their adverse event profiles. Although published studies of in vitro assays have studied the relative potencies of COX-2 versus COX-1 inhibition, providers should be cautious about extrapolating the relative safety of one NSAID over another NSAID. Non-steroidal anti-inflammatory drugs are commonly referred to as non-selective (e.g., ibuprofen, naproxen, diclofenac, indomethacin), relatively selective (e.g., etodolac, meloxicam, and nabumetone), or selective (e.g., celecoxib). However, the FDA classifies all these agents, including celecoxib, as members of the NSAID class. Likewise, these drugs all have similar warnings, precautions, and contraindications for use (see [Table F-1](#)).

B. Non-steroidal Anti-inflammatory Drugs and Risk of Serious Adverse Upper Gastrointestinal Events

Various factors can contribute to an increase in the risk for NSAID-related, serious upper GI adverse events (i.e., GI perforation, ulcer, bleeding). These factors include a prior history of serious upper GI adverse event or history of ulcers, prior history of an NSAID-related GI adverse event, concomitant use of anticoagulants, advanced age, use of oral CS, and high-dose NSAIDs.^[234]

Although not included in the systematic evidence review and, thus, not considered in determining the strength of Recommendation 8, a meta-analysis by Bhala et al. (2013) reviewed individual participant data from 280 clinical trials of NSAIDs (including COX-2 selective inhibitors) versus placebo and 474 trials of NSAIDs versus another NSAID and examined rates of serious vascular and/or GI adverse events.^[235] Authors found that all NSAIDs (including celecoxib) increased the risk for any serious upper GI complication including perforation, obstruction, or bleeding by 2 – 4 times when compared to

placebo.[235] Patients with a higher baseline risk for complicated upper GI events appeared to predict a higher rate of events. The Prospective Randomized Evaluation of Celecoxib Integrated Safety versus Ibuprofen or Naproxen (PRECISION) study monitored the rate of CV, GI, and renal adverse events of celecoxib, ibuprofen, and naproxen in 24,081 patients at high risk for CVD and with rheumatoid arthritis (RA) or OA not responding to acetaminophen.[236] All patients received esomeprazole 20 – 40 mg daily throughout the trial. Over 20 months, there were no differences in clinically significant GI events between treatments (celecoxib=0.7%, naproxen=0.7%, ibuprofen=0.9%). Confidence in the results from PRECISION is limited by large numbers of participants who stopped their study drug (68.8%), discontinued follow-up (27.4%) and by a lower average daily dose of celecoxib used (209 mg) in comparison to average daily doses of ibuprofen (2045 mg) and naproxen (852 mg).[236] The PRECISION study was not included in the systematic evidence review conducted for this CPG and, thus, was not considered in determining the strength of Recommendation 8.[236]

To minimize the likelihood that high-risk patients experience NSAID-induced serious upper GI events, providers may consider several options, including the addition of a proton-pump inhibitor (PPI) or misoprostol.[237,238] In patients at greatest risk of experiencing an NSAID-associated serious upper GI adverse event (e.g., a patient with a recent complicated ulcer with hospital admission), alternative treatment is advised. However, providers could consider the use of a COX-2 selective NSAID combined with a PPI if treatment with NSAIDs is necessary.[239] Evidence comparing the use of a non-selective or relatively COX-2 selective NSAID combined with a PPI versus a COX-2 selective NSAID plus a PPI in patients at greatest risk is lacking. However, many patients will be at sufficiently high risk to warrant avoidance of NSAIDs.

C. Non-steroidal Anti-inflammatory Drugs and Risk of Cardiovascular Events

Although not included in the systematic evidence review and, thus, not considered in determining the strength of Recommendation 8, Bhalal et al. (2013) conducted a meta-analysis of RCTs that explored rates of CV adverse events and complicated upper GI adverse events in individuals taking NSAIDs, celecoxib or other COX-2 selective NSAIDs.[235] This meta-analysis included 280 trials comparing NSAIDs to placebo (n=124,513 patients; 68,342 person-years) and 474 trials (n=229,296 patients; 165,456 person-years) comparing NSAIDs to another NSAID. Most trials used higher daily dose NSAIDs (e.g., ibuprofen 2,400 mg, diclofenac 150 mg, naproxen 1,000 mg). Major vascular events (e.g., fatal or non-fatal myocardial infarction [MI], fatal or non-fatal stroke, coronary heart disease death) were increased in patients receiving a COX-2 selective inhibitor (RR: 1.37, 95% CI: 1.14 – 1.66, p=0.0009) or diclofenac (RR: 1.41, 95% CI: 1.12 – 1.78, p=0.0036). These vascular events were influenced primarily by an increase in major coronary events. Ibuprofen was associated with a higher rate of major coronary events (RR: 2.22, 95% CI: 1.10 – 4.48, p=0.0253) but did not significantly increase major vascular events (RR: 1.44, 95% CI: 0.89 – 1.27).[235] Naproxen did not increase major vascular events (RR: 0.93, 95% CI: 0.69 – 1.27) or major coronary events (RR: 0.84, 95% CI: 0.52 – 1.35). The risk of any stroke was not significantly increased for any NSAID studied. Heart failure events increased in all NSAID groups versus placebo. Overall, for every 1,000 patients receiving a COX-2 inhibitor or diclofenac for one year, an additional three patients had a major vascular event (one of which was death) compared to placebo. In an analysis of annual risk for major vascular events, an increased risk was predicted but was not observed in patients with higher baseline CV risk. However, data were limited in patients with known CVD or those with risk >10% over five years.

Although not included in the systematic evidence review and, thus, not considered in determining the strength of Recommendation 8, the PRECISION study was a large, multicenter, prospective RCT comparing two commonly used non-selective NSAIDs (i.e., ibuprofen and naproxen) and celecoxib in 24,081 patients with RA or OA and with known CVD or at high risk for CVD who required treatment with NSAIDs.^[236] PRECISION's goal was to examine the noninferiority of celecoxib versus ibuprofen and naproxen regarding differences in CV risk.^[236] The study also monitored and reported the risk for GI and renal events. The primary composite outcome included death from CV causes, including hemorrhagic death, non-fatal MI, or stroke. A secondary outcome of major adverse CV events included the primary endpoint plus coronary revascularization or hospitalization for unstable angina or transient ischemic attack. There were no statistical differences in the primary CV outcome measure between celecoxib and ibuprofen or naproxen, supporting noninferiority of moderate doses of celecoxib. Confidence in the results from PRECISION is limited by large numbers of participants who stopped their study drug (68.8%), discontinued follow-up (27.4%) and by a lower average daily dose of celecoxib used (209 mg) in comparison to average daily doses of ibuprofen (2,045 mg) and naproxen (852 mg).^[236] Although observational studies and meta-analyses of earlier studies supported a possible neutral CV effect of naproxen, results from PRECISION do not support a difference in CV risk between celecoxib, naproxen, and ibuprofen. As a result, CV risk or presence of known CVD should be considered when prescribing any NSAID or COX-2 inhibitor and the use of any of these agents should be avoided in these patients if possible.

D. Non-steroidal Anti-inflammatory Drugs and Risk of Renal Disease

Use of non-selective or COX-2 selective NSAIDs can result in renal papillary necrosis, acute tubular necrosis, acute interstitial nephritis with or without nephrotic syndrome, renal insufficiency, fluid and electrolyte disturbances, acute renal failure, or other renal-related injuries in an estimated 1 – 5% of patients.^[240,241] All available agents approved for use in the U.S. include a warning for such events in their prescribing information. The risk for renal adverse events increases in patients who are dependent upon a compensatory increase in the production of renal prostaglandins to maintain renal perfusion. Patients at higher risk for renal injury from any NSAID or COX-2 inhibitor include those with preexisting renal disease, volume depletion (e.g., diuretics, vomiting), congestive heart failure, liver dysfunction, cirrhosis with ascites, use of angiotensin-converting enzyme inhibitors or angiotensin receptor blockers, and older patients.^[242,243]

In healthy patients, renal prostaglandins do not play a significant role in maintaining renal perfusion. However, in situations of reduced volume, hypotension, and reduced renal perfusion, the production of renal prostaglandins increases to maintain renal blood flow, glomerular filtration rate (GFR), and limit ischemia. Administration of any NSAID or COX-2 selective NSAID in these patients reduces the compensatory vasodilatory renal prostaglandins and can result in reduced renal perfusion, reduced GFR, and can lead to renal damage.^[244] Although there are other mechanisms of NSAID-induced renal injury, hemodynamically mediated acute renal insufficiency is the most common cause, has known risk factors, and is most frequently reversible once the offending agent is discontinued.

In the PRECISION study, renal events were prospectively monitored in a population of more than 20,000 patients with RA or OA pain not controlled with acetaminophen and receiving either celecoxib, ibuprofen, or naproxen for a mean follow-up of 20 months.^[236] Eligible patients had baseline serum creatinine (SCr) values within normal limits. Renal events included the occurrence of SCr of ≥ 2 mg/

deciliter (dL), hospitalization for acute renal failure, or the initiation of renal replacement therapy (e.g., hemodialysis, peritoneal dialysis). There were no differences in renal events between celecoxib and naproxen, but a lower rate of renal events occurred in the celecoxib group versus the ibuprofen group (hazard ratio [HR]: 0.61, 95% CI: 0.44 – 0.85).

The use of NSAIDs or COX-2 inhibitors should generally be avoided in patients with CKD, especially in patients with an eGFR of ≤ 30 ml/min. However, in patients with OA whose pain is not controlled with other non-NSAID treatments, potential risks and benefits of NSAIDs should be considered on a case-by-case basis. [\[245\]](#)

Appendix G: Nutraceuticals and Dietary Supplements

The 2019 systematic evidence review examined 16 nutraceuticals and dietary supplements: avocado and soybean extract, Boswellia serrata extract, cannabidiol (CBD oil), chondroitin, curcumin, collagen, glucosamine, glucosamine plus chondroitin, MSM, omega-3 fatty acids, pycnogenol (pine bark), rosehip, traditional Chinese medicine, vitamins D and E, and willow bark extract. The Work Group's recommendations regarding nutraceutical and dietary supplements can be found in [Recommendation 17](#). Additional information is below. Cannabidiol and omega-3 fatty acids were included in the search strategy but did not return any literature meeting the inclusion criteria.

A. Avocado and Soybean Extract

An SR by Liu et al. (2018) compared the efficacy and safety of avocado soybean unsaponifiables in five RCTs for patients with hip and knee OA.[\[169\]](#) The study found significant effects for reduction of pain and improvement in function at a dose of 300 mg/day compared to a placebo in the short- (<3 months) and medium-term (4 – 6 months). No clinically significant effects for pain reduction or improvement of function were reported in the long-term (>6 months) when compared to a placebo. Evidence suggests a low level of harm from the use of avocado soybean unsaponifiables.

B. Boswellia Serrata Extract

An SR by Liu et al. (2018) (n=186) and an RCT by Majeed et al. (2019) (n=48) reported statistically significant differences in favor of Boswellia serrata extract for pain reduction compared to the placebo.[\[166,169\]](#) However, the results were not statistically significant and sample sizes for both studies were small. Additionally, there is limited research on adverse events associated with Boswellia serrata extract.

C. Chondroitin, Glucosamine, and Glucosamine plus Chondroitin

Treatment with chondroitin, glucosamine, and combination of chondroitin/glucosamine did not show improvement in pain in patients with OA of the hip and knee.[\[167-171\]](#) This CPG's systematic evidence review yielded 10 studies with a patient pool of approximately 10,000. The confidence in the quality of evidence was low. Studies that revealed a statistically significant difference for chondroitin, glucosamine, and their combination were sponsored by industry and permitted the use of oral NSAIDs as a rescue drug or concomitantly.[\[171\]](#) Studies without industry involvement failed to show any clinically significant difference in pain. In a meta-analysis by Zhu et al. (2018), chondroitin showed more GI adverse events, while other studies on glucosamine or combination did not show statistically significant adverse event rates.[\[167\]](#) Wide dose ranges and dosing frequency variations were noted among the studies, with dose ranges from 800 – 2,000 mg per day at different dosing intervals.[\[171\]](#)

D. Curcumin

In one SR with five RCTs, curcumin was found to have positive effects on pain and function compared to the placebo at the 1 – 3 months follow-up in patients with knee OA.[\[165\]](#) No significant differences in adverse events were reported between curcumin and placebo. Dosing and formulations varied between interventions. The first RCT, Haroyan et al. (2018), comparing curcumin to the placebo used CuraMed capsule (containing 552 – 578 mg of BCM-95 as a dry extract, and 49 – 52 mg of volatile oil from curcuma

longa L. rhizome, and 22 – 23.4 mg aromatic tumerone) TID.[246] The authors noted that BCM-95 complex has been shown to have a bioavailability approximately 6.93 fold greater than that of normal curcumin. The second RCT, Madhu et al. (2013), utilizes *Curcuma longa* extract (NR-INF-02), 500 mg capsule BID.[247] The remaining three RCTs included in the SR used curcumin capsule, 600 mg/day, highly-bioavailable curcumin (Theracumin), 180 mg capsule six times/day, and C3 curcuminoid complex 500 mg capsule TID.[165]

Compared to an NSAID, evidence from Bannuru et al. (2018) with two RCTs and one additional RCT by Shep et al. (2019) found no significant between-group difference for pain reduction, function, or quality of life at 4 – 6 weeks follow-up.[164,165] The RCT by Shep et al. (2019) utilized curcumin BCM-95 500 mg capsules TID for the intervention arm.[164] There was a significant reduction in withdrawals due to adverse events favoring curcumin over both ibuprofen and diclofenac. One RCT by Srivastava et al. (2016) examined the combination of curcumin (500 mg/day of *Curcuma longa*) plus NSAIDs compared to NSAIDs alone and found a statistically significant improvement in pain (as measured by the VAS at two and four months, and WOMAC at two months, but not four) and function.[163] However, the results were not clinically significant. There was no significant difference in adverse events reported.

E. Collagen

In a meta-analysis by Garcia-Coronado et al. (2019), collagen-based supplements significantly improved pain as measured by VAS, but not WOMAC when compared to a placebo.[162] The follow-up times were 10 – 48 weeks. There were various collagen sources tested and doses across studies included in the meta-analysis. Two of the trials utilized a chicken collagen hydrolysate-based supplement. The remaining three trials utilized chicken undenatured type II collagen, porcine/bovine collagen peptides, and porcine/bovine collagen hydrolysate. Collagen daily doses ranged from 2 g (one trial), 10 g (three trials), and 40 g (one trial). No statistically significant differences were reported between groups for adverse events in an SR by Liu et al. (2018) with one RCT included with 10 g/day of collagen hydrolysate as the intervention.[169]

F. Methylsulfonylmethane

Evidence from three RCTs in an SR by Liu et al. (2018) lasting <3 months indicated MSM significantly improved pain and function compared to a placebo.[169] Limited evidence from one small RCT (n=25) in the treatment arm showed no significant difference between MSM and placebo for any adverse events.

G. Pycnogenol (Pine Bark)

Two RCTs in an SR by Liu et al. (2018) lasting <3 months suggest that pycnogenol (pine bark) significantly improved function compared to a placebo.[169] At three months, no adverse events were reported in one small RCT (n=100).

H. Rosehip

There is limited evidence regarding the efficacy of rosehip compared to placebo for pain or adverse events. One small RCT (n=90) by More et al. (2017), using a proprietary blend Rosaxan (MA212: 20 g *R. canina* L.ripe fruit puree, 4 g *R.canina* L.ripe fruit juice concentrate, 160 mg *U. dioica* L. leaf dry extract [nettle], 108 mg *H. procumbens* root dry extract [devil's claw]) at a dose of 40 ml/day, reported statistically significant improvement in pain as measured by the WOMAC at six and 12 weeks and no significant difference in adverse events at 12 weeks.[161] Of note, the intervention group received

several active ingredients in addition to the Rosaxan (MA212), including vitamin D (200 international units [IU]) and R. canina.

I. Traditional Chinese Medicine

Evidence from one small RCT by Lao et al. (2015) suggests no statistically significant differences between traditional Chinese medicine and placebo for pain at 2 or 8 weeks.[\[248\]](#) No differences were also reported by a second small RCT by Hua et al. (2013) at the 12- and 16-week follow-up.[\[160\]](#) The risk of adverse events reported across two RCTs was low. There was variation in the supplements included under the umbrella term “traditional Chinese medicine.” The dosing of Huo-Luo-Xiao-Ling-Dan used in the Lao et al. (2015) study included 10 capsules per day (4,000 mg/day) during the first two weeks and 14 capsules per day (5,600 mg/day) for the next six weeks of a blend of 11 herbs.

J. Vitamin D

Evidence from a meta-analysis by Gao et al. (2017) found a statically significant improvement in pain and function in patients with knee OA.[\[172\]](#) The benefit was seen at daily doses >2000 IU vitamin D daily. However, the Work Group concluded that the weighted mean difference (WMD) of -1.74 on the WOMAC pain subscale (0 – 20) and WMD of -2.21 on the WOMAC function subscale (0 – 68) was not clinically significant. Of note, there was a wide variation in the treatment regimens of the SRs included in the meta-analysis, ranging from 800 – 60,000 IU daily. There was no significant increase in adverse events versus placebo. The Recommended Dietary Allowance (RDA) of vitamin D for most adults is 600 IU.[\[249\]](#)

K. Vitamin E

An RCT by Tantavisut et al. (2017) indicated a statistically significant improvement in pain and function at two months,[\[173\]](#) but, according to an SR and meta-analysis conducted by Liu et al. (2018), this improvement was not evident at greater than four months.[\[169\]](#) Although Tantavisut et al. (2017) showed no significant adverse events at two months,[\[173\]](#) there is evidence outside the systematic evidence review that vitamin E at higher doses (i.e., ≥400 IU/day) may lead to significant increases in bleeding, prostate cancer, and all-cause mortality.[\[250\]](#) Of note, the SR and meta-analysis by Liu et al. (2018) and the RCT by Tantavisut et al. (2017) included trial doses of 400 IU and 500 IU of vitamin E daily.[\[169,173\]](#) The RDA of vitamin E for most adults is 22.4 IU.[\[250\]](#)

L. Willow Bark Extract

Evidence from two RCTs in one SR by Liu et al. (2018) lasting <3 months suggest no statistically significant difference between willow bark extract (680 mg BID) and placebo for pain, function, or adverse events.[\[169\]](#)

Appendix H: Participant List

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Appendix I: Literature Review Search Terms and Strategy

A. EMBASE with EMBASE.com Syntax

Question	Set #	Concept	Strategy
Question 1 – What are the benefits and harms of FDA-approved oral pharmacotherapy for treatment of OA (osteoarthritis) of the hip and knee?	#1	Adults 18+ with OA of the hip and/or knee General OA terms	osteoarthritis/de OR (arthrit*:ti,ab NOT rheumatoid:ti) OR OA:ti OR ('osteo-arthritis' OR osteoarthrit* OR 'degenerative joint*' OR 'joint pain'):ti,ab
	#2	Hip and knee	'hip osteoarthritis'/de OR 'knee osteoarthritis'/de OR ((hip/exp OR knee/exp OR (hip OR hips OR knee*):ti) AND (joint* OR pain*):ti,ab)
	#3	Combine population sets	#1 OR #2
	#4	Oral pharmacotherapy General terms	pharmacologic* OR pharmacotherap*:ti OR (analgesic*:ti AND oral:ti,ab) OR ('non-opiate*' OR nonopiate* OR 'non-opioid*' OR nonopioid*):ti
	#5	Acetaminophen	paracetamol/de OR (acetaminophen OR panadol OR paracetamol OR tylenol*):ti,tn
	#6	Nonselective NSAIDs	'nonsteroid antiinflammatory agent'/exp OR (((nonsteroid*' OR nonsteroid*) NEXT/1 ('antiinflammator*' OR antiinflammator*)) OR ('acetylsalicylic acid' OR advil* OR aleve* OR anacin* OR aspirin OR diclofenac OR ibuprofen OR motrin* OR naproxen OR NSAID* OR salicylate*)):ti,tn
	#7	Selective COX-2 inhibitors	'cyclooxygenase 2 inhibitor'/exp OR (celebrex* OR celexocib OR ((cox OR cyclo-oxygenase OR cyclooxygenase) NEXT/1 inhibit*) OR coxib*):ti,tn
	#8	Duloxetine	duloxetine/de OR cymbalta*:ti,tn OR duloxetine:ti
	#9	Combine intervention sets	#4 OR #5 OR #6 OR #7 OR #8
	#10	Combine population and intervention sets	#3 AND #9
	#11	Apply general hedges	See General Hedges at the end of this table
	#12	Apply meta-analyses and RCTs hedges	See Study Type Hedges at the end of this table

Question	Set #	Concept	Strategy
<p>Question 2 – What are the benefits and harms and comparative effectiveness of FDA approved intra-articular injections of pharmacotherapy agents for treatment of moderate – severe OA of the hip and knee? (a) In candidates for joint replacement of the hip and/or knee, should joint injections be avoided in the involved joint for three months before surgery?</p>	#1	Adults 18+ with OA of the hip and/or knee General terms	osteoarthritis/de OR (arthrit*:ti,ab NOT rheumatoid:ti) OR OA:ti OR ('osteo-arthrits' OR osteoarthrit* OR 'degenerative joint*' OR 'joint pain'):ti,ab
	#2	Hip and knee	'hip osteoarthritis'/de OR 'knee osteoarthritis'/de OR ((hip/exp OR knee/exp OR (hip OR hips OR knee*):ti) AND (joint* OR pain*):ti,ab)
	#3	Combine population sets	#1 OR #2
	#4	FDA approved intra-articular injections of pharmacotherapy agents General	'intraarticular drug administration'/exp OR viscosupplement/de OR viscosupplementation/de OR ('joint injection*' OR (('intra articular' OR intraarticular) AND (administ* OR deliver* OR drug* OR inject*)) OR viscosupplement*):ti,ab
	#5	Corticosteroids	(corticosteroid/exp OR (betamethasone OR corticoid* OR cortisone OR corticosteroid* OR dexamethasone OR glucocorticoid* OR hydrocortisone OR methylprednisolone OR prednisolone OR steroid* OR triamcinolone):ti,ab OR zilretta:ti,ab,tn) AND ('intra-articular' OR intraarticular OR inject*):ti,ab
	#6	Hyaluronic acid	'hyaluronic acid'/de OR ha:ti OR hyaluron*:ti,ab OR synovial*:dn,tn OR (adant* OR arthrease* OR arthrum* OR artz* OR biohy OR durolane* OR euflexxa* OR fermathron* OR 'gel-on' OR 'gel-one*' OR 'gel-syn*' OR healon* OR HYA OR hyalgan* OR hyalubrix* OR hylan* OR hyruan* OR monovisc* OR neovisc* OR nuflexxa* OR orthovisc* OR ostenil* OR replasyn OR structovial* OR supartz* OR suplasyn* OR suvenyl* OR synject* OR synocrom* OR synvisc* OR variofill*):ti,ab,dn,tn
	#7	Combine intervention sets	#4 OR #5 OR #6
	#8	Combine population and intervention sets	#3 AND #7
	#9	Apply general hedges	See General Hedges at the end of this table
	#10	Apply meta-analyses and RCTs hedges	See Study Type Hedges at the end of this table

Question	Set #	Concept	Strategy
Question 3 – What are the benefits and harms of intra-articular orthobiologics regenerative medicine [stem cell injections or others (e.g., platelet rich plasma, amniotic fluid, amniotic membrane)] for treatment of OA of the hip and knee?	#1	Adults 18+ with OA of the hip and/or knee General	osteoarthritis/de OR (arthrit*:ti,ab NOT rheumatoid:ti) OR OA:ti OR ('osteo-arthritis' OR osteoarthritis* OR 'degenerative joint*' OR 'joint pain'):ti,ab
	#2	Hip and knee	'hip osteoarthritis'/de OR 'knee osteoarthritis'/de OR ((hip/exp OR knee/exp OR (hip OR hips OR knee*):ti) AND (joint* OR pain*):ti,ab)
	#3	Combine population sets	#1 OR #2
	#4	Intra-articular orthobiologics regenerative medicine General and platelet-rich plasma	orthobiologic*:ti OR 'thrombocyte rich plasma'/exp OR ('leukocyte rich' OR 'platelet autologous plasma' OR 'platelet concentrate' OR 'platelet gel' OR 'platelet releasate*' OR 'platelet rich fibrin' OR ('platelet rich' NEXT/2 'growth factor') OR 'platelet rich plasma'):ti,ab OR (PRF OR PRGF OR PRP):ti
	#5	Bone marrow	'autologous bone marrow transplantation'/de OR ('bone marrow aspirate' OR 'bone marrow concentrate' OR 'bone marrow derived'):ti,ab
	#6	Stem cells	'adipose tissue'/de OR 'adipose derived stem cell'/de OR 'adipose tissue cell'/exp OR 'mesenchymal stem cell'/exp OR 'stem cell transplantation'/exp OR (adipose NEXT/2 derived NEXT/2 stem) OR 'adipose tissue' OR 'autologous conditioned serum' OR 'autologous fat' OR 'autologous stem cell*' OR 'mesenchymal stem cell*' OR (('micro-fractured' OR microfractured OR 'micro-fragmented' OR microfragmented) NEXT/2 ('adipose tissue' OR fat)) OR 'stem cell therapy'
	#7	Amniotic fluid and membrane	amnion/de OR 'amniotic fluid cell'/exp OR 'amniotic membrane dressing'/de OR chorion/exp OR 'umbilical cord'/exp OR (amnion OR 'amniotic fluid' OR 'amniotic membrane' OR 'amniotic tissue' OR chorion OR 'placenta-derived'):ti,ab OR amniofix*:tn OR amniotic:ti OR placenta*:ti
	#8	Prolotherapy	prolotherapy/exp OR prolotherapy:ti,ab
	#9	Combine intervention sets	#4 OR #5 OR #6 OR #7 OR #8
	#10	Combine population and intervention sets	#3 AND #9
	#11	Apply general hedges	See General Hedges at the end of this table
	#12	Apply meta-analyses, RCTs, and observational studies hedges	See Study Type Hedges at the end of this table

Question	Set #	Concept	Strategy
Question 4 – What are the comparative benefits and harms of topical pharmacotherapy agents versus oral pharmacotherapy for treatment of OA of the hip and knee?	#1	Adults 18+ with OA of the hip and/or knee General	osteoarthritis/de OR (arthrit*:ti,ab NOT rheumatoid:ti) OR OA:ti OR ('osteo-arthritis' OR osteoarthrit* OR 'degenerative joint*' OR 'joint pain'):ti,ab
	#2	Hip and knee	'hip osteoarthritis'/de OR 'knee osteoarthritis'/de OR ((hip/exp OR knee/exp OR (hip OR hips OR knee*):ti) AND (joint* OR pain*):ti,ab)
	#3	Combine population sets	#1 OR #2
	#4	FDA approved topical pharmacotherapy agents Topical administration	'cutaneous drug administration'/de OR 'topical drug administration'/de OR 'transdermal drug administration'/de OR (cutaneous* OR topical* OR transdermal* OR aerosol* OR balm* OR cream* OR creme* OR emulsion* OR foam* OR hydrogel* OR gel OR gels OR lotion* OR liniment OR nanoemulsion* OR ointment* OR (plaster* NOT cast*) OR rub OR rubs OR salve*):ti,ab OR (epicutaneous* OR oil OR oils OR patch* OR spray*):ti
	#5	Specific topical agents	capsaicin/de OR lidocaine/de OR menthol/de OR 'salicylic acid methyl ester'/de OR (arnica OR aspercreme* OR bengay* OR biofreeze* OR camphor* OR capsaicin OR capsicum OR 'deep relief*' OR (diclofenac NEAR/3 (gel OR patch OR topical)) OR ibuleve* OR 'icy hot*' OR lidocaine OR 'methyl salicylate' OR 'methylsalicylate' OR pennsaid* OR powergel* OR voltarol):ti,ab,tn
	#6	Combine intervention sets	#4 OR #5
	#7	Combine population and intervention sets	#3 AND #6
	#8	Apply general hedges	See General Hedges at the end of this table
	#9	Apply meta-analyses and RCTs hedges	See Study Type Hedges at the end of this table

Question	Set #	Concept	Strategy
Question 5 – What are the benefits and harms of tramadol and other opioids as an alternative or adjunct to nonopioid therapies for managing moderately-severe to severe OA of the knee and hip?	#1	Adults 18+ with OA of the hip and/or knee General	osteoarthritis/de OR (arthrit*:ti,ab NOT rheumatoid:ti) OR OA:ti OR ('osteo-arthritis' OR osteoarthrit* OR 'degenerative joint*' OR 'joint pain'):ti,ab
	#2	Hip and knee	'hip osteoarthritis'/de OR 'knee osteoarthritis'/de OR ((hip/exp OR knee/exp OR (hip OR hips OR knee*):ti) AND (joint* OR pain*):ti,ab)
	#3	Combine population sets	#1 OR #2
	#4	Tramadol and nontramadol opioids as alternatives or adjuncts to nonopioid therapies	'opiate agonist'/exp OR 'narcotic analgesic agent'/exp OR (opiate* OR opioid* OR narcotic OR buprenorphine OR codeine OR fentanyl OR hydrocodone OR hydromorphone OR methadone OR morphine OR naloxone OR oxycodone OR oxycontin* OR tapentadol OR tramadol):ti
	#5	Combine population and intervention sets	#3 AND #4
	#6	Remove undesired studies	#5 NOT (arthroplast* OR arthroscop* OR 'hip replacement' OR 'knee replacement' OR pre-operative OR preoperative OR peri-operative OR perioperative OR post-operative OR postoperative OR 'post-surg*' OR postsurg*):ti
	#7	Apply general hedges	See General Hedges at the end of this table
	#8	Apply meta-analyses, RCTs, and observational studies hedges	See Study Type Hedges at the end of this table

Question	Set #	Concept	Strategy
Question 6 – What are the benefits and harms of dietary supplements and nutraceuticals for treatment of OA of the hip and knee?	#1	Adults 18+ with OA of the hip and/or knee General	osteoarthritis/de OR (arthrit*:ti,ab NOT rheumatoid:ti) OR OA:ti OR ('osteo-arthritis' OR osteoarthrit* OR 'degenerative joint*' OR 'joint pain'):ti,ab
	#2	Hip and knee	'hip osteoarthritis'/de OR 'knee osteoarthritis'/de OR ((hip/exp OR knee/exp OR (hip OR hips OR knee*):ti) AND (joint* OR pain*):ti,ab)
	#3	Combine population sets	#1 OR #2
	#4	Dietary supplements and nutraceuticals General	supplementation/exp OR 'dietary supplement'/de OR 'medicinal plant'/exp OR nutraceutical/de OR 'nutrition supplement'/exp OR 'plant medicinal product'/exp OR vitamin/exp OR (((diet* OR food* OR herb* OR medicinal OR mineral* OR nutritional) NEXT/2 (supplement* OR remedies OR remedy)) OR 'anti-oxidant*' OR antioxidant* OR ayurvedic OR 'chinese medicine' OR extract OR extracts OR nutraceutical* OR 'traditional medicine'):ti
	#5	Specific supplements and nutraceuticals	cannabidiol/de OR capsaicin/de OR chondroitin/de OR diacerein/de OR 'dimethyl sulfone'/de OR glucosamine/exp OR 'omega 3 fatty acid'/de OR ((avocado NEXT/1 soy*) OR boswellia OR cannabidiol OR chondroitin OR (collagen NEAR/2 (hydrol* OR supplement*)) OR curcum* OR ('curcumin free' NEXT/1 turmeric) OR diacerein OR 'fish oil' OR glucosamine OR 'green tea' OR L-carnitine OR methylsulfonylmethane OR 'n-3' OR olive OR 'omega 3' OR paniculata OR 'passion fruit peel*' OR pycnogenol OR 'rose-hip*' OR rosehip* OR 'willow bark' OR (vitamin NEXT/1 (C OR D OR E))):ti
	#6	Combine intervention sets	#4 OR #5
	#7	Combine population and intervention sets	#3 AND #6
	#8	Apply general hedges	See General Hedges at the end of this table
	#9	Apply meta-analyses, RCTs, and observational studies hedges	See Study Type Hedges at the end of this table

Question	Set #	Concept	Strategy
Question 7 – What are the benefits and harms of complementary and integrative health treatments of OA of the hip and knee as either monotherapy or adjunctive?	#1	Adults 18+ with OA of the hip and/or knee General	osteoarthritis/de OR (arthrit*:ti,ab NOT rheumatoid:ti) OR OA:ti OR ('osteo-arthrits' OR osteoarthrit* OR 'degenerative joint*' OR 'joint pain'):ti,ab
	#2	Hip and knee	'hip osteoarthritis'/de OR 'knee osteoarthritis'/de OR ((hip/exp OR knee/exp OR (hip OR hips OR knee*):ti) AND (joint* OR pain*):ti,ab)
	#3	Combine population sets	#1 OR #2
	#4	Complementary and integrative health treatments General	'alternative medicine'/exp OR ((alternative OR complementary OR integrative) NEXT/3 (approach* OR medicine OR modalit* OR therapies OR therapy OR treatment*)):ti
	#5	Specific treatments	acupuncture/exp OR balneotherapy/exp OR homeopathy/de OR 'manipulative medicine'/exp OR massage/de OR meditation/de OR mindfulness/de OR 'relaxation training'/de OR 'tai chi'/de OR yoga/de OR (acupuncture OR acupressure OR balneotherapy OR cupping OR homeopath* OR 'manual therapy' OR (magnet* NEXT/1 therapy) OR magnets OR manipulation OR massage OR meditation OR (mind NEXT/2 body) OR mindfulness OR moxibustion OR 'qi gong' OR qigong OR 'tai chi' OR yoga):ti
	#6	Combine intervention sets	#4 OR #5
	#7	Combine population and intervention sets	#3 AND #6
	#8	Apply general hedges	See General Hedges at the end of this table
	#9	Apply SR and RCT study hedges	See Study Type Hedges at the end of this table

Question	Set #	Concept	Strategy
Question 8 – What diagnostic testing is needed to confirm the diagnosis of OA? Weight-bearing radiographs?	#1	Adults 18+ with OA of the hip and/or knee General	osteoarthritis/de OR (arthrit*:ti,ab NOT rheumatoid:ti) OR OA:ti OR ('osteo-arthrits' OR osteoarthrit* OR 'degenerative joint*' OR 'joint pain'):ti,ab
	#2	Hip and knee	'hip osteoarthritis'/de OR 'knee osteoarthritis'/de OR ((hip/exp OR knee/exp OR (hip OR hips OR knee*):ti) AND (joint* OR pain*):ti,ab)
	#3	Patellofemoral joint	'patellofemoral joint'/de OR (patellar OR patellofemoral):ti
	#4	Combine population sets	#1 OR #2 OR #3
	#5	Focus on weight-bearing studies	('weight-bearing'/mj OR ('extended knee' OR 'frog-leg' OR seated OR sit OR squatting OR stand OR standing OR stress OR upright OR 'weight bearing' OR weightbearing):ti) AND ('hip radiography'/de OR 'joint radiography'/de OR 'knee radiography'/de OR radiography/de OR 'radiography device'/de OR 'stress radiograph'/de OR 'x ray system'/exp OR (film OR films OR radiograph* OR radiolog* OR x-ray*):ti,ab)
	#6	Focus on radiography studies	('weight-bearing'/de OR ('extended knee' OR 'frog-leg' OR seated OR sit OR squatting OR stand OR standing OR stress OR upright OR 'weight bearing' OR weightbearing):ti,ab) AND ('hip radiography'/mj OR 'joint radiography'/mj OR 'knee radiography'/mj OR radiography/mj OR 'radiography device'/mj OR 'stress radiograph'/mj OR 'x ray system'/exp/mj OR (film OR films OR radiograph* OR radiolog* OR x-ray*):ti)
	#7	Combine intervention sets	#5 OR #6
	#8	Combine population and intervention sets	#4 AND #7
	#9	Apply general hedges	See General Hedges at the end of this table
	#10	Limit to SRs and diagnostic cohort studies	No Study Type Hedges were applied; studies to be identified by hand

Question	Set #	Concept	Strategy
Question 9 – What are the benefits and harms of electrostimulation devices on hip and knee OA?	#1	Adults 18+ with OA of the hip and/or knee General	osteoarthritis/de OR (arthrit*:ti,ab NOT rheumatoid:ti) OR OA:ti OR ('osteo-arthritis' OR osteoarthrit* OR 'degenerative joint*' OR 'joint pain'):ti,ab
	#2	Hip and knee	'hip osteoarthritis'/de OR 'knee osteoarthritis'/de OR ((hip/exp OR knee/exp OR (hip OR hips OR knee*):ti) AND (joint* OR pain*):ti,ab)
	#3	Combine population sets	#1 OR #2
	#4	Electrostimulation devices General terms	'transcutaneous electrical nerve stimulation'/de OR 'neuromuscular electrical stimulation'/de OR 'neuromuscular stimulator'/de OR (((('micro current' OR microcurrent) NEXT/1 electric* NEXT/1 therapy) OR PENS OR (percutaneous NEXT/1 electric* NEXT/1 nerve NEXT/1 stimulat*) OR TENS OR (transcutaneous NEXT/1 electric* NEXT/1 nerve NEXT/1 stimulat*) OR ((electric* OR electro*) NEXT/1 stimulat*) OR electrostimulat* OR ((nerve* OR neuro OR neuromuscular) NEXT/1 stimulat*) OR neurostimulat*):ti
	#5	Specific brand name devices	('h-wave*' OR biowave* OR 'alpha-stim*'):ti,dn
	#6	Combine intervention sets	#4 OR #5
	#7	Combine population and intervention sets	#3 AND #6
	#8	Apply general hedges	See General Hedges at the end of this table
	#9	Apply SR and RCT study hedges	See Study Type Hedges at the end of this table

Question	Set #	Concept	Strategy
<p>Question 10 – What are the benefits and harms of weight loss on short-term and long-term complications and outcomes of hip and knee OA? Does this: Vary by BMI: including 25 – 29, 30 – 35, 35 – 40, >40? Vary by pain severity? Delay need for surgical treatment or improve surgical outcomes?</p>	#1	Adults 18+ with OA of the hip and/or knee General	osteoarthritis/de OR (arthrit*:ti,ab NOT rheumatoid:ti) OR OA:ti OR ('osteo-arthritis' OR osteoarthrit* OR 'degenerative joint*' OR 'joint pain'):ti,ab
	#2	Hip and knee	'hip osteoarthritis'/de OR 'knee osteoarthritis'/de OR ((hip/exp OR knee/exp OR (hip OR hips OR knee*):ti) AND (joint* OR pain*):ti,ab)
	#3	Combine population sets	#1 OR #2
	#4	Adults 18+ with OA of the hip and/or knee with BMI >25 kg/m ²	'obese patient'/de OR obesity/exp OR (obes* OR overweight OR BMI):ti,ab
	#5	Diet therapy; Exercise; Diet and exercise	diet/exp OR 'diet therapy'/exp OR exercise/exp OR kinesiotherapy/exp OR (aerobics OR diet* OR exercis* OR fitness OR jogging OR 'physical activity' OR walking OR 'weight training' OR running):ti,ab
	#6	General weight loss	'body weight loss'/de OR 'body weight management'/exp OR (BMI AND lower*):ti,ab OR (weight AND (lose* OR losing OR loss OR reduc*)):ti,ab
	#7	Combine intervention sets	(#4 AND #5) OR #6
	#8	Combine population and intervention sets	#3 AND #7
	#9	Apply general hedges	See General Hedges at the end of this table
	#10	Apply SR and RCT study hedges	See Study Type Hedges at the end of this table

Question	Set #	Concept	Strategy
Question 11 – What is the comparative effectiveness of physical therapy for OA of the hip and knee? - Manual versus non-impact PT; - Timing; - Modalities of care delivery (e.g., in-person or virtual); - Dose/intensity of PT	#1	Adults 18+ with OA of the hip and/or knee General	osteoarthritis/de OR (arthrit*:ti,ab NOT rheumatoid:ti) OR OA:ti OR ('osteo-arthritis' OR osteoarthritis* OR 'degenerative joint*' OR 'joint pain'):ti,ab
	#2	Hip and knee	'hip osteoarthritis'/de OR 'knee osteoarthritis'/de OR ((hip/exp OR knee/exp OR (hip OR hips OR knee*):ti) AND (joint* OR pain*):ti,ab)
	#3	Combine population sets	#1 OR #2
	#4	Physical therapy General Note: the Emtree term 'manipulative medicine'/exp and the keywords 'manual therapy' and 'manipulation' are associated with chiropractic care and physical therapy. These terms were searched with KQ 7 above and therefore were not included with the search for this KQ (even though they are relevant) to avoid retrieving duplicate search results.	physiotherapy/exp/mj OR (mobilisation OR mobilization OR physiotherap* OR (physical NEXT/1 therapist*) OR 'physical therapy'):ti
	#5	Non-impact activity (e.g., aquatic PT, cycling)	aquatic exercise/de OR cycling/de OR hydrotherapy/de OR treadmill/de OR 'treadmill exercise'/de OR (aquatic* OR conditioning OR cycling OR hydrotherapy OR 'low impact' OR 'non-impact' OR nonimpact OR resistance OR strength* OR stretch* OR training OR treadmill):ti
	#6	Combine intervention sets	#4 OR #5
	#7	Combine population and intervention sets	#3 AND #6
	#8	Apply general hedges	See General Hedges at the end of this table
	#9	Apply SR and RCT study hedges	See Study Type Hedges at the end of this table
Question 12 – What are the benefits and harms of various self-management interventions for OA of the hip and knee?	#1	Adults 18+ with OA of the hip and/or knee General	osteoarthritis/de OR (arthrit*:ti,ab NOT rheumatoid:ti) OR OA:ti OR ('osteo-arthritis' OR osteoarthritis* OR 'degenerative joint*' OR 'joint pain'):ti,ab
	#2	Hip and knee	'hip osteoarthritis'/de OR 'knee osteoarthritis'/de OR ((hip/exp OR knee/exp OR (hip OR hips OR knee*):ti) AND (joint* OR pain*):ti,ab)
	#3	Combine population sets	#1 OR #2
	#4	Self-management strategies General concepts and specific programs	'self care'/mj OR (self NEXT/1 (care OR help OR directed OR manag*)):ti OR (program OR programs OR programm*):ti OR ('arthritis toolkit' OR 'better choices better health' OR tomando):ti,ab

Question	Set #	Concept	Strategy
Question 12 – What are the benefits and harms of various self-management interventions for OA of the hip and knee? (cont.)	#5	Exercise	exercise/exp/mj OR kinesiotherapy/exp/mj OR physical activity/exp/mj OR sport/exp/mj OR 'activity guidelines':ti,ab OR (aerobics OR (aerobic* NEXT/1 activit*) OR athletic* OR bicycl* OR bike OR bikes OR biking OR danc* OR exercis* OR fitness OR golf* OR jog OR jogger* OR jogging OR kinesiotherap* OR land-based OR pilates OR run OR runner* OR running OR sport OR sports OR swim* OR walk* OR water-based OR tennis OR 'weight lifting' OR (work* NEXT/1 (out OR outs)) OR workout*):ti
	#6	Thermal modalities	cryotherapy/de OR thermotherapy/mj OR ((superficial NEXT/3 (cold OR contrast OR cool* OR heat* OR hot OR warm*)):ti,ab OR cryotherapy:ti OR hot OR thermal):ti
	#7	Assistive devices, orthoses, orthotics	orthosis/exp OR orthotics/de OR 'walking aid'/exp OR ((assistive NEXT/1 device*) OR brace OR braces OR bracing OR cane OR canes OR crutch* OR footwear OR insole* OR orthos* OR orthotic* OR shoe* OR taping OR splint OR splints OR walker* OR (walking NEXT/1 (aid OR aids OR device* OR stick*)) OR (wedge NOT osteotom*) OR wedges):ti
	#8	Combine intervention sets	#4 OR #5 OR #6 OR #7
	#9	Combine population and intervention sets	#3 AND #8
	#10	Remove search terms related to qi gong, tai chi, and yoga, as they were already searched with KQ 7, above (this reduces duplicate search results)	#9 NOT ('tai chi'/de OR yoga/de OR ('qi gong' OR qigong OR 'tai chi' OR yoga):ti)
	#11	Remove search terms related to high BMI and weight loss (with exercise) as they were already searched with KQ 10, above (this reduces duplicate search results)	#10 NOT ('obese patient'/de OR obesity/exp OR 'body weight loss'/de OR 'body weight management'/exp OR (obes* OR overweight OR BMI):ti,ab OR (BMI AND lower*):ti,ab OR (weight AND (lose* OR losing OR loss OR reduc*)):ti,ab)
	#12	Remove search terms related to aquatic and non-impact exercises as they were already searched with KQ 11, above (this reduces duplicate search results)	#11 NOT (aquatic exercise/de OR cycling/de OR hydrotherapy/de OR treadmill/de OR 'treadmill exercise'/de OR (aquatic* OR conditioning OR cycling OR hydrotherapy OR 'low impact' OR 'non-impact' OR nonimpact OR resistance OR strength* OR stretch* OR training OR treadmill):ti)
	#13	Apply general hedges	See General Hedges at the end of this table
	#14	Apply SR and RCT study hedges	See Study Type Hedges at the end of this table

Question	Set #	Concept	Strategy
General Hedges Applied to Each Search		Exclude animal and experimental studies	NOT ([animals]/lim OR (animal* OR experimental OR (vitro NOT vivo) OR canine OR dog OR dogs OR mouse OR mice OR rabbit* OR rat OR rats OR rodent* OR sheep OR swine):ti)
		Exclude studies focusing on children	NOT ((adolescen* OR child* OR infant* OR juvenile* OR neonat* OR newborn* OR paediatric* OR pediatric*):ti NOT adult:ti)
		Limit to English language publications and results with abstracts	AND [english]/lim AND [abstracts]/lim
		Remove undesired publication and study types (e.g., case reports, conferences, editorials)	NOT ('conference paper'/exp OR [conference abstract]/lim OR [conference paper]/lim OR [conference review]/lim OR ('case report' OR book OR editorial OR erratum OR letter OR note OR 'short survey')/de OR (book OR conference OR editorial OR erratum OR letter OR note OR 'short survey'):it OR ('a case' OR 'a patient' OR 'year old'):ti,ab OR (book OR 'conference proceeding'):pt OR ('case report' OR comment OR protocol):ti)
		Limit to results added to the database since the prior literature search (December 2012)	AND [30-11-2012]/sd
		Exclude studies on other arthritic conditions	NOT ((fibromyalg* OR gout OR psoriasis OR psoriatic OR rheumat* OR spondylo*):ti NOT osteoarthritis:ti)
		Exclude studies on osteoarthritis/pain other than hip or knee	NOT (ankle OR foot OR hallux OR hand OR hands OR (low* NEXT/1 back) OR lumbar OR pubic OR pubis OR 'osteoid osteoma' OR scoliosis OR shoulder* OR spinal OR spine OR wrist*):ti
Study Type Hedges Applied as Needed (per Key Question Specific Criteria provided earlier in this report)		Limit to meta-analyses and systematic reviews	AND ('meta analysis'/de OR 'randomized controlled trial (topic)'/de OR 'systematic review'/de OR (EMBASE OR 'meta analysis' OR 'meta analytic' OR metaanaly* OR 'research synthesis' OR (systematic NEXT/3 review) OR pooled OR pooling OR RCTs OR search*):ti,ab OR ('critical review' OR 'evidence based' OR systematic*):ti OR [cochrane review]/lim)
		Limit to randomized controlled trials	AND ('random sample'/de OR 'randomized controlled trial'/de OR randomization/de OR (random* OR RCT):ti,ab)

EMBASE.com Syntax:

- * = truncation character (wildcard)
- NEAR/*n* = search terms within a specified number (*n*) of words from each other in any order
- NEXT/*n* = search terms within a specified number (*n*) of words from each other in the order specified
- / = search as a subject heading
- exp = “explodes” controlled vocabulary term (e.g., expands search to all more specific related terms in the vocabulary’s hierarchy)
- mj = denotes a term that has been searched as a major subject heading
- de = non-major subject heading
- :lnk = floating subheading
- :it,pt = source item or publication type
- lim = limit
- sd = entry date (date that the record is added to the database)
- :ti = limit to title
- :ti,ab = limit to title and abstract fields

Appendix J: Alternative Text Description of Algorithm

Algorithm: Management and Treatment of Osteoarthritis of the Hip and/or the Knee

The following outline narratively describes [Algorithm: Management and Treatment of Osteoarthritis of the Hip and/or the Knee](#). An explanation of the purpose of the algorithm and description of the various shapes used within the algorithm can be found in the [Algorithm](#) section. The sidebars referenced within this outline can also be found in the [Algorithm](#) section.

1. The algorithm begins with Box 1, in the shape of a rounded rectangle: “Patient diagnosed with OA of the hip and/or knee”
2. Box 1 connects to Box 2, in the shape of a rectangle: “Assess pain, severity, and functional limitations”
3. Box 2 connects to Box 3, in the shape of a rectangle: “Develop individualized treatment plan with core non-surgical management approaches (see Sidebar 1)”
4. Box 3 connects to Box 4, in the shape of a hexagon, and asks the question: “Has the patient’s pain or functional limitation improved on re-evaluation?”
 - a. If the answer is “Yes” to Box 4, then continue to Box 5, in the shape of a rectangle: “Continue long-term management of OA and reassess annually or as needed”
 - b. If the answer is “No” to Box 4, then continue to Box 6, in the shape of a rectangle: “Offer referral to physical therapy and/or combination pharmacotherapy (see Sidebars 2 and 3)”
5. Box 6 connects to Box 7, in the shape of a hexagon, and asks the question: “Has the patient’s pain or functional limitation improved on re-evaluation?”
 - a. If the answer is “Yes” to Box 7, then continue to Box 5, in the shape of a rectangle: “Continue long-term management of OA and reassess annually or as needed”
 - b. If the answer is “No” to Box 7, then continue to Box 8, in the shape of a rectangle: “Referral for additional physical therapy”
6. Box 8 connects to Box 9, in the shape of a hexagon, and asks the question: “Has the patient’s pain or functional limitation improved on re-evaluation?”
 - a. If the answer is “Yes” to Box 9, then continue to Box 5, in the shape of a rectangle: “Continue long-term management of OA and reassess annually or as needed”
 - b. If the answer is “No” to Box 9, then continue to Box 10, in the shape of a rectangle: “Obtain weight-bearing plain radiographs prior to referral for surgical consultation (see Appendix K)”
7. Box 10 connects to Box 11, in the shape of a rectangle: “Refer for surgical consultation”

Appendix K: Referrals for Surgical Consultation

For patients with OA of the hip and/or knee considered for surgical consultation, the Work Group suggests that providers obtain plain radiographs within six months of referral to surgical consultation. This appendix is based on a recommendation in the 2014 VA/DoD OA CPG. This was added as an appendix rather than a recommendation because the Work Group could not find high quality evidence meeting the GRADE criteria in the literature to support this as a recommendation. However, the Work Group would like to highlight that this is standard clinical practice and therefore is important to include in this CPG.

The Work Group also felt it was crucial to include an important imaging study, which concludes that imaging helps the surgeon and patient make a decision with regard to surgical options and treatment of OA of the hip and/or knee. A retrospective cohort study (n=383) by Chang et al. (2010) with one-year follow-up data evaluated the radiographic severity of OA using WOMAC scores as preoperative measures and WOMAC scores and level of patient satisfaction as postoperative outcomes.[\[251\]](#) The study concluded that the severity of radiographic OA had no significant associations with postoperative outcomes. A prospective cohort study (n=69) by Lundblad et al. (2012) reviewed preoperative radiographs and histological samples in patients undergoing total knee arthroplasty (TKA) and related the findings to pain at rest and movement both preoperatively and postoperatively according to VAS scores.[\[252\]](#) The study concluded there is a correlation between the grade of radiographic OA and change in pain with movement at 18 months after TKA despite the poor correlation between preoperative pain and the grade of radiographic OA among patients scheduled for TKA.

On balance, the Work Group determined that preoperative radiographs are essential for surgical planning. It is standard practice to obtain preoperative weight-bearing radiographs when planning knee arthroplasty procedures. Most surgeons prefer an x-ray prior to performing the procedure and these x-rays are commonly weight-bearing radiographs. There have been no studies that have specifically looked at the differences between weight-bearing versus non-weight-bearing radiographs, hence, the Work Group was unable to make any specific recommendations regarding weight-bearing versus non-weight-bearing radiographs in the recommendation.

Obtaining preoperative radiographs does not cause excessive harm to patients and it is an important tool in preoperative planning and patient management. Patients would like their providers to have all the information they need to plan their operative procedure and would understand that providers would need to know what their hip and/or knee looks like before the procedure. There is very minimal harm in the form of radiation exposure; therefore, the Work Group determined the benefits outweigh the harms/burden. Providers may also consider that some patients may not be candidates for surgery given their age or comorbidities.

More research is needed to compare the value of weight-bearing and non-weight-bearing radiographs in the preoperative workup of OA of the knee. It will be important to see the effect weight-bearing radiographs have on the provider's decision-making process for TKA. Since it is common clinical practice to obtain weight-bearing radiographs, it would be important to know if there is a statistically significant difference in weight-bearing versus non-weight-bearing radiographs in the diagnostic severity of OA.

Appendix L: Abbreviations

Abbreviation	Definition
ADMSC	adipose-derived mesenchymal stem or stromal cells
AHRQ	Agency for Healthcare Research and Quality
BMI	body mass index
CDC	Centers for Disease Control and Prevention
CI	confidence interval
CIH	complementary and integrative health
CKD	chronic kidney disease
cm	centimeters
CMS	Centers for Medicare & Medicaid Services
COI	conflict of interest
COR	contracting officer's representative
COX	cyclooxygenase
CPG	clinical practice guideline
CS	corticosteroid
CSI	corticosteroid injection
CV	cardiovascular
CVD	cardiovascular disease
dL	deciliters
DoD	Department of Defense
EBPWG	Evidence-Based Practice Work Group
eGFR	estimated glomerular filtration rate
FDA	Food and Drug Administration
g	grams
GFR	glomerular filtration rate
GI	gastrointestinal
GRADE	Grading of Recommendations Assessment, Development, and Evaluation
HA	hyaluronic acid
HR	hazard ratio
ITT	intention-to-treat
IU	international units
kg	kilograms
KLGS	Kellgren and Lawrence Grading Scale
KOOS	Knee Injury and Osteoarthritis Outcome Score
KQ	key question
LFT	liver function test
mg	milligrams
MI	myocardial infarction
MID	minimally important difference

Abbreviation	Definition
min	minute
ml	milliliters
MRI	magnetic resonance imaging
MSC	mesenchymal stem or stromal cells
MSM	methylsulfonylmethane
NICE	National Institute for Health and Care Excellence
NSAID	non-steroidal anti-inflammatory drug
OA	osteoarthritis
OMERACT-OARSI	Outcome Measures in Rheumatology Clinical Trials – Osteoarthritis Research Society
OTC	over-the-counter
PICOTS	the population, intervention, comparison, outcome, timing, and setting
PCC	patient-centered care
PPI	proton-pump inhibitor
PRECISION	Prospective Randomized Evaluation of Celecoxib Integrated Safety versus Ibuprofen or Naproxen
PRP	platelet-rich plasma
RA	rheumatoid arthritis
RCT	randomized controlled trial
RDA	recommended dietary allowance
RR	relative risk
SCr	serum creatinine
SDM	shared decision making
SMD	standard mean difference
SP	substance P
SR	systematic review
TENS	transcutaneous electrical nerve stimulation
TKA	total knee arthroplasty
U.S.	United States
USPSTF	U.S. Preventive Services Task Force
VA	Department of Veterans Affairs
VAS	Visual Analog Scale
VHA	Veterans Health Administration
VSI	viscosupplementation injection
WOMAC	Western Ontario and McMaster Universities Osteoarthritis Index
YLDs	years lived with disability

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