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 recommendations.

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 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 1.0 – 2014

Prepared by:

THE NON-SURGICAL MANAGEMENT OF HIP & KNEE OSTEOARTHRITIS

Working Group

With support from:

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&

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Executive Summary

According to the Centers for Disease Control and Prevention (CDC), 13.9 percent of adults age 25 years and older and 33.6 percent of adults age 65 years and older are affected by osteoarthritis (OA). Arthritis appears to be a significant burden among Veterans of the United States (US) Armed Forces. [1] Research suggests that military service-related overuse and injuries may be a contributing factor for the increased risk of developing OA. One study examined the incidence of OA among active duty US Service Members between 1999 and 2008 where they concluded that rates of OA were "significantly higher in military populations than in comparable age groups in the general population." Severe OA of the hip and knee causes debilitating pain and is a common cause of mobility impairment in elderly patients. [2]

The Department of Veterans Affairs (VA) and Department of Defense (DoD) have an obligation to ensure that all patients with OA receive a full range of high quality care. This clinical practice guideline (CPG) recommends a framework that includes a structured evaluation and diagnosis of Veterans and Service Members who may be suffering from hip and knee OA. Additionally, the CPG provides treatment options, including pharmacological, non-pharmacological, complementary and alternative medicine, as well as options for referral for surgical consultation.

Topics discussed in this CPG include:

- Diagnosis and evaluation of OA
- Comparative effectiveness of pharmacological therapies for OA
- Comparative effectiveness of non-pharmacologic therapies
- Comparative effectiveness of complementary and alternative medicine
- Referrals for surgical consultation

OA is typically diagnosed based on the patient's medical history and a physical examination. Patients with OA may have morning joint stiffness that usually resolves within 30 minutes. As the disease progresses, prolonged joint stiffness and joint enlargement may also become evident. Although radiographs are not required to make a diagnosis of knee OA, they can be used to confirm the diagnosis and to rule out fracture, osteonecrosis, malignancy, or other conditions. Primary care providers could consider radiographs such as the weight-bearing tunnel or Rosenberg view to aid in differential diagnosis and guide the overall treatment plan.

A management plan for a patient with OA involves a partnership between the patient and primary care provider to develop an individualized course of treatment that can provide optimal results. Decisions regarding pharmacological therapy should be based on a risk benefit assessment, patient preference, and resource utilization. This process will allow selection of pharmacologic agents with proven benefit to be used in conjunction with non-pharmacologic interventions. Non-pharmacologic therapies (i.e., physical therapy (including aquatic therapy, land-based strength therapy, and manual physical therapy), as well as acupuncture and chiropractic care) should also be considered during the development of a patient's management plan. Lastly, the primary care provider may consider referral

for surgical evaluation for OA patients that do not find relief through pharmacologic and/or non-pharmacologic therapies.

The goal of this guideline is to assist primary care providers in developing a comprehensive care program for patients with OA in order to achieve maximum functionality and independence, as well as improve patient and family quality of life.

Background

Public Health Burden of Osteoarthritis to the U.S. Population

Arthritis, of which osteoarthritis is the most common type, is the most frequent cause of disability among adults in the United States. In 2005, The National Arthritis Data Work Group estimated that 27 million US adults, ages 18 or older, had one or more type of clinical OA, representing more than ten percent of the US adult population. Consequently, clinical OA affects quality of life (QoL) in many patients through pain and functional limitations. [3] The economic burden of direct and indirect costs associated with OA is also significant, likely exceeding $60 billion annually. [2]

Veterans and Service Members

Most information on OA is reported on elderly populations with less data about the prevalence of OA in younger and physically active populations. While OA is clearly considered a disease that affects older patients, increasing in prevalence with advancing age, recently many studies document that OA is also a common problem in patients younger than the age of 65. Occupational physical demands and traumatic joint injury have been associated with the development of OA. Studies also suggest that physical activity involving repetitive joint loading may be associated with incidence of OA. [2] The active duty U.S. Service Members population provides an excellent opportunity to examine the prevalence of OA in a young and physically active group that is regularly exposed to repetitive joint loading during physical activity and occupational tasks.

A total of 108,266 patients with incident cases of OA and 13,768,885 person-years of follow-up were documented in the Defense Medical Surveillance System during a 10-year study period. On average, 10,827 incident cases of OA were diagnosed each year of the study among 1,376,889 active duty US Service Members. The overall incidence rate for OA during the study period within the military population was 7.86 (95% CI 7.82–7.91) cases per 1,000 person-years. Females experienced a slightly higher incidence rate for OA when compared to males. The adjusted incidence rate for OA was ~20 percent higher in women when compared to men (rate ratio 1.19, 95% CI 1.17-1.21). Age was a significant factor among older Service Members (>40 years) who experienced a much greater incidence of OA compared to younger Service Members (<20 years) (rate ratio 18.61, 95 % CI 17.57-19.57). [2]

Occupational risk factors including military rank and branch of military service were associated with variation in the incidence of OA in a current study. Junior and senior enlisted Service Members and those serving in the Army experienced the highest incidence rates for OA. Scher et al. [4] reported similar findings for the incidence rate of primary hip OA in a military population. It is likely that Service Members in these occupational groups engage in regular hip and knee bending and medium, heavy, or very heavy physical demands on a regular basis. They also engage in physical activities involving significant joint loading, particularly in the lower extremity. When comparing rates of OA in military versus general populations, rates of OA are significantly higher in the military population compared to the general population of the same age group. [2]

Methods

The recommendations presented in this CPG are based on a systematic appraisal of the published evidence on non-surgical interventions for managing OA. In areas where the evidence is particularly lacking, expert opinion served as the basis for the recommendation. Published evidence was identified through extensive searches of the following databases: MEDLINE, PreMEDLINE, EMBASE, (via the OVID SP platform using the one-search and de-duplication features), the Cochrane Database of Systematic Reviews, the Database of Abstracts of Reviews of Effects, and the Health Technology Assessment Database. Searches were designed to identify unique reviews, trials, and technology assessments. Searches of the World Wide Web were also performed to capture relevant grey literature that has not been indexed to the databases listed above. The searches covered the time period of January 2002 through December 2012.

In general, full-text clinical studies or systematic reviews published in peer-reviewed journals were considered as evidence in this CPG. Stand-alone abstracts, letters, editorials, and non-English language papers were excluded from the searches. Other study selection criteria varied depending on the context of the study (e.g., diagnostic study, intervention study, or referral study). For instance, intervention studies must have been prospective, randomized or nonrandomized comparative trials with an independent, concurrent control group that enrolled at least 25 patients per treatment arm. Diagnostic studies, on the other hand, could have been either prospective or retrospective, but must have linked use of diagnostic technologies with improvement in clinical outcomes and enrolled at least 10 patients. Diagnostic studies that only considered diagnostic test properties (i.e., sensitivity or specificity) were not included as evidence in this report.

This guideline focuses primarily on the following patient-centered outcomes: pain, function, and harms. The evidence from each included study was abstracted into evidence tables and narratively synthesized. The methodological quality of the included systematic reviews and independent clinical studies was assessed using the U.S. Preventive Services Task Force (USPSTF) method. Each study was assigned a rating of Good, Fair, or Poor based on sets of criteria that varied depending on study design. Detailed lists of criteria and definitions of Good, Fair, or Poor ratings for different study designs appear in the USPSTF procedure manual. [5] The strength of the evidence was assessed along the following criteria: methodological quality, consistency of findings across studies, directness of the evidence (e.g., head-to-head comparisons provide the most direct evidence), and precision (i.e., the degree of certainty around an outcome's effect size).

Overall, the evidence base for this guideline consisted of 155 studies. The majority of the evidence addressed pharmacological or non-pharmacological interventions for OA of the knee. Fewer studies addressed interventions for OA of the hip. All the evidence addressing pharmacological and non-pharmacological interventions came from head-to-head comparative trials that compared one intervention to another or one intervention to a placebo or sham condition. Inconsistencies in the evidence are discussed in the text describing the basis of a recommendation. Very few studies considered the contribution of diagnostic methods, such as various imaging modalities and laboratory tests, to improve clinical outcomes of adults with OA of the hips and/or knees.

Finally, the evidence addressing the association of various indications (e.g., patient signs and symptoms, imaging findings) for referral to surgery (partial or total joint replacement) was mostly indirect. Ideally, studies addressing indications for referral to surgery would be randomized or non-randomized prospective controlled trials of patients with OA of the hip or knee (advanced enough to be considered surgical candidates) that assigned patients with similar diagnostic imaging findings or signs and/or symptoms to either more intensive non-surgical treatment such as joint injections or total/partial joint replacement surgery. However, the literature searches did not identify any such studies.

Scope and Structure

The Veterans Affairs (VA) and Department of Defense (DoD) Evidence-Based Practice Working Group (EBPWG) was established and first chartered in 2004, with a mission to advise the "…Health Executive Council 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 for the VA and DoD populations. This Clinical Practice Guideline (CPG) is intended to provide primary care clinicians with a framework by which to evaluate the individual needs and preferences of patients with OA, leading to improved clinical outcomes. It is designed to be adapted by individual facilities in consideration of local needs and resources. The algorithm serves as a guide that providers can use to determine best interventions and timing of care for their patients in order to optimize quality of care and clinical outcomes.

Although this CPG represents the practice on the date of its publication, medical practice is evolving and this evolution requires continuous updating based on published information. New technology and more research will improve patient care in the future. This CPG can assist in identifying and prioritizing areas for research, and optimizing the allocation of resources. Future studies examining the results of clinical practice guidelines may lead to the development of new practice-based evidence.

Target Audience

This CPG is designed for primary care providers in an ambulatory care setting. The modules can also be used to coordinate and standardize care within specialty teams.

Population

This CPG applies to any adult patient eligible for care in the VHA or DoD healthcare delivery systems who has chronic joint complaints in the absence of acute trauma. Such patients should be screened for, and if necessary, be treated for hip and knee OA as described in this guideline.

Intervention

The interventions reviewed and discussed in this CPG are physical therapy, pharmacologic, and surgical approaches. In this context, physical therapy approaches are described as any traditional, manual, land-based, and aquatic therapy that can be used as mono- or adjunctive to pharmacologic and surgical interventions. Pharmacologic approaches include all medications currently indicated for the management of osteoarthritis. As this CPG is intended for non-surgical management of OA, the discussion on surgical approaches is limited to considerations for patient referral. This CPG did not

consider or review the evidence for behavioral therapies (i.e., cognitive behavioral therapy) for the management of OA.

Patient-Centered Care

Guideline recommendations are patient-centered. Regardless of setting, or the availability of professional expertise, any patient in the healthcare system should be provided with the interventions that are recommended in this guideline and found to be appropriate to the patient's specific condition.

Treatment and care should take into account a patient's needs and preferences. Good communication between healthcare professionals and the patient is essential. It should be supported by evidence-based information tailored to the patient's needs. The information that patients are given about treatment and care should be culturally appropriate and available to people who do not speak or read English or who have limited literacy skills. It should also be accessible to people with additional needs such as physical, sensory or learning disabilities.

Care of Service Members in transition between facilities, services, or from the DoD health care system to the VHA should have a transition plan and be managed according to best practice guidance. Health care teams should work jointly to provide assessment and services to patients within this transitioning patient population. Management should be reviewed throughout the transition process, and there should be clarity about who is the lead clinician to ensure continuity of care.

This guideline is structured by six modules addressing the following components of care:

Module A: **Diagnosis and Evaluation** – Any adult eligible for care in the VHA or DoD healthcare delivery system who has chronic joint complaints in the absence of acute trauma should be evaluated for OA.

Module B: **Core Non-Surgical Treatment Principles –** As part of a shared decision making process, a plan should be developed to determine the effectiveness of selected non-pharmacologic and/or pharmacologic interventions and to monitor for adverse events. The close monitoring for efficacy and adverse events will determine if a program or intervention should be modified, continued, or terminated. Overarching principles such as the utilization of shared-decision making and patient-centeredness should be incorporated in the care and management of patients with OA.

Module C: **Physical Therapy Approaches** – Patients with diagnosed OA should be referred to a physical therapist for management of resultant pain, impairments, functional limitations, and disability. Reducing risk for falls and improving functional mobility should be a primary focus.

Module D: **Pharmacologic Therapies** – The patient and health care provider should develop an individualized course of pharmacologic treatment that has optimal effectiveness for each patient with OA. This process involves a complete medical assessment of the

patient that will allow an understanding of the risk and benefits that may be anticipated with pharmacologic therapies.

Module E: **Complementary and Alternative Medicine** – Patients with diagnosed OA may explore the use of dietary supplemental and alternative therapies, such as acupuncture and chiropractic care, to alleviate pain.

Module F: **Referrals for Surgical Consultation** – Patients are referred for surgical consultation when the OA leads to a significant impact on their QoL and /or they are not responding to nonsurgical treatment.

Strength of Recommendations

In order for the clinician to be aware of the evidence base behind the recommendations and the weight that should be given to each recommendation, the recommendations are keyed according to the level of confidence with which each recommendation is made. The graded recommendations are based on two main dimensions: 1) net benefit of an intervention and 2) certainty of evidence associated with that net benefit. When evidence is limited, the level of confidence also incorporates clinical consensus with regard to a particular clinical decision. The strength of recommendation is based on the level of the evidence and graded using the USPSTF rating system (see Table 1. Strength of Recommendation Rating). The discussion following the recommendations for each annotation includes the quality of the evidence that has been considered and the strength of recommendations (SR).

Table 1. Strength of Recommendation Rating (SR) [5]

Grade	Definition	Suggestions for Practice
A	The USPSTF recommends the service. There is high certainty that the net benefit is substantial.	Offer or provide this service.
B	The USPSTF recommends the service. There is high certainty that the net benefit is moderate or there is moderate certainty that the net benefit is moderate to substantial.	Offer or provide this service.
C	The USPSTF recommends selectively offering or providing this service to individual patients based on professional judgment and patient preferences. There is at least moderate certainty that the net benefit is small.	Offer or provide this service for selected patients depending on individual circumstances.
D	The USPSTF recommends against the service. There is moderate or high certainty that the service has no net benefit or that the harms outweigh the benefits.	Discourage the use of this service.
I Statement	The USPSTF concludes that the current evidence is insufficient to assess the balance of benefits and harms of the service. Evidence is lacking, of poor quality, or conflicting, and the balance of benefits and harms cannot be determined.	If the service is offered, patients should understand the uncertainty about the balance of benefits and harms.

Grade of EO for Expert Opinion: To grade the recommendations for the guideline, the Working Group members used a variation of the USPSTF grading framework to provide a grade of EO for "Expert Opinion." Given that evidence-based clinical practice guidelines have to be used in real practice settings for Veterans and Service Members, a grade of I for insufficient evidence may not provide useful guidance for supporting clinical decisions. In particular, we considered certain instances in which evidence suggests a Substantial or Moderate net benefit, but the certainty/strength of that evidence is Low. In those instances, rather than concluding that the evidence is insufficient to support a clinical decision, we relied on Expert Opinion to support a recommendation. A grade of EO does not imply that the evidence is strong (it is still Low). Rather, it suggests 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). The final CPG document represents a synthesis of current scientific knowledge and clinical practice regarding the non-surgical management of hip and knee OA. It attempts to be as free as possible of bias toward any theoretical or empirical approach to treatment.

Recommendations with grades A or B typically employ the terms "should" or "should consider", respectively, as it indicates that the certainty of the evidence and magnitude of net benefits is high. Recommendations with a grade C typically use the phrase "may" or "may consider" and recommendations with a grade D use a negative phrase such as "do not". Recommendations with insufficient evidence are stated as such with no positive or negative implication, while expert opinion recommendations may use any of these phrases. It is important to note that these are merely guidelines and should not be accepted as the rule. For example, some recommendations in this CPG with a C grade, may use the term "should" rather than the more common, "may". Careful consideration was given by the Champions regarding the terminology used in each recommendation and may not necessarily follow the guidelines as described above.

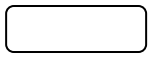
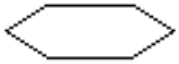
This CPG is the product of many months of diligent effort and consensus building among knowledgeable individuals from the VHA and the DoD. An experienced moderator facilitated the multidisciplinary Working Group. The draft document was discussed in a face-to-face group meeting. The content and validity of each section was thoroughly reviewed in a series of conference calls. The final document is the product of those discussions and has been approved by all members of the Working Group. The list of participants is included in **Appendix G** of the guideline.

Algorithm

One of the key components of the OA CPG is an algorithm intended to facilitate clinical decision making at the point of care. A clinical algorithm provides a graphical representation of a guideline, using standardized symbols to illustrate each recommendation. The use of the algorithm was chosen based on evidence that such a format improves data collection, diagnostic and therapeutic decision-making, and changes patters of resources use. This format allows the provider to follow a systematic approach to critical information needed at the major decision points in the clinical process, and includes:

- An ordered sequence of steps of care

- Recommended observations
- Decisions to be considered
- Actions to be taken

	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.

A clinical algorithm diagrams a guideline into a step-by-step decision tree, using standardized symbols to display each step, as developed by the Society for Medical Decision-Making committee. [6] In this format, arrows connect the numbered boxes, indicating the order in which the steps should be followed. Standardized symbols (below) 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.

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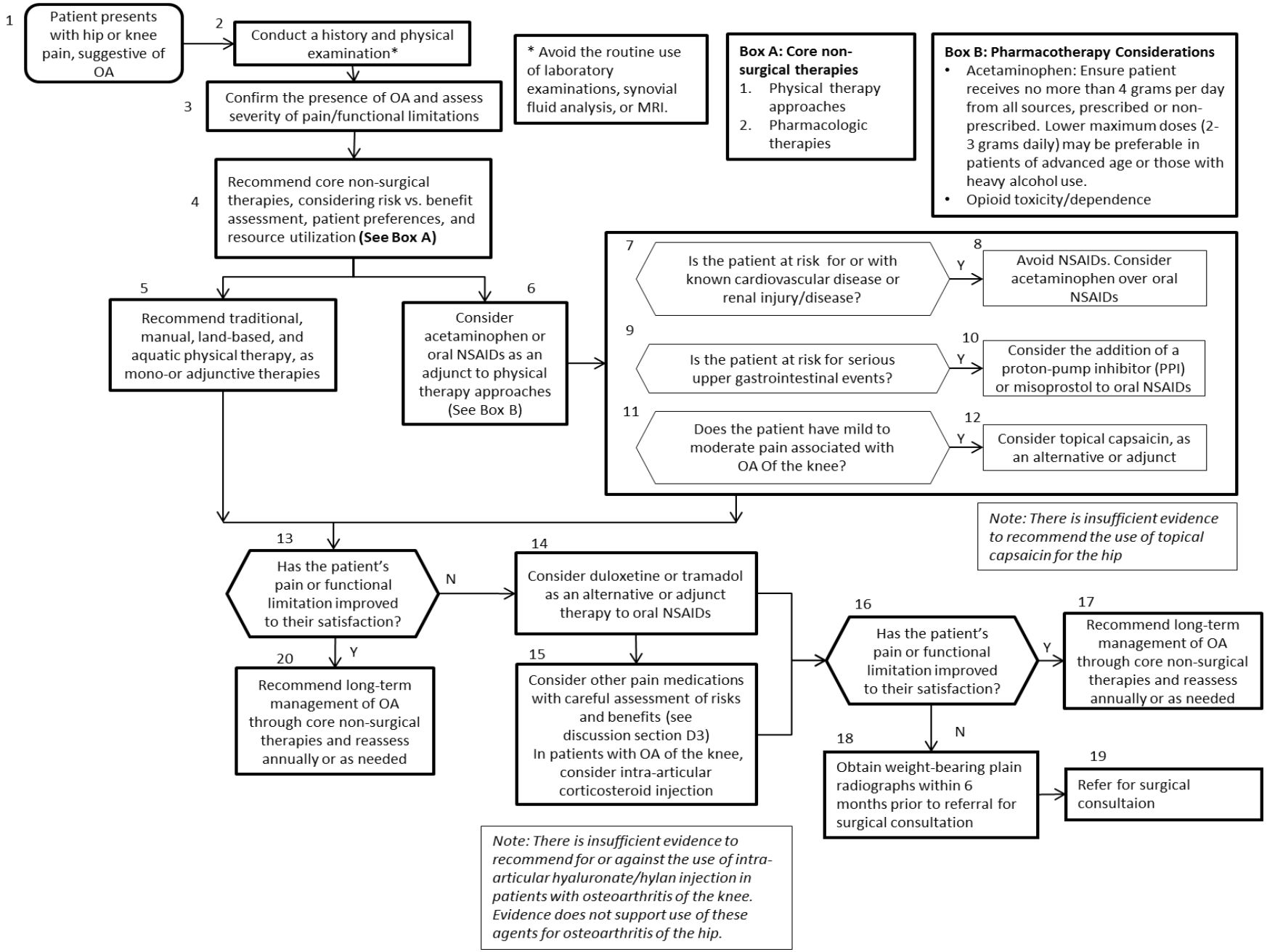
* Bolded names are members of the Editorial Panel. All of the Work Group members' contact information is available in Appendix F.

Recommendations

Recommendations	GRADE
Diagnosis and Evaluation	
1. Clinicians should conduct a history and physical examination for all patients, with an emphasis on the musculoskeletal examination.	EO
2. Clinicians may use plain radiography to confirm the clinical diagnosis of hip and knee osteoarthritis.	C
3. Clinicians should not use magnetic resonance imaging (MRI) as an evaluative tool to diagnose, confirm, or manage the treatment of osteoarthritis.	D
4. Clinicians should avoid routine use of laboratory examinations or synovial fluid analysis to diagnose osteoarthritis of the hip and/or knee.	EO
Core Non-Surgical Treatment Principles	
5. 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
6. For patients with osteoarthritis of the hip and/or knee, clinicians should attempt the core non-surgical therapies prior to referral to surgery.	C
7. 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
8. 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
9. 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
Physical Therapy Approaches	
10. 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
11. 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
12. For adults with osteoarthritis of the knee who do not tolerate land-based therapeutic exercise, clinicians should consider adjunctive aquatic physical therapy.	C
13. 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
Pharmacologic Therapies	
14. 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
15. Clinicians should ensure that patients receive no more than four grams of acetaminophen daily from all sources of prescribed and non-prescribed medications.	A
16. In patients requiring treatment with oral NSAIDs and who are at risk for serious upper gastrointestinal (GI) adverse events, clinicians should consider the addition	A

Recommendations	GRADE
of a proton-pump inhibitor (PPI) or misoprostol.	
17. 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
18. 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
19. There is insufficient evidence to recommend for or against the use of topical capsaicin for the hip as first line or adjunctive therapy.	I
20. 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
21. 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
22. For patients with symptomatic osteoarthritis of the knee, clinicians may consider intra-articular corticosteroid injection.	C
23. 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
24. For patients with moderate to severe osteoarthritis of the hip, clinicians may consider imaging/ultrasound directed corticosteroid injection to reduce pain.	C
25. Intra-articular injection of hyaluronate/hylan is not recommended for patients with osteoarthritis of the hip.	EO
Complementary and Alternative Therapies	
26. 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
27. 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
28. 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
Referrals for Surgical Consultation	
29. 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
30. 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
31. 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

Algorithm


1
Patient presents with hip or knee pain, suggestive of OA
2
Conduct a history and physical examination*
3
Confirm the presence of OA and assess severity of pain/functional limitations
* Avoid the routine use of laboratory examinations, synovial fluid analysis, or MRI.
Box A: Core non-surgical therapies
1. Physical therapy approaches
2. Pharmacologic therapies
Box B: Pharmacotherapy Considerations
• Acetaminophen: Ensure patient receives no more than 4 grams per day from all sources, prescribed or non-prescribed. Lower maximum doses (2-3 grams daily) may be preferable in patients of advanced age or those with heavy alcohol use.
• Opioid toxicity/dependence
4
Recommend core non-surgical therapies, considering risk vs. benefit assessment, patient preferences, and resource utilization (See Box A)
5
Recommend traditional, manual, land-based, and aquatic physical therapy, as mono-or adjunctive therapies
6
Consider acetaminophen or oral NSAIDs as an adjunct to physical therapy approaches (See Box B)
7
Is the patient at risk for or with known cardiovascular disease or renal injury/disease?
Y
8
Avoid NSAIDs. Consider acetaminophen over oral NSAIDs
9
Is the patient at risk for serious upper gastrointestinal events?
Y
10
Consider the addition of a proton-pump inhibitor (PPI) or misoprostol to oral NSAIDs
11
Does the patient have mild to moderate pain associated with OA Of the knee?
Y
12
Consider topical capsaicin, as an alternative or adjunct
Note: There is insufficient evidence to recommend the use of topical capsaicin for the hip
13
Has the patient's pain or functional limitation improved to their satisfaction?
N
14
Consider duloxetine or tramadol as an alternative or adjunct therapy to oral NSAIDs
Y
20
Recommend long-term management of OA through core non-surgical therapies and reassess annually or as needed
15
Consider other pain medications with careful assessment of risks and benefits (see discussion section D3)
In patients with OA of the knee, consider intra-articular corticosteroid injection
16
Has the patient's pain or functional limitation improved to their satisfaction?
Y
17
Recommend long-term management of OA through core non-surgical therapies and reassess annually or as needed
N
18
Obtain weight-bearing plain radiographs within 6 months prior to referral for surgical consultation
19
Refer for surgical consultaion
Note: There is insufficient evidence to recommend for or against the use of intra-articular hyaluronate/hylan injection in patients with osteoarthritis of the knee. Evidence does not support use of these agents for osteoarthritis of the hip.

Module A: Diagnosis & Evaluation

A1. History & Physical Examination

Background

The diagnosis of OA can usually be made solely on the basis of a patient history and physical examination. This section emphasizes the key patient history and physical features of this condition in the hip and knee. OA is a clinical syndrome characterized by joint pain, joint stiffness, and limitation of range of motion, decreased physical functioning, and decreased quality of life (QoL). Pain is typically worse after activity and generally without morning stiffness which, if present, lasts usually less than 30 minutes.

Recommendation

1. Clinicians should conduct a history and physical examination for all patients, with an emphasis on the musculoskeletal examination. [EO]

Discussion

A thorough physical examination coupled with a detailed history is required for the diagnosis of OA. [7] Symptoms may be symmetric or asymmetric. Patients with OA may have morning joint stiffness that usually resolves within 30 minutes. Joint stiffness may also occur with mild to moderate activity. As the disease progresses, prolonged joint stiffness and joint enlargement may also become evident. A late manifestation of the disease may be crepitus or a grating sensation in the joint. Any limitations in joint movement may be due to a flexion contracture or a mechanical obstruction. Common physical examination findings include pain and crepitus with active motion, joint line tenderness, deformity, restricted painful movements and occasional effusions. Patients that are asymptomatic are not included in this guideline. Other conditions should be considered in symptomatic patients without radiographic evidence for OA. [8] Laboratory evaluation is not generally needed or helpful in the diagnosis of OA, but may be useful to rule out other conditions. Radiographs may provide objective findings consistent with OA, but are not a requirement for making the diagnosis. (See Appendix C. Patient History and Physical Examination.)

OA has multiple risk factors and includes both biomechanical and systemic components. Biomechanical risk factors include obesity, joint injury, occupational or recreational overuse, and muscle weakness. Systemic risk factors include age, gender, genetics, and bone density. Obesity is the most common modifiable risk factor for the development of OA. Evidence suggests an increased susceptibility to both hip and knee OA with increasing body mass index (BMI).

A history of acute joint injury, including fractures of the articular cartilage or subchondral bone, joint dislocations, ligamentous injury, and meniscus injuries are linked to the subsequent development of post-traumatic OA. The musculature surrounding joints, particularly the quadriceps muscle at the knee, assists in both joint stability and function. Quadricep weakness from diffuse OA is common and has been identified as an independent risk factor in the development of knee OA.

Occupational or recreational overuse is of particular concern to the VA/DoD population. Specific activities which require kneeling or squatting along with heavy lifting are associated with high rates of

both hip and knee OA. Additionally, repetitive or high-intensity training or sport activities that involve twisting or pivoting moments at the knee or hip, as well as participation in contact sports involving direct joint impact, have been implicated in the development of OA.

Knee deformity such as genu varum or genu valgum resulting in an altered mechanical axis has been found to increase the risk of developing knee OA. Furthermore, osseous deformities found about the hip in the form of cam or pincer lesions found in femoroacetabular impingement (FAI) may be associated with an increased risk of hip OA.

Age and gender also play significant roles in both susceptibility and symptom severity with OA. The prevalence of OA increases significantly with age with studies demonstrating a ten-fold increase in OA between the ages of 30 and 65 years. While males are more likely to develop OA at an earlier age (younger than 45), by the age of 55, females are ten percent more likely to have OA than their male counterparts. Although the precise genetics of OA is complex and not completely understood, several epidemiologic studies demonstrate a genetic contribution to the development of OA. Genome studies have demonstrated both sex-specific and site-specific genes that may contribute to OA. A family history of OA, therefore, represents an independent risk factor in the development of the disease. [9-24]

It is also important for primary care providers to recognize presence of certain red flags that suggest an alternative diagnosis and should prompt an immediate evaluation. [25] Severe local inflammation, erythema, and progressive pain unrelated to usage suggest an alternative diagnosis such as septic arthritis, crystalline arthritis, inflammatory arthritis, mechanical derangement, or serious bone pathology. Additionally, mechanical symptoms such as catching or locking may also serve as red flags suggesting an alternative diagnosis. The presence of any of these symptoms should prompt an immediate evaluation outside the scope of this guideline. Likewise, the involvement of other joints outside the hip or knee expands the differential diagnosis beyond OA.

A2. Plain Radiography

Background

Radiography can be useful in confirming a suspect diagnosis of OA and may eliminate other potential diagnoses from consideration.

Recommendation

2. Clinicians may use plain radiography to confirm the clinical diagnosis of hip and knee osteoarthritis. [C]

Discussion

In adults with non-traumatic knee pain, the consensus of the working group is to obtain a weight-bearing anterior-posterior (AP) knee as well as a weight-bearing flexed knee view in 30 degrees of flexion (also known as a tunnel or Rosenberg view), in addition to a lateral and merchant view (also known as a sunrise or skyline view). Although radiographs are not required to make a diagnosis of

knee OA, they can be used to confirm the diagnosis and to rule out fracture, osteonecrosis, malignancy, or other red flags. [26,27]

In adults with non-traumatic hip or groin pain, the consensus of the working group is to obtain a weight-bearing (standing) AP pelvis radiograph and non-weight bearing frog lateral of the affected hip. Plain radiographs may be used to confirm the diagnosis and to rule out fracture, osteonecrosis, malignancy, (either primary or metastatic) or other red flags.

Common radiographic findings of hip and knee OA include joint space narrowing, increased subchondral sclerosis, marginal osteophyte formation, subchondral cysts and joint subluxation. Weight-bearing radiographs of the knee especially the Rosenberg view are the most sensitive for detecting early joint space narrowing.

A3. Magnetic Resonance Imaging (MRI)

Background

Magnetic resonance imaging (MRI) has a very limited role in the evaluation of OA. A review of the literature failed to provide any evidence of utility or benefit in the diagnosis or management of OA.

Recommendation

3. Clinicians should not use magnetic resonance imaging (MRI) as an evaluative tool to diagnose, confirm, or manage the treatment of osteoarthritis. [D]

Discussion

The diagnosis of OA can be made by a thorough physical examination and plain radiographs may be used to confirm the diagnosis. The literature review did not demonstrate any evidence of improved outcomes in OA patients who underwent an MRI examination as part of their evaluation. Some studies have shown a utility of MRI for identifying articular cartilage degeneration. However, given the heterogeneity of MRI sequences and findings, as well as the lack of studies evaluating MRI for monitoring disease progression and improving clinical outcomes, a definitive conclusion regarding its global clinical utility for guiding diagnosis and treatment is not possible. Consequently, MRI is not recommended as an evaluative tool to diagnose or confirm OA. In patients with OA who have concomitant signs and symptoms of loose body, meniscal pathology or an injury or incident with a sudden onset of pain and effusion, MRI may be indicated. Meniscal and loose body findings may include locking, where the knee is stuck in flexion, usually due to a flipped meniscal fragment or a loose body. If there is radiographic evidence for OA and no mechanical symptoms or acute injury suggesting a concomitant internal derangement, MRI is not recommended as it may lead to an erroneous diagnosis and exaggerated patient expectations. Advanced imaging, including MRI, is only useful if other underlying, more severe conditions are presumed. Therefore, as a tool for routine diagnosis for OA, MRI is not recommended. [28]

A4. Routine Use of Laboratories and Synovial Fluid Analysis

Background

The literature review revealed little evidence of benefit from laboratory evaluation of blood, urine, or synovial fluid in the evaluation of OA. These relatively few available studies found that laboratory tests or synovial fluid analysis may be of benefit only when considering an alternative diagnosis or when red flags are present.

Recommendation

4. Clinicians should avoid routine use of laboratory examinations or synovial fluid analysis to diagnose osteoarthritis of the hip and/or knee. [EO]

Discussion

Laboratory tests on blood, urine, or synovial fluid are not required for the diagnosis of hip and knee OA. Literature review found no evidence of laboratory studies improving outcomes in OA. Laboratory and synovial fluid evaluation may be useful to confirm or exclude coexistent inflammatory disease or other conditions in patients with suggestive symptoms or signs. [25]

Module B: Core Non-Surgical Treatment Principles

The following management principles must be considered when developing and implementing a comprehensive treatment plan consisting of non-surgical interventions for OA.

B1. Patient Education

Background

The development of an individualized evaluation and management plan is recommend for patients with OA. Dicussions between the patient and provider should allow for a patient-centered evaluation and management plan to address the patients needs. Patient education is a critical piece within the patient-provider relationship that empowers and enabes patients to make well informed, shared decisions related to their care. Furthermore, evidence suggests that patient compliance with physical exercise, energy conservation, and joint protection is increased by patient education. [29]

Recommendation

5. 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]

Discussion

The development of a management plan in patients with OA requires a partnership between the patient and their health care providers to develop an individualized course of treatment that can provide the optimal program for each patient with OA. This process involves a complete medical assessment of the patient that will allow an understanding of the risks and benefits that may be anticipated. The decision for any pharmacologic and non-pharmacologic intervention should be based on consideration of patient history, assessment findings, a risk benefit analysis, patient preference, and resource utilization. This process will allow selection of pharmacologic agents with proven benefit to be used in conjunction with non-pharmacologic interventions. Once a therapy is selected, a plan should be developed to determine the effectiveness of the therapy and monitor for adverse events. The close monitoring for efficacy and adverse events will determine if a program should be continued or terminated.

B2. Comprehensive Management Plan

Background

As part of a comprehensive, core treatment and management plan for patients with OA of the hip or knee, consideration should be given to the least invasive interventions prior to referral for surgical intervention. Physical therapists are highly educated and skilled, licensed providers who prescribe safe and appropriate therapeutic exercises and interventions. Physical therapists should be involved early in the development of a comprehensive plan to manage symptoms, reduce fall risk, and maximize patient function.

Recommendation

6. For patients with osteoarthritis of the hip and/or knee, clinicians should attempt the core non-surgical therapies prior to referral for surgery. [C]
7. 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]

Discussion

Clinicians should attempt the core non-surgical therapies prior to the referral for surgery. A typical treatment program should consist of patient education on their condition, activity and lifestyle modification, to include a therapeutic exercise program targeting the quadriceps and the gluteus medius as well a weight reduction program (as appropriate), judicious use of topical or oral NSAIDs and/or acetaminophen and the use of an appropriate walking aid or assistive device. This plan should be based upon a patient-centered, shared decision making process.

Exercise in general has been a longstanding recommendation within numerous scholarly publications as one of the core elements in a comprehensive management plan for patients with OA of the hip or knee. Despite this support from the literature, patients and some health care providers commonly think that exercise may make symptoms from OA worse and/or should be avoided. Although it is true that some forms of high impact or high intensity physical activity should be avoided, the literature has shown that the correct type, frequency, and duration of the appropriate exercises can be beneficial for reducing pain, improving function and improving flexibility in patients with hip or knee OA. Thus, education and skilled intervention are key factors in the effective management of OA.

As part of an overall comprehensive management plan, physical therapy can augment the medical plan and pharmacologic interventions by providing patients with a safe and effective therapeutic exercise program, interventions to normalize gait and joint kinematics, patient education related to lifestyle and activity modifications, reducing risk for falls, and a comprehensive home program designed to make patients independent with self management strategies.

Upon clinical examination, patients with moderate to severe OA of the hip or knee commonly exhibit weakness within regional muscles surrounding or local to the affected joint. The literature indicates that, although the exact pathogenesis of OA is unknown, weakness often precedes or accompanies the osteoarthritic process. Whether this weakness is a result of a neurogenic mechanism (autogenic inhibition from pain), age related decrease of muscle volume (sarcopenia), or disuse is unclear. However, a combination of these contributing factors is most likely. Regardless of the cause of the weakness, in cases where hip or knee OA progresses it typically leads to disuse, decreased shock absorbing capabilities, and decreased load transfer capabilities (contralaterally and ipsilaterally), as well as overall deconditioning (decreased aerobic capacity). It is also well documented within the literature that muscle weakness within key muscle groups (namely quadriceps and gluteus medius) leads to further disuse and atrophy of the surrounding/adjacent and regional muscle groups and accelerates the joint stiffness and progression (such as degradation of hyaline cartilage, etc.) associated with hip and knee OA. Weakness has been identified as a biomechanical risk factor for the development of OA and specifically quadriceps weakness as a primary risk factor for knee OA.

According to Barbour et al, the direct annual medical costs associated with falls among older adults is nearly $30 billion. While falls are common among older adults, research also suggests that falls are common among middle aged adults. Poor neuromuscular function and weakness is common among persons with arthritis. Decreased gait speed and impaired balance are risk factors for falling and common among those with arthritis. The single most effective strategy to effectively reduce falls involves exercise or physical therapy to improve gait, balance, and lower body strength. Research has shown this combination to reduce risk of falls by 14% to 37%. Effective programs should focus on improving balance, be progressively more challenging, and involve at least 50 hours of practice. [30]

Early intervention which provides a tailored therapeutic exercise program to focus on regaining quadriceps and gluteal strength, flexibility, range of motion, and aerobic conditioning is in line with nationally accepted guidelines and appears to be key to improving pain and function. For these reasons, it is recommended and imperative that clinicians refer for physical therapist services early on in the management of patients diagnosed with OA of the hip and/or knee. Referring patients with OA to a physical therapist to provide skilled services promotes patient compliance, safety (as some patients require close monitoring and may need ongoing screening for medical referral), decreased fall risk, and appropriate exercise prescription. [31-34]

B3. Weight Reduction in Patients with Knee or Hip Osteoarthritis and Elevated BMI

Background

Obesity is a well-recognized risk factor for the development of hip and knee OA. The Work Group recommends permanent weight reduction in overweight patients with knee or hip OA. This position is supported in knee OA by several randomized controlled trials and systematic reviews. Furthermore, patients with BMI greater than 30 kg/m^2 have an increased rate of surgical complications such as infection, most notably in patients with knee OA.

Recommendations

8. 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]
9. 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]

Discussion

It is well-established in previously published guidelines that weight reduction is a cornerstone of non-pharmacologic therapy for the management of hip or knee OA. A review of the literature revealed two well-designed RCTs in which patients with knee OA self-reported improvements in pain and disability after losing weight. [35,36] It is also noted that patients who engaged in exercise or weight loss programs experienced the greatest benefit.

Although the literature is sparse on the effect of weight loss in patients with hip OA, it is our expert opinion that weight loss in patients with hip OA would be beneficial. Providers may refer to the

VA/DoD Clinical Practice Guideline for Screening and Management of Overweight and Obesity[1] for current evidence based recommendation on the treatment of obesity.

[1] See the VA/DoD Clinical Practice Guideline for Screening and Management of Overweight and Obesity available at: http://www.healthquality.va.gov/guidelines/CD/obesity/VADoDCPGManagementOfOverweightAndObesityFinal.pdf

Module C: Physical Therapy Approaches

C1. Manual Physical Therapy

Background

Manual physical therapy techniques are hands-on interventions that aim to restore or normalize the joint mechanics and integrity of the surrounding tissues. These techniques are provided by a skilled, licensed physical therapist who has completed training, residency, fellowship, or certification in orthopedic manual physical therapy. These techniques include, but are not limited to, soft tissue mobilization (STM), joint manipulation/mobilization, range of motion (ROM), manual stretching, and massage. Such physical therapists are skilled to provide a thorough evaluation of the body system to identify and treat movement related dysfunctions that may be causing, aggravating, or contributing to joints affected with OA.

Recommendations

10. For patients with OA 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]
11. For patients with OA 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]

Discussion

After review of the literature, there is not enough evidence to support manual physical therapy over traditional physical therapy/ therapeutic exercise alone. This absence of evidence comparing the two therapies precludes a preference or recommendation be made for one over the other. However, combining the two interventions appears to be beneficial and should be considered for OA of the hip and knee, with stronger evidence to support offering the combination as a promising intervention for OA of the knee. The literature reviewed focused not on replacing traditional therapeutic exercise with manual physical therapy, but rather focused on the comparative effectiveness of a therapeutic exercise program, plus the combination/addition of manual physical therapy. [31-33]

The benefits of the adjunctive manual physical therapy combined with supervised therapeutic exercise were the same for the hip and knee; however, the quality and strength of the evidence differed. Within some of the studies reviewed, the addition of manual physical therapy added a skilled, hands-on component of interventions that were administered during a treatment session before or after patients completed the prescribed therapeutic exercises. [31]

C2. Aquatic Therapy

Background

No comparative studies were discovered for manual physical therapy as compared to aquatic physical therapy. However, some general guidelines and recommendations may be drawn from the evidence regarding the efficacy of each intervention as an effective option to be considered.

Recommendation

12. For adults with osteoarthritis of the knee who do not tolerate land-based therapeutic exercise, clinicians should consider adjunctive aquatic physical therapy. [C]

Discussion

Some evidence suggests that aquatic therapy leads to less discomfort and is better tolerated than traditional, land based physical therapy. Examples of reported discomfort with land based therapeutic exercise includes: increased blood pressure, swelling of the knee, and increased pain/discomfort during exercise. The improved tolerance associated with aquatic or pool based physical therapy is possibly due to the overall intensity and reduced full weight bearing associated aquatic therapy as compared with land based therapeutic exercise. Intensity and impact on the affected joints during therapeutic exercise should be considered. Low to no impact activities are indicated and are typically better tolerated. The heated water typically provided in therapy pools may also provide a temporary analgesic affect for arthritic joints, as pain and temperature both travel on the lateral spinothalamic tract and it is theorized that this interferes with the afferent pain signal transmission.

For OA of the knee, evidence supports both traditional therapeutic exercise and aquatic physical therapy as equally effective in terms of pain reduction and functional improvement for OA of the knees. However, patient reported complaints (e.g., knee swelling) occur more often in patients undergoing land based therapeutic exercises. Even though there is sufficient evidence to support aquatic physical therapy and land-based physical therapy in terms of improving pain and function in patients with knee OA, there is limited evidence to distinguish between the two therapies. This makes aquatic physical therapy a viable consideration for those patients who have not or will likely not tolerate land based physical therapy and therapeutic exercise. [31,37-42]

For OA of the hip, there is little evidence to recommend or discourage either treatment modality (traditional land based versus aquatic therapy) in terms of pain reduction, increased function or harms. Despite the lack of certainty in the literature, therapeutic exercises that target local muscle (particularly quadriceps and gluteus medius) strengthening and overall aerobic fitness should be included in the core treatment plan. These key muscles are joint stabilizers and promote shock absorption and load transferring forces to be distributed appropriately throughout the body system. [32,33,39]

When it comes to aquatic physical therapy, there is tremendous value in engaging the patient in a patient centered decision making process. Patient preferences, fears/apprehension about the pool environment, and facility or local area resources should be considered when deciding whether or not to refer for aquatic physical therapist services. Clinicians should educate patients that participation in physical therapist prescribed exercise is safe and beneficial.

Aquatic physical therapy is provided by a skilled, licensed physical therapist who has experience or certification in evaluating individuals and developing a customized plan of care to be carried out in a therapeutic pool. This includes screening for contraindications, monitoring high risk individuals, and knowing when to appropriately refer for medical intervention.

No evidence was identified within the literature for a head to head comparison of manual physical therapy versus aquatic physical therapy. Despite lack of comparative effectiveness, the evidence does support either therapy as a beneficial and viable intervention for pain reduction and improvement of function in patients with hip or knee OA. [34,43-52]

C3. Walking Aids

Background

In patients with OA of the hips or knees, the goals of treatment are to control pain, and the resultant disability, while providing education on the disease process and/or its treatment. Walking aids, such as walkers, crutches and canes, are prescribed to reduce the load on affected joint(s) - thereby reducing pain while improving balance. The totality of the intended effect is an overall improvement in functional mobility. Among the available selection of walking aids, the cane is the most commonly prescribed outpatient intervention. Canes may be used on the ipsilateral or contralateral side for patients with OA. The rationale is that the cane, by sharing the load of the body weight with the upper extremity, increases the support base and balance.

Recommendations

13. 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]

Discussion

The load on weight-bearing structures can be readily reduced if the burden is shared with the arms through an assistive device. When the hip abductors are weak, using a cane in the opposite hand can reduce the forces across the hip joint to less than half the normal, depending on the amount of force exerted on the cane. A cane can also unload the medial knee compartment – the most commonly affected compartment in knee OA. For patients with OA of the knee, there is no clear evidence that either the contralateral or ipsilateral method of cane use is better at reducing muscle strain. However, studies suggest that contralateral cane use can effectively diminish pain and improve function and some aspects of quality of life in patients with knee OA. [53] Tibial strain rates are significantly decreased with both methods although peak ground reaction forces at heel strike are maximally decreased when both the cane and the heel strike the ground in cadence. Similarly, an ambulation aid placed anteriorly can assist the hip and spinal extensor muscles. [34,51,52,54-62]

Unfortunately, many patients have difficulty determining the degree of weight-bearing support they should apply to their ambulation aids. Furthermore, gait pattern(s) required for cane ambulation also decreases the efficiency of walking. Walking aids are associated with a large number of accidents (frequently falls) requiring urgent medical treatment. Thus, the patient's functional requirements should be matched with the proper walking aid and the clinician must consider whether the patient has sufficient strength, exercise tolerance, balance, coordination and judgment to master the prescribed aid. Before a patient uses an ambulation aid, contractures may need to be overcome or muscles strengthened. These factors speak to the skill required to effectively evaluate a patient for the most appropriate assistive device and ensure proper fit and training is performed. The upper extremity muscle groups used most often are the shoulder girdle depressors, elbow extensors, wrist

movers and finger flexors. In the lower extremity, the hip extensors, hip abductors and knee extensors are particularly important.

The social meanings that people attribute to walking aids are important factors to consider as they affect patient compliance with the use of walking aids. Providers should reach shared decisions with patients about the use of walking aids based on awareness of the factors that might influence a patient's choice to use the prescribed aids. The prescription of a cane should take into account the substantial increase in energy expenditure, especially in the first month of use. When prescribed appropriately, energy expenditure is less of a factor for concern by the end of the second month due to adaptation. Final selection of an ambulation aid should be made only after the patient has had an opportunity to learn how to use the fitted walking aid appropriately, preferably under the supervision of a physical therapist and/or the prescribing provider. A physical therapist training a patient to use an ambulation aid should include education on safely negotiating carpet, throw rugs and rough ground as well as on inclines and stairs. The patient should also be taught how to circumvent obstacles and appropriate methods to use the aid while transferring during activities of daily living. [34,51,52,54-62]

Module D: Pharmacologic Therapies

For recommendations on specific pharmacologic therapies, the guideline panel did not attempt to differentiate agents within a specific drug class when multiple agents are present.

D1. Acetaminophen and Non-steroidal Anti-inflammatory Drugs

Background

Acetaminophen and non-steroidal anti-inflammatory drugs (NSAIDs) are both widely available and are commonly used by patients who are seeking pain relief from OA. Both acetaminophen and NSAIDs have been shown to reduce pain associated with OA of the hip and/or knee when compared to placebo. Initial selection of drug therapy and dose will depend upon a number of factors including severity of pain, individual patient factors, comorbid conditions (e.g., cardiovascular disease, renal impairment and history of gastrointestinal adverse events), previous pharmacologic therapy for OA, and patient preference.

Recommendations

14. 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]
15. Clinicians should ensure that patients receive no more than four grams of acetaminophen daily from all sources of prescribed and non-prescribed medications. [A]
16. In patients requiring treatment with oral NSAIDs and who are at high risk for serious adverse upper gastrointestinal (GI) events, clinicians should consider the addition of a proton-pump inhibitor (PPI) or misoprostol. [A]
17. 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]

Discussion

Oral NSAIDs are commonly prescribed for OA of the hips or knees and are generally well tolerated. Their long-term use is limited by adverse effects such as increased cardiovascular events, GI perforation, ulceration, and bleeding, and renal impairment. The risks of these complications increase with age, drug-drug and drug-disease interactions, and probably duration of use. [63] These risks are especially important concerning the typically older population affected by OA who often have comorbidities and take multiple medications. Alternative therapies to reduce these risks are limited.

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 more mild disease or with mild symptoms. Therefore, in patients with moderate to severe levels of pain at baseline and with no contraindications to treatment with NSAIDs, initial treatment with a NSAID can be considered. [64]

Acetaminophen has both analgesic and antipyretic effects but lacks potent anti-inflammatory activity. When taken in usual doses (two to four grams per day), acetaminophen is recognized as the preferred initial choice for the management of OA in most patients; especially those patients with

milder disease or symptoms of OA and in those patients with risks associated with taking NSAIDs including presence of renal disease, cardiovascular disease or at risk for cardiovascular disease, history of gastrointestinal ulcers, those receiving oral anticoagulants or corticosteroids, and the elderly (e.g., greater than 65 years).

Although acetaminophen is a relatively safe analgesic when taken in usual doses (up to a maximum of four grams daily), the risk for acute liver injury and liver failure is increased in patients taking doses greater than 4,000 mg daily. [65,66]

The recommendation to use topical NSAID therapy as an alternative to oral NSAIDs is supported by evidence from studies that have compared various topical and oral NSAIDs (i.e., ibuprofen, diclofenac, piroxicam and others) in patients with knee OA. The results have consistently shown that the topical and oral formulations of any given NSAID are similar in terms of improvement in pain and function in patients with knee OA. [67] In a meta-analysis of placebo-controlled trials, the number needed for treatment (NNT) for at least 50 percent pain relief over 8 to 12 weeks was 6.4 for diclofenac topical solution and 11 for the gel formulation. [67]

Results from two studies showed that oral diclofenac has a higher incidence of adverse GI symptoms, whereas topical diclofenac has a higher incidence of local application site reactions, commonly dry skin, rash, and pruritus. The absolute risk of adverse GI symptoms of topical diclofenac has been shown to be decreased by 12 percent to 17 percent compared with oral diclofenac. [68,69] For topical NSAIDs collectively, the reduction in the incidence of gastrointestinal events has been shown to be 36 percent relative to the oral formulations. However, there is insufficient evidence to compare topical and oral NSAIDs in terms of serious GI adverse events (perforation, ulcers or bleeding).

Results from single studies suggested other potential safety advantages of topical NSAIDs over oral NSAIDs, namely a lower incidence of respiratory events [70] and lower incidence of psychiatric disorders. [71] One study showed decreases in hemoglobin by about 30 g/l and increases in serum creatinine by 3 ml/min with oral diclofenac relative to the topical formulation. [72]

In a systematic review focusing on older patients (≥ 60 years of age) with OA, topical NSAIDs seemed to be about as effective as oral NSAIDs and to be associated with a lower risk of severe adverse GI symptoms, defined as “events that produced significant impairment of functioning or incapacitation and were a definite hazard to patient’s health.” [73] However, the severe GI adverse events were not adequately documented in the review. GI bleeds were the closest to meeting the definition of severe adverse GI symptoms, but there was no definite difference between the oral and topical NSAIDs. In the absence of direct evidence, providers should take into account the uncertainty of the magnitude of net benefit when considering topical NSAIDs in patients at high risk for GI adverse events.

Clinicians should understand the limitations of the available evidence. There is insufficient evidence to compare topical and oral NSAIDs in terms of serious GI adverse events (perforation, ulcers, or bleeding), cardiovascular events, renal impairment and hepatotoxicity. [74] There is a lack of long-term studies. A 52-week, non-controlled observational study of diclofenac solution showed that the agent’s longer term adverse event profile was consistent with those in shorter term studies; [75] however,

comparative trials extending beyond 12 weeks have not been performed. The effects of dosage size (e.g., resulting from oligoarticular versus multiarticular application) on efficacy and safety have also not been studied. Overall, there is insufficient evidence to guide choice of topical over oral NSAIDs in older and elderly patient subgroups. Similarly, there is insufficient evidence available on the comparative safety of topical and oral NSAIDs in patients at high risk for cardiovascular, gastrointestinal, renal and hepatic complications. [76]

The decision to use a topical NSAID (versus oral NSAID with or without PPI) should be based on consideration of patient preference, adverse event potential (including GI adverse events), and resource utilization. Other factors should also be taken into consideration. Smaller joints close to the skin surface (e.g., knees and hands) are more amenable than large joints to topical NSAID effects, and the evidence discussed here is applicable to OA of the knee. Topical NSAIDs have not been studied for hip OA. Diclofenac is the only NSAID currently approved by FDA in topical formulations (solution and gel) for OA. No studies have directly compared the solution and gel formulations in patients with OA. Other adverse events associated with topical NSAIDs may be due to components of the formulation rather than the NSAID itself (e.g., unpleasant odor from the dimethyl sulfide metabolite of dimethylsulfoxide (DMSO) in diclofenac solution). [73]

Considerations for selecting oral NSAIDs

Non-steroidal anti-inflammatory drugs (NSAIDs) possess anti-inflammatory, analgesic, and antipyretic properties that arise from inhibition of the enzyme cyclooxygenase (COX 1 and COX-2). COX 1 is produced constitutively in most tissues and is responsible for prostaglandin synthesis important for the maintenance of the gastric mucosal barrier and platelet aggregation. COX 2 is an inducible isoform present at sites of inflammation. In general, inhibition of COX-2 is responsible for the analgesic effect, while inhibition of COX-1 is responsible for the adverse GI events and anti-platelet effect of the NSAIDs. [77]

The NSAID class is a heterogeneous class of drugs which 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 been done to determine relative potencies of COX-2 versus COX-1 inhibition, providers are cautioned against extrapolation of these in vitro findings to conclude relative safety between NSAIDs. NSAIDs are commonly referred to as nonselective (e.g., ibuprofen, naproxen, diclofenac, indomethacin, etc.), relatively selective (e.g., etodolac, meloxicam and nabumetone) or selective (e.g., celecoxib). However, the US Food and Drug Administration (FDA) considers all of these agents as members of the NSAID class, including celecoxib, and they all have similar warnings, precautions and contraindications for use. (See Appendix C. list of Pharmaceutical Contraindications and Boxed Warnings.) Table 2 below displays considerations associated with initiating a NSAID.

Table 2. Considerations when initiating a NSAID (COX-2 selective inhibitor or Nonselective NSAID)

Patient Characteristics	No/Low GI Complication Risk	High GI Complication Risk
No history or no sufficient risk for Cardiovascular or Cerebrovascular Disease	Nonselective NSAID (ibuprofen, naproxen, etc.)*	If possible, consider other treatment modalities. NSAID or salsalate[a] + PPI or

Patient Characteristics	No/Low GI Complication Risk	High GI Complication Risk
(And not receiving low-dose ASA)		misoprostol
		Hospital admission for UGI bleeding (Very high risk): Celecoxib + PPI
History of or sufficient risk for Cardiovascular or Cerebrovascular Disease (On ASA or consider adding ASA)	If possible, consider other treatment modalities. Nonselective NSAID (naproxen)	If possible, consider other treatment modalities. Nonselective NSAID (naproxen) plus a PPI or misoprostol

*Generic nonselective NSAID, Adapted from Fendrick 2004, and Scheiman and Fendrick 2005. [78,79]

NSAIDs and risk of serious adverse upper gastrointestinal (GI) events

There are a number of factors that can contribute to an increase in the risk for NSAID related serious upper GI adverse events (GI perforation, ulcer or bleeding). These factors include prior history of serious upper GI adverse event or history of ulcers, prior history of NSAID related GI adverse event, concomitant use of warfarin or other anticoagulant, advanced age, use of oral corticosteroids and high dose NSAIDs. [80]

There is limited evidence suggesting a lower incidence of endoscopically identified ulcers, for several NSAIDs including celecoxib, meloxicam and etodolac versus nonselective NSAIDs. However, the correlation between findings of short-term endoscopically identified ulcers and the relative incidence of clinical significant serious adverse upper GI events (e.g., perforation, ulcers or bleeding) with longer-term use is not known. In the Celecoxib Long-Term Arthritis Safety Study (CLASS), the incidence of complicated ulcers (gastrointestinal bleeding, perforation or obstruction) was not different between celecoxib and the combined group of patients treated with either ibuprofen or diclofenac. Furthermore, those patients receiving low dose aspirin in combination with celecoxib had a four-fold higher rate of complicated ulcers compared to those not receiving low dose aspirin. Therefore, any GI safety advantage of the more COX-2 selective NSAIDs may be lost concurrent low dose aspirin is used. In patients with a history of ulcers (higher risk patients), rates of complicated and symptomatic ulcers were greater with celecoxib alone (2.56 percent) and celecoxib plus low dose aspirin (6.85 percent) at 48 weeks versus those patients without a prior history of ulcer disease (0.78 percent celecoxib and 2.19 percent celecoxib + aspirin). [81,82] In a meta-analysis of individual participant data from 280 clinical trials of NSAIDs versus placebo and 474 trials of NSAIDs versus another NSAID, rates of serious vascular and/or GI adverse events were examined. In the meta-analysis, all NSAIDs (including celecoxib) increased the risk for any serious upper GI complication including perforation, obstruction or bleeding by two- four times when compared to placebo. Higher baseline risk for complicated upper GI events appeared to be predictive of a higher rate of events. [83]

There are several options that can be considered for high-risk patients who require treatment with NSAIDs to minimize their risk of experiencing NSAID-induced serious upper GI events, including addition of a proton-pump inhibitor (PPI) [84] or misoprostol. [85] In patients at greatest risk of experiencing a NSAID associated serious upper GI adverse event (e.g., patient with recent complicated ulcer with hospital admission); it is recommended that patients and providers consider alternative treatment. However, if treatment with NSAIDs is deemed necessary, use of a COX-2

selective NSAID combined with a PPI can be considered. [86] Evidence comparing use of a nonselective or relatively COX-2 selective NSAID combined with a PPI versus a COX-2 selective NSAID plus a PPI in patients at greatest risk are lacking. However, many patients will be at sufficiently high risk to warrant avoidance of NSAIDs.

NSAIDs and risk of cardiovascular events

To date, there are no published, prospective clinical trials examining the cardiovascular risk of NSAIDs, including celecoxib. The Prospective Randomized Evaluation of Celecoxib Integrated Safety versus Ibuprofen or Naproxen (PRECISION) study is underway and with plans to recruit 20,000 patients with OA or rheumatoid arthritis who have or are at risk for cardiovascular disease. In this study, the symptomatic benefit, GI, renal and cardiovascular safety will be examined. Results of PRECISION are not expected until 2015. There are, however, numerous published observational studies with many demonstrating an increased cardiovascular risk with NSAIDs, including celecoxib. A systematic review of population based controlled observational studies was done to determine the cardiovascular risk of NSAIDs and included 31 case control and 21 cohort studies. Of the NSAIDs most extensively studied, the highest risks were seen with rofecoxib (RR 1.45, 95% CI 1.33-1.59) and diclofenac (RR 1.4, 95% CI 1.27-1.55) and the lowest risk with naproxen (RR 1.09, 95% CI 1.02-1.16) and ibuprofen (RR 1.18, 95% CI 1.11-1.25). Cardiovascular risk appeared to increase with higher NSAID doses, including high dose ibuprofen but was also apparent with lower doses of rofecoxib, celecoxib and diclofenac. Naproxen was reported to be risk neutral at all doses studied. In the less extensively studied NSAIDs, etoricoxib (RR 2.05, 95% CI 1.45-2.88), etodolac (RR 1.55, 95% CI 1.28-1.87) and indomethacin (RR 1.3, 95% CI 1.19-1.41) had the highest risk. However in pair-wise comparisons, cardiovascular risk with etodolac was not significantly different than ibuprofen or naproxen. [87] A 2011 meta-analysis of 31 clinical trials of NSAIDs in 116,429 patients showed a trend towards an increased risk of myocardial infarction, stroke, and cardiovascular death for all NSAIDs (ibuprofen, diclofenac, celecoxib, etoricoxib, rofecoxib, lumiracoxib and naproxen) compared to placebo, with some of the differences reaching statistical significance. [88] The authors concluded from the data that little evidence suggests cardiovascular safety of any of the agents studied, but naproxen appears to have the lowest risk. In a second meta-analysis, individual participant data from randomized clinical trials were used to determine rates of adverse cardiovascular and complicated upper GI events in individuals taking NSAIDs, including celecoxib and other COX-2 selective inhibitors. [83] Two hundred eighty 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 were included. Most trials used higher dose NSAIDs (ibuprofen 2400 mg, diclofenac 150 mg or naproxen 1000 mg daily). Major vascular events (e.g., fatal or nonfatal MI, fatal or nonfatal stroke, coronary heart disease death, etc.) 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), 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). 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). Risk of any stroke was not increased significantly by any of the NSAIDs studied. Heart failure was increased in all NSAID groups versus placebo. Overall, of 1000 patients receiving a COX-2 inhibitor or

diclofenac for one year, an additional three had a major vascular event (one of which was death) compared to placebo. In analysis of baseline annual risk for major vascular events, an increased risk is predicted in those patients with higher cardiovascular risk at baseline. As a result, cardiovascular risk or presence of known cardiovascular disease should be considered when prescribing any NSAID and NSAIDs avoided in these patients if possible. [83]

NSAIDs and the risk of renal disease

Use of nonselective or COX-2 selective NSAIDs can result in renal papillary necrosis, acute tubular necrosis, renal insufficiency, fluid and electrolyte disturbances, acute renal failure or other renal-related injury in an estimated one to five percent of patients. [89,90] 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 is increased 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 NSAIDs or COX-2s include those with preexisting renal disease, volume depletion (e.g., diuretics and vomiting), congestive heart failure, liver dysfunction, cirrhosis with ascites, use of angiotensin converting enzyme inhibitors (ACEs) or angiotensin receptor blockers (ARBs) and older patients. [91,92] 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, production of renal prostaglandins is increased to maintain renal blood flow, glomerular filtration rate (GFR) and limit ischemia. Administration of NSAIDs or COX-2s in these patients reduces the compensatory vasodilatory renal prostaglandins and can result in reduced renal perfusion; [93] reduced GFR and can lead to renal damage. Although there are other mechanisms of NSAID induced renal injury, hemo-dynamically mediated acute renal insufficiency is the most common cause, has known risk factors and is most frequently reversible once the offending agent is discontinued.

Although use of NSAIDs should generally be avoided in patients with CKD, a discussion of potential risks and benefits should be considered on a case-by-case basis in patients with arthritis whose pain is not controlled with other non-NSAID modalities. [94]

Although there are no prospective studies specifically examining the risk for renal complications from NSAIDs or COX-2 inhibitors in patients at risk, there are several case-control studies that have been conducted. [95] [95] [96]. In these studies, heavy or regular use of acetaminophen was associated with a higher risk for renal failure or renal impairment compared to no use in patients aged 18-75 years. [95,96] Moderate to heavy use of NSAIDs did not increase the risk but the absolute numbers taking NSAIDs were very small. Heavy cumulative lifetime use of NSAIDs was associated with a greater risk. The use of aspirin was not associated with an increased risk in one study but risk was similar to acetaminophen in the other. However, adjustments were not made for important confounders such systemic disease in either study that examined use of acetaminophen or aspirin and risk for renal failure.

In a cohort of healthy men, no association was found for use of acetaminophen, aspirin or NSAIDs and risk for renal injury. Use of nonselective or selective NSAIDs by an older population of patients was

associated with a similar, greater risk for acute renal failure. In this nested case-control study, the highest risk was observed within the first 30 days of use; and decreased thereafter. [97]

In a group of patients dependent upon circulating prostaglandins for maintaining renal perfusion and GFR, addition of a NSAID to existing therapy with a diuretic plus an ACEI or ARB resulted in a higher rate of acute renal failure. [98] Addition of a NSAID to therapy with either a diuretic, ACEI or ARB did not increase the risk. Finally, in one cohort and one small prospective study, risk factors for developing renal impairment from NSAIDs included older age, renal insufficiency, coronary artery disease, male gender, elevated systolic pressure, high-dose NSAIDs and use of diuretics. [99] [100]

D2. Topical Capsaicin

Background

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

Capsaicin works by reversibly depleting substance P (SP), an endogenous neuropeptide involved in the pathogenesis and modulation of pain. Capsaicin is derived from chili peppers and its application stimulates release of SP, initially causing a painful and 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 are limited to temporary burning, stinging and pain at the site of application.

Recommendations

18. In patients with mild to moderate pain associated with osteoarthritis of the knee, topical capsaicin can be considered as first line therapy or adjunctive therapy. [C]
19. There is insufficient evidence to recommend the use of topical capsaicin for the hip as first line or adjunctive therapy. [I]

Discussion

Limited data show that topical capsaicin, applied three to four times daily, results in minimal improvement in pain associated with OA of the knee, but without systemic adverse events. A favorable response to treatment may take up to two weeks to occur. Data for OA of the hip are more limited as most studies that did include patients with hip OA did not separate the results by affected joint. All four studies assessing the benefit of topical capsaicin are small and of short duration (less than three months) and three of the four studies are more than ten years old. [101-104] Adverse events are local (burning and stinging at the application site) and resolve in most patients with continued use. Patients and caregivers should be educated to wash their hands after application of capsaicin and to avoid contact with irritated skin, eyes or mucous membranes.

Capsaicin as Monotherapy for Osteoarthritis

There were two published double-blinded, placebo-controlled trials assessing the efficacy and safety of topically applied capsaicin for the treatment of pain associated with OA of the knee. In both studies,

use of acetaminophen was permitted but not use of NSAIDs or COX-2 inhibitors and patients having had recent intra-articular joint injections were excluded. In the study by Kosuwon W, et al., [105] 100 patients with OA of the knee were randomized to receive topical capsaicin gel 0.0125 percent or placebo applied three times daily for four weeks and then crossed over to the alternate treatment for four weeks; separated by a one week washout period. Improvement in pain was assessed using visual analog scale (VAS) and total WOMAC score and subscales to measure changes in pain, stiffness and function. At four weeks, the mean difference in VAS between capsaicin and placebo was 0.72 (95% CI 0.17-1.27) in favor of capsaicin. Although the difference was statistically significant, the clinical significance of the difference was negligible. Additionally, the authors concluded that the total WOMAC and WOMAC subscales were statistically improved in favor of capsaicin versus placebo, the differences were small (Mean difference in total WOMAC at 4 weeks: -3.42, 95% CI -2.34 to -4.51). Use of acetaminophen as a rescue did not differ between groups. Burning sensation was reported by more than 60 percent of patients but no patients stopped treatment because of it. This study was included in a Cochrane systematic review of topical herbal therapies for OA. The authors of the Cochrane review did not conclude a meaningful difference of capsaicin versus placebo when applied in the capsaicin concentration studied. [101] In the second study by Altman et al., [102] 113 patients with at least moderate OA pain (knee, ankle, elbow, wrist and shoulder) were randomized to receive capsaicin cream 0.025 percent or placebo vehicle applied four times daily for 12 weeks. At least 70 percent of patients in each group had knee OA. At 12 weeks, more patients had improved pain (e.g., pain better, much better or completely gone) using the physician's global evaluation versus placebo (81 percent capsaicin versus 54 percent placebo, p=0.03) and improvements in patient's global evaluation was similar (81 percent capsaicin versus 56 percent placebo, p=0.03). Using VAS, pain was statistically improved versus placebo beginning at week four through the end of the 12-week study. Protocol violation, involving improper use of acetaminophen (use for OA pain) or use of unauthorized pain medications, was similar in both groups. No differences were reported for improvements in health assessment questionnaire or morning stiffness between groups. Burning and stinging at the application site was reported in 46 percent of patients and resolved in all but three patients by week 12. [102]

Capsaicin as Adjunctive Therapy for Osteoarthritis

There were two double-blinded, placebo-controlled studies examining the efficacy and safety of topical capsaicin as adjunctive therapy in patients with moderate to severe pain arising from OA. Concomitant medications for arthritis were not altered during either study. In both trials, capsaicin 0.025 percent was applied topically four times daily to the front and back and to each side of the knee or affected joint for a period of four to six weeks. In the study by Deal et al., [103] 70 patients with OA of the knee and 31 patients with rheumatoid arthritis were randomized to capsaicin or placebo vehicle for four weeks. Physician's global improvement of knee pain was significantly better in the capsaicin versus placebo group for patients OA (p=0.023). Improvements in pain using VAS statistically favored capsaicin at week two but not at week four. Overall change from baseline in VAS was statistically significant for the capsaicin group since baseline VAS scores were higher in the capsaicin group versus placebo (Mean VAS: capsaicin 66.6 versus placebo 50.5, p=0.004). Mild to moderate burning sensation was reported by 44 percent of capsaicin users and two capsaicin treated patients withdrew due to

adverse events. [103] In the second study by McCleane, the efficacy of capsaicin was compared to placebo vehicle, glyceryl trinitrate and capsaicin plus glyceryl trinitrate in 200 patients with OA of the knee, hip, shoulder or hand (Results are only provided for 267 patients). [104] Ninety nine patients had either hip or knee OA. Improvements in mean VAS pain scores were statistically greater with capsaicin, glyceryl trinitrate and the combination from baseline. Change in VAS from baseline was not statistically significant for placebo. No difference was observed between the reduction from baseline in VAS pain scale between capsaicin and glyceryl trinitrate but the change from baseline with the combination was statistically better than either active treatment alone ($p<0.05$). Results were not separated by affected joint (e.g., hip versus knee, etc.). Odds ratio of patients favoring treatments was higher for capsaicin (OR=2.4, 95% CI 1.2-5.1) and glyceryl trinitrate (2.1, 95% CI 1.1-4.4) versus placebo. However, the odds ratio favoring the combination was the highest (OR=5, 95% CI 3.8-6.4). [104]

D3. Other Pain Management Pharmacotherapies

Background

OA is associated with significant pain. Several medications with primarily analgesic effects have been studied in OA patient and demonstrated to relieve pain. The greatest challenge in deciding whether to use these agents is the risk benefit assessment with a particular concern for the risk of chronic pain medication treatment. Ongoing communication between the provider and patient with OA should always monitor the benefit to the patient of all medications prescribed and continually assess adverse events to assure that a benefit is being received by the patient and that this benefit justifies the current and/or potential adverse events with these agents.

Recommendations

20. 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]
21. 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]

Discussion

Duloxetine

Duloxetine is a serotonin-norepinephrine reuptake inhibitor (SNRI) that is FDA-approved for the management of chronic musculoskeletal pain such as OA for patients with OA of the knee who have an inadequate response or intolerance to NSAIDs. Duloxetine may be considered because it has a different mechanism of action and safety profile. Duloxetine may simultaneously treat certain concomitant conditions, since it is indicated for other disorders that may commonly accompany chronic pain due to OA, such as lower back pain, generalized anxiety disorder and major depressive disorder.

Duloxetine 60 to 120 mg daily resulted in moderate improvement in pain and small increase in function in patients with symptomatic knee OA.[106,107] Only the 60-mg dose was approved because no incremental benefit and increases in the incidence of adverse events were seen with the higher

dose. Another trial showed analgesic and functional benefits in older patients (≥ 65 years of age). [108] Compared with NSAIDs alone, adding duloxetine to NSAID therapy has been shown to provide moderate additional analgesic and functional benefits. [109]

Duloxetine therapy can be limited by adverse gastrointestinal, central nervous system and other reactions. The most common adverse events in clinical trials were nausea, dry mouth, fatigue, somnolence and constipation. [106,109,110] When duloxetine is added on to a NSAID, the incidence of adverse events (i.e., nausea, dry mouth, constipation, fatigue, decreased appetite and dizziness) and withdrawals due to intolerance is slightly to moderately increased relative to those for NSAID therapy alone. (See Appendix D. Pharmacologic Treatment). The decision to use duloxetine should be based on consideration of patient preference, adverse event potential (including risks for bleeding, hepatotoxicity, urinary retention, suicidality, orthostasis / syncope and serotonin syndrome), and resource utilization.

Tramadol

Tramadol is a dual-mechanism analgesic with centrally acting, weak opioid and weak serotonin-norepinephrine reuptake inhibitor properties. The opioid analgesic effects of tramadol result primarily from its active metabolite, (+)-O-desmethyltramadol (M1), which is six times more potent than tramadol in producing analgesia and 200 times more potent as a mu-receptor agonist.

Tramadol is a therapeutic option for patients who have inadequate response to acetaminophen, NSAIDs (including COX-2 inhibitors and topical NSAIDs), and duloxetine. Tramadol may be preferable to NSAIDs, particularly in elderly patients with OA, because it lacks the renal, cardiovascular, and gastric ulcerative effects seen with NSAIDs, and lacks the risks of worsening hypertension or congestive heart failure.

Tramadol is available as immediate-release (IR) and extended-release (ER) formulations that may be used for chronic pain including OA, although the ER formulation may be preferred for persistent pain requiring around-the-clock analgesia. An IR combination tramadol/acetaminophen product is also available for short-term (five days or less) treatment of acute pain; however, there is no evidence to support its use for breakthrough OA pain.

Patients who do not have an adequate response to nondrug, non-opioid and tramadol therapies have recalcitrant OA pain. The last group of pharmaco-therapeutic agents to consider is opioids other than tramadol, including more potent opioids as well as tapentadol. These opioids are considered to have higher abuse and addiction potential than tramadol. Tapentadol (a schedule II controlled substance) is similar to tramadol in that it has weak opioid and SNRI properties. Its analgesic mechanisms, however, are attributed to the opioid effects and inhibition of norepinephrine reuptake. There is substantially more evidence to support tramadol therapy than there is with other opioids. Tapentadol IR is FDA-approved for treatment of moderate to severe acute pain based on a short-term (ten day) study in patients with end-stage OA who were candidates for joint replacement surgery. [111]

Therapy with opioids other than tramadol is relegated to last-line and ideally short-term treatment in patients with severe OA pain because of the well-known risks of opioids, lack of evidence for improved

physical function, lack of long-term studies and the emerging reports of adverse events such as endocrine dysfunction and sleep-disordered breathing associated with long-term opioid therapy in chronic pain.[2] Patients should be selectively considered for a trial of opioid therapy. Screening and management of risks related to long-term opioid therapy should be integral components of the treatment plan. Special attention to be given to regularly reassessing the need to continue opioid therapy and considering tapering off opioid therapy if treatment is not beneficial or risks outweigh benefits.

D4. Intra-articular Injections (Corticosteroids and Hyaluronic Acid)

Background

Corticosteroid and hyaluronate/hylan (HA) injectable products are available in numerous formulations that are commonly used by healthcare providers for intra-articular injection of the knee and less commonly of the hip; and are typically reserved for second or third-line treatment of OA. Intra-articular corticosteroids are commonly used to reduce pain in patients with OA of the knee and less commonly of the hip. Available evidence provides support for reducing pain in patients with OA of the knee but evidence is limited for hip OA.

Recommendations

22. For patients with symptomatic osteoarthritis of the knee, clinicians may consider intra-articular corticosteroid injection. [C]
23. There is insufficient evidence to recommend for or against the use of intra-articular hyaluronate/hylan injection in patients with OA 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]
24. For patients with moderate to severe osteoarthritis of the hip, clinicians may consider imaging/ultrasound directed corticosteroid injection to reduce pain. [C]
25. Intra-articular injection of hyaluronate/hylan is not recommended for patients with symptomatic osteoarthritis of the hip. [EO]

Discussion

Corticosteroid injections are generally considered after a therapeutic trial of conservative and pharmacologic measures have not resulted in adequate pain relief or the patient has contraindications to pharmacologic therapies; as a strategy to delay surgery; or in those patients in whom surgery is

[2] See the VA/DoD Clinical Practice Guideline for Opioid Therapy for Chronic Pain. Available at: http://www.healthquality.va.gov/guidelines/Pain/cot/

contraindicated. Pain relief is rapid and relatively short-lived with pain relief occurring within the first week and lasting only three to four weeks.

Local adverse events are the most commonly reported adverse events from steroid injections. These include pain on injection, redness, post injection flare and skin discoloration. The rate of joint infection is considered to be very low when strict aseptic techniques are followed. [112] Systemic effects include rapid suppression of serum cortisol, adrenocorticotropin hormone (ACTH) and inflammatory markers (erythrocyte sedimentation rate [ESR], C-reactive protein [CRP] and cytokines, returning to baseline levels in one to four weeks. In diabetics, a transient, short-term increase in blood glucose levels has been reported. The evidence for an effect on blood pressure is mixed but facial flushing can occur. [113] The clinical significance of these changes is unclear and is likely dependent upon the individual patient. There has been concern regarding the potential for intra-articular corticosteroid injections leading to joint destruction and tissue atrophy but more recent evidence does not support this assertion. In a study of patients with OA of the knee, steroid injections were given every three months for two years versus saline injections. Radiologic studies did not show a difference in joint deterioration between groups over the two year period and local and systemic adverse events were not reported. [114,115]

In a review of various pharmacologic interventions for OA of the knee, trials assessing the effect of intra-articular steroid injections compared to placebo showed a benefit in reducing pain in patients with moderate OA of the knee. [116]

If intra-articular steroid injections are administered in the hip, they should be performed using strict aseptic techniques and guided by fluoroscopy or ultrasound since the hip joint is more challenging to access and if done improperly, may damage the neighboring femoral nerve, artery or other structures near the anterior hip joint. [117]

Evidence is lacking to appropriately identify those patients that may experience the most benefit from intra-articular HA/hylan administration for OA of the knee. However, there is some evidence to suggest that patients with more severe or advanced disease with significant joint space narrowing may be less likely to benefit. [118] Because evidence supports only a modest effect in reducing pain and only a limited effect in improving function in patients with OA of the knee, the use of HA/hylan products should be reserved for patients who have not responded to conservative measures and in whom pharmacologic therapies have not resulted in adequate pain reduction or these therapies are contraindicated. Furthermore, use of these agents may be considered as a strategy to delay surgery or for those patients that are not surgical candidates.

At this time, there are no high quality studies that have demonstrated the use of HA intra-articular hip injections is an effective practice to delay the need for total hip arthroplasty. Additionally, the injections are not currently FDA-approved for use in the hip. Because there is a lack of evidence supporting the safe and effective use of intra-articular HA/hylan in patients with OA of the hip, its use in these patients cannot be recommended at this time.

Seven studies comparing corticosteroids to HA in patients with OA were identified. These studies compared corticosteroid to hyaluronate injections and include one systematic review and six randomized controlled trials (RCTs). [113,119-122]

The available evidence demonstrates that the onset of pain relief is more rapid with steroid versus HA/hylan injections with greater benefit within the first four weeks post-injection. At four weeks, similar benefit was observed and beyond week eight, HA/hylan are more effective than steroids for reducing pain in patients with OA of the knee.

A number of professional organizations have recently updated clinical practice guidelines for patients with OA of the knee and have updated recommendations regarding intra-articular injections. (See Table 3 below for details.)

Table 3. Clinical Practice Guidelines for the Management of OA from Professional Organizations

Professional Organization	Place in Therapy	Comments
American Academy of Orthopaedic Surgeons (AAOS)	IACS: Unable to recommend for or against	IACS: Inconclusive
	IAHA: Cannot recommend	IAHA: Strong recommendation, citing that the evidence to support their recommendation is high quality. However, existing evidence is mostly of low quality as asserted by most authors of systematic reviews
American College of Rheumatology (ACR)	IACS: Conditionally recommend	No details provided
	IAHA: No recommendations regarding use	No details provided
National Institute for Clinical Excellence (NICE)	IACS: Should be considered as an adjunct to core treatments for the management of moderate to severe OA of the knee	IACS: Short term benefit, minimal harms
	IAHA: Do not recommend use	IAHA: Balance between effectiveness in reducing painful OA (clinical benefit), number of injections and potential harms

IACS=intraarticular corticosteroids, IAHA=intraarticular hyaluronic acid

Based on the available evidence and the number of injections per course of HA (depending upon the product), it is recommended that clinicians should consider a trial of intra-articular corticosteroid injections for adults with osteoarthritis of the knees prior to considering use of intra-articular HA/hylan.

Module E: Complementary & Alternative Medicine

E1. Nutritional Supplements/Nutraceuticals/Dietary Supplements

Background

Dietary supplements are commonly consumed by patients for diverse health and personal reasons and are often incorrectly perceived by consumers to be as effective as drugs without negative side effects. Within the United States, there is minimal regulation imposed upon the dietary supplement industry and supplements are not required to be approved by the FDA before they are sold to comsumers. The 1994 Dietary Supplement Health and Education Act (DSHEA) requires that the dietary supplement manufacturers not make misleading or false claims.[3] The DSHEA also requires that the supplement is safe before it reaches consumers and in the case of an adverse health event, manufacturers are required to report the event to the FDA. However, there are no requirements for supplement manufacturers to demonstrate effectiveness of their product. Glucosamine and chondroitin sulfate are marketed as nutritional supplements in the US and despite the limited data for benefit, the uptake of these agents by US consumers has increased significantly in patients with OA

It is important for healthcare providers to have frank conversations with patients who choose to take dietary supplements, so that the patient has realistic expectations and is making an informed choice regarding their care and how to spend personal resources. It is also important that healthcare providers are aware of the dietary supplements their patients are taking, so that potential drug-supplement interactions can be mitigated and adverse events can be appropriately reported.

Recommendations

26. 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]
27. 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]

Discussion

Dietary Supplements

There is insufficient evidence to support the use of dietary supplements for relief of pain and improved function in adults with hip and knee OA. Research on the effectiveness of dietary supplements for managing pain and improving function in adults with OA is frequently funded by the supplement industry, which generates concern regarding potential bias in study design and analysis, reporting and publication of results. Aside from potential study design and publication bias, studies assessing dietary

[3] http://www.fda.gov/regulatoryinformation/legislation/federalfooddrugandcosmeticactfdcact/significantamendmentstothefdcact/ucm148003.htm

supplements are commonly of lesser quality and often include a smaller sample size, unclear blinding methodology, variable study duration and variable follow up. Additionally, in the studies reviewed, there was inconsistency and a great deal of variability in the measurement tools used to assess key outcomes (e.g., pain and function). Doses varied among studies of the same supplement, and often proprietary blends of components were studied. The majority of the research focused on hip OA versus knee OA. All of these factors contributed to challenges in evaluating the quality and consistency of the literature for various supplements as it pertained to the management of pain and function in those with OA of the hip and knee. This information is provided to support informed dialogue between the healthcare provider and patient, particularly for those patients who may be unduly influenced by marketing or anecdotal information on claims of dietary supplement effectiveness. (See Appendix E. Nutraceuticals and Dietary Supplements.)

Patients who choose to utilize dietary supplements should have realistic expectations of their potential benefit; knowledge of potential risks; and should balance this with the cost of the dietary supplements. Healthcare providers should encourage patients to disclose and discuss their supplement use with the medical team and providers should document supplement use in the medical record. This may help to avoid a negative drug supplement interaction and potentially lessen adverse events associated with dietary supplement use.

The Human Performance Resource Center (HPRC) is a DoD initiative under the Force Health Protection and Readiness Program. [123] Both patients and healthcare providers can access these resources to assist in informed decisions regarding any dietary supplement use. Additionally, there is information on the site to guide healthcare providers in reporting any adverse events associated with a dietary supplement. [124]

Chondroitin Sulfate and Glucosamine

Review of the evidence suggests that there were negligible health benefits, (i.e, improved pain and function) and an absence of statistically significant effectiveness of glucosamine, chondroitin sulfate, or the combination in trial participants. There were seven RCTs on chondroitin sulfate, of which four showed a statistically significant reduction in pain. Out of these four, two studies showed only short term pain reduction. However, three of these four studies allowed the use of rescue medications during the study period. Additionally, there was a lack of consistency in defining “clinically meaningful” across the studies, particularly for pain.

The Cochrane systematic review found no difference in efficacy for glucosamine versus NSAIDs. Similar results were found for pain management as there was no difference in efficacy between glucosamine and polyherbal supplementation. [125-133]

For chondroitin sulfate a statistically significant difference in pain was noted in 2 studies, but only short-term. Although there appears to be minimal risk of harm in adults treated with glucosamine, chondroitin sulfate, or a combination of the two, there is insufficient data to support use for the treatment of adults with symptomatic OA of the hip and/or knee.

Much of the research on nutritional supplements were funded by industry. The studies found statistically significant improvements however the high risk of potential funding bias resulted in lower certainty of the evidence.

E2. Acupuncture and Chiropractic Care

Background

Acupuncture is available and is promoted as a pain modifying intervention for patients with OA of the hip or knee. Many who suffer from OA of the hip or knee may also experience stiffness, loss of joint motion and mobility irrespective of pain. Whether acupuncture is applicable to these various clinical complaints adds another dimension to its possible utility. Acupuncture is performed via a variety of formats including adding temperature and electric stimulation in addition to the needling itself. A number of studies have been published on the effects of needle acupuncture against sham needling. There remains concern about the appropriateness of a needling sham and how blinding could be adequately controlled.

Chiropractic care is also often used in the treatment of OA. Unfortunately, there is a paucity of research available to make evidence based statements on efficacy. Chiropractic care is not always specified for the involved joint, but may be directed solely to the axial skeleton, rather than involving the appendicular skeleton. A difference is seen when looking at results for motion, mobility, pain control and function. All of these results have varied outcomes.

Recommendation

28. In patients with hip and/or knee osteoarthritis, there is insufficient evidence to recommend for or against referral for short term trial of needle acupuncture or chiropractic therapy for relief of pain and improved function. [I]

Discussion

Acupuncture

In the review of the available literature, including a Cochrane review, the use of acupuncture as an adjunct to other treatment modalities did not find an additional effect. When all acupuncture versus sham controlled trials were combined, patients experienced statistically significant, but clinically irrelevant, short term improvement in pain and function over sham treated patients. However, there was much heterogeneity among the individual studies' effect sizes and some studies identified no difference in efficacy. When sham controlled trials were limited to those with adequate patient blinding, the heterogeneity and the effect sizes decreased. There remains a question concerning needling sham as an appropriate control as evidence exists, in non-OA research, that needle insertion at non-acupuncture sites may have a physiologic effect. Overall, these acupuncture trials lacked a level of certainty over a clinically important improvement over the sham comparator. There clearly is a need for further well controlled prospective studies to clarify the value and efficacy of this intervention. [134-138] Harms were documented in many studies which included local site bleeding or bruising and potential infection.

Chiropractic Care

Chiropractic care is often used in the treatment of OA. Unfortunately, there is a paucity of research available to make evidence based statements on efficacy. Chiropractic care is not always specified for the involved joint, but may be directed solely to the axial skeleton, rather than involving the appendicular skeleton. A difference is also seen when looking at results for motion, mobility, pain control and function. All of these results have varied outcomes.

Chiropractic studies on OA of the hip and/or knee were limited to a single systematic review of fair quality. While the review identified no harm results, there was not overwhelming evidence for efficacy in improving function and controlling pain. In light of these findings, it is important that healthcare providers consider the cost versus relative research proven benefit when discussing this alternative. [139]

Specificity of application to the involved joint or joints should be considered in the referral, with an understanding that appendicular joint issues may involve the axial skeleton as well. There is certainly a great need for more research on the application of chiropractic care in the treatment of OA of the hip and/or knee.

Module F. Referrals for Surgical Consultation

Background

Patients with OA of the hip or knee can be managed in primary care with various modalities until mechanical symptoms or intractable pain results in diminished physical ability and impact the quality of life (QoL). At that time the primary care provider should engage in frank discussions with the patient regarding further treatment options that encompass realistic treatment goals and the patient's values. One of the possible interventions is surgical intervention such as a total knee or hip arthroplasty. If the patient is agreeable, then consultation with an orthopedic surgeon is appropriate. Prior to surgical consultation, radiologic imaging may be needed to expedite the orthopedic surgery consultation.

Recommendations

29. 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]
30. 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]
31. 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]

Discussion

Considerations for Referrals

In advanced stages of OA of the hip and knee, noninvasive treatments such as medications and physical therapy are of limited value. Risk factors may be modifiable; therefore, identifying them prior to surgery may lead to beneficial lifestyle modifications that could reduce the risk of a poor surgical outcome prior to the patient undergoing surgery.

Joint replacement can effectively alleviate pain and restore function; however, it is associated with risk and does not prolong life. The potential benefits of joint replacement must be weighed against the risk of surgical mortality and morbidity and the discomfort and inconvenience associated with recovery. [140] A simple decision tree based on WOMAC outcomes can help to determine the appropriate application of total hip replacement (THR). It could also be used to evaluate clinical practice or for quality control. [141]

While the studies attempted to identify risk factors associated with poor surgical outcomes, the studies could not recommend the preclusion of a surgical referral as a recommendation for the treatment of hip and knee OA.

Therefore, appropriate due diligence by the primary care provider should be employed to engage the patient in shared decision making about the benefits of intensifying lifestyle modification (weight loss, smoking cessation, controlling diabetes and hypertension) and consider adjusting medication for depression, as needed, to improve postoperative outcomes and to minimize postsurgical complications.

Moreover, the indirect research body of evidence does not recommend precluding a referral for surgery. Indeed, it must be noted, not all patients with the previously mentioned modifiable risk factors will necessarily have a poor postoperative outcome.

Elderly patients who had knee or hip replacements for severe OA took several weeks to recover, but experienced excellent long-term outcomes. Clinicians often do not discuss joint replacement surgery with elderly patients who might benefit. [140] Total knee arthroplasty (TKA) has been established as a highly successful procedure for treating patients with advanced OA. Several key factors play a crucial role in obtaining successful TKAs, and these include well-selected patients, appropriate implants, well performed surgical procedures, and adequate postoperative rehabilitation. Patient age, radiographic severity of OA, and severity of symptoms including response to other treatment modalities are typically considered as the three key factors in selecting the patients for TKA. [142]

There are no systematic reviews or randomized controlled trials concerning the use of advanced imaging such as MRI versus plain radiographs. The review of the evidence revealed studies that indirectly addressed the role of radiographic imaging. A total of seven studies were reviewed, five studies addressed imaging in knee OA and two addressed hip OA. [226-229] [230]

There is insufficient evidence regarding the use of advanced imaging in OA of the hip. Again, there were no studies that compared any advanced imaging to plain radiographs. Although no studies were found that evaluated the use of various imaging studies, two of the studies cited required plain radiographic documented OA of the hip as inclusion criteria. [143,144] The evidence is lacking to support the use of advanced radiologic imaging for the evaluation of OA in adults prior to referral for surgical evaluation.

Injection Therapy prior to Referral for Total/Partial Joint Replacement Surgery

Adults with OA of the hips and knees commonly receive intra-articular corticosteroid injections to the affected joints. The use of intra-articular knee hyaluronic acid (HA) has also become widespread. HA injection of the hip joint is less common (and is not FDA approved); however some anecdotal success has been reported. Intra-articular injections are often used as a bridge to surgery or as an attempt to improve patient function and thus delay the need for a total joint arthroplasty.

Intra-articular use of corticosteroids was first reported in 1951. [145] Since that time, the intra-articular use of corticosteroids to treat knee osteoarthritis has become commonplace. Fluoroscopy or ultrasound guided intra-articular hip corticosteroid injections have also become increasing utilized in the past decade.

Despite the widespread use of intra-articular corticosteroids for the hip and knee in osteoarthritis, no randomized controlled trials or non-randomized prospective controlled studies have addressed their efficacy in the delaying of surgical interventions to these joints. Creation of a high quality study addressing this question is difficult as the decision to proceed to a major surgical intervention involves incorporation of many patient-dependent variables, making standardization complex. The efficacy of an intra-articular injection may or may not be the deciding factor to proceed to surgery for any individual patient. (See Section D4. Intra-Articular Injections (Corticosteroids and Hyaluronic Acid).)

Three studies [146-148] have examined the effect of HA injections in delaying the need for total knee replacement surgery. The first study [148] was a retrospective cohort study with an overall poor quality rating (USPSTF criteria for cohort studies), as it did not statistically adjust for potential confounding variables. The other two studies [146,147] were retrospective case series found to be of fair quality. No study compared their treatment arm to a placebo or non-intervention arm. The majority of the patients in the three studies were candidates for knee replacement who had been unsuccessfully treated with conservative forms of therapy (e.g., anti-inflammatory medication, weight reduction, shoe modification and exercise). Mean patient age ranged from 59.4 to 72 years, and all of the studies had more females than males.

These studies reported that some patients treated with HA injections did not need to undergo surgery and did well with the injection series (58.7 percent in the Anand paper, 75 percent in the Waddell group, 81 percent for Barrett & Siviero with improved QoL scores in 67.3 percent of knees) [146-148] and recommended HA as part of the core treatment program for knee OA prior to a total joint arthroplasty. The evidence to support these recommendations is considered weak at this time. [149] As some patients have clinical improvement with HA injections and harms are limited, we recommend that clinicians may consider a trial of hyaluronic acid intra-articular to the knee prior to surgical referral.

Appendix A: Guideline Development Process

Introduction

The methodology used in the development of the clinical practice guideline for non-surgical management of osteoarthritis (Version 1.0 - 2014) follows the *Guideline for Guidelines*, an internal working document of the Veterans Health Administration (VHA) and Department of Defense (DoD) Evidence-based Practice Working Group (EBPWG). [150] 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 within the VA and DoD, known as the Work Group, and ultimately, the submission of a new CPG.

The Champions and Work Group members for this CPG were charged with developing evidence-based clinical practice recommendations and publishing a guideline document to be used by providers within the VA/DoD healthcare system. Specifically, the Champions for this CPG were responsible for identifying the key evidence questions of greatest clinical relevance, importance, and interest for rehabilitation of a patient with an upper extremity amputation. In addition, Champions assisted in:

a. Conducting the evidence review, including providing direction on inclusion and exclusion criteria
b. Assessing the level and quality of the evidence
c. Identifying appropriate disciplines to be included as part of the Work Group
d. Directing and coordinating the Work Group
e. Participating throughout the guideline development and review processes

The VA Office of Quality, Safety and Value, in collaboration with the DoD, identified four clinical leaders as Champions for the 2014 OA CPG. The Lewin Group (Lewin) and their sub-contractors ECRI Institute and Duty First Consulting, held the first conference call for this Guideline in August 2012, with participation from the contracting officer's representatives (COR), leaders from the VA and DoD evidence-based guideline development program, and the Champions. During this call, the project team discussed the scope of the guideline initiative, the roles and responsibilities of the Champions, the project timeline, and the approach for developing evidence questions for a systematic review on the nonsurgical management of OA. During this call, the team also identified a list, from which the Work Group members were recruited, of clinical specialties and areas of expertise that are important and relevant to OA. The specialties areas included are dietetics, family practice, internal medicine, nursing, orthopedics, primary care, pharmacy and rheumatology.

Methodology

The guideline development process for the VA/DoD OA CPG consisted of the following steps:

- Identifying the key evidence questions
- Conducting a systematic review of the literature
- Convening a three and a half day face to face meeting with the CPG Champions and Work Group members

- Submitting a final CPG on to the VA/DoD Evidence-Based Practice Working Group

The following is a detailed description of each of these steps.

Key Question Formulation

Following a series of discussions on the highest priority topics related to VA and DoD populations regarding OA, the Champions, in consultation with the Work Group, identified a set of 19 key questions to guide the systematic review of the literature. The key questions followed the industry standard PICOTS framework for evidence questions, as developed by the Agency for Healthcare Research and Quality (AHRQ). [151] Table A-1 provides a brief overview of the PICOTS typology. Lewin described this method in detail during the biweekly teleconference held with the Champions and guided them into identifying and prioritizing topics of interest for this CPG.

Table A-1. PICOTS Framework [152]

P	Patients, Population or Problem	A description of the patients of interest. It includes the condition(s), populations or sub-populations, disease severity or stage, comorbidities, and other patient characteristics or demographics.
I	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.
C	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.
O	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.
(T)	Timing, if applicable	Describes the duration of time that is of interest for the particular patient outcome, benefit, or harm to occur (or not occur).
(S)	Setting, of applicable	Describes the setting or context of interest. Setting can be a location (such as primary, specialty, or inpatient care).

The key questions, listed in table A-2, cover the following topics:

- Diagnosis and evaluation of OA
- Comparative effectiveness of drugs for OA
- Comparative effectiveness of non-pharmacologic therapies
- Comparative effectiveness of complementary and alternative medicine
- Surgical referral

Table A-2. Key Evidence questions for the OA CPG

Key Questions
Diagnostic Questions
1. In adults with clinical symptoms and signs consistent with OA of the hips or knees, which imaging strategies, including plain radiograph, MRI, and CT contribute to improved clinical outcomes?
2. In adults with clinical symptoms and signs consistent with OA of the hips or knees, do laboratory tests contribute to improved clinical outcomes?
3. In adults with clinical symptoms and signs consistent with OA of the knees, does synovial fluid analysis contribute to improved clinical outcomes?
Intervention Questions
4. In adults with OA of the hips or knees, what is the comparative effectiveness of acetaminophen to placebo with respect to pain, improved function, and harms?
5. In adults with OA of the hips or knees, what is the comparative effectiveness of intra-articular corticosteroids to intra-articular hyaluronates with respect to pain, improved function, and harms?
6. In adults with OA of the hips or knees, what is the comparative effectiveness of intra-articular hyaluronates to sham injections with respect to pain, improved function, and harms?
7. In adults with OA of the hips or knees, what is the comparative effectiveness of joint injections to oral NSAIDs (selective or non-selective) with respect to pain, improved function, and harms?
8. In adults with OA of the hips or knees, what is the comparative effectiveness of topical NSAIDs to oral NSAIDs (selective or non-selective) with respect to pain, improved function, and harms?
9. In adults with OA of the hips or knees, what is the comparative effectiveness of traditional land-based strengthening exercises to aquatic therapy with respect to pain, improved function, and harms?
10. In adults with OA of the hips or knees, what is the comparative effectiveness of traditional land-based strengthening exercises to manual physical therapy with respect to pain, improved function, and harms?
11. In adults with OA of the hips or knees, what is the comparative effectiveness of aquatic therapy to manual therapy with respect to pain, improved function, and harms?
12. What is the comparative effectiveness of walking aids or devices (e.g., cane ambulation to OA unloader braces for the knees) used to treat OA of the hips or knees with respect to pain, improved function, and harms?
13. In adults with OA of the hips or knees, what is the comparative effectiveness of chiropractic care to usual therapy with respect to pain, improved function, and harms?
14. In adults with OA of the hips or knees, what is the comparative effectiveness of acupuncture to usual therapy with respect to pain, improved function, and harms?
15. In adults with OA of the hips or knees, what is the comparative effectiveness of nutritional supplements (e.g., glucosamine) to usual therapy with respect to pain, improved function, and harms?
Referral Questions
16. In patients with clinical symptoms and signs consistent with OA, what imaging findings indicate that referral for total/partial joint replacement surgery is the best option for achieving optimal clinical outcomes?
17. For adults with OA of the hips or knees, what patient symptoms or signs (e.g., level of pain and/or disability) indicate that referral for total/partial joint replacement surgery is the best option for achieving optimal clinical outcomes?
18. In adults with OA of the hips or knees, what patient-centered risk factors would preclude referral for surgery?
19. For adults with OA of the hips or knees, should a trial of injection therapy (corticosteroids or visco-supplementation) be attempted before referral for total/partial joint replacement surgery?

Evidence Review

The methods guiding this systematic review are described below. In part, these methods follow the guidelines for conducting a systematic review set forth by the Agency for Healthcare Research and Quality (AHRQ) in the *Methods Guide for Effectiveness and Comparative Effectiveness Reviews*. [153] The methods also follow the guidance set forth by the VA/DoD in the *Guideline for Guidelines* document. [150]

A systematic review of the literature consists of several distinct steps. ECRI Institute conducted the evidence review for this CPG, by following the process outlined below:

1. Defining the inclusion and exclusion search criteria
2. Developing a search strategy (i.e., search logic using MeSH (Medical Subject Headings) terminology and key words)
3. Screening the results based on abstracts and titles (i.e., identifying relevant studies and excluding duplicate records)
4. Reviewing the full text of remaining studies and abstracting relevant data points (i.e., population, comparator, results, etc.)
5. Assessing the internal and external validity of abstracted studies
6. Summarizing the evidence
7. Interpreting the results

Criteria for Study Inclusion/Exclusion

The inclusion criteria are listed below in separate categories pertaining to the following: general criteria relevant to all studies included in the evidence base; criteria that is specific to studies that address the diagnostic questions; criteria specific to studies that address the pharmacological and non-pharmacological intervention questions; and criteria specific to studies that address the referral questions.

General Criteria

- Clinical studies published on or after January 1, 2002, and systematic reviews published on or after January 1, 2008
- Studies must be published in English
- Publication must be a full-length clinical study or systematic review; abstracts alone were not included. Similarly, letters, editorials, and other publications that are not full-length, clinical studies were not accepted as evidence
- Study must have enrolled a patient population in which at least 85 percent of patients had OA (post-traumatic or idiopathic) of the hips or knees
- Studies must have enrolled adults 18 years or older. In studies that mixed adults and children, at least 85 percent of the enrolled patients must have been 18 years or older
- Study included 50 percent or more of patients at final follow-up

- Studies that enrolled adults with osteonecrosis, rheumatoid arthritis, or other inflammatory joint disease were excluded

Diagnosis/Evaluation Studies

- Studies must have enrolled ≥ 10 patients
- Studies must have linked use of diagnostic technologies with improvement in clinical outcomes. This ideally requires a study that compares clinical outcomes after diagnostic technology evaluation versus clinical evaluation, or compares clinical outcomes linked to different diagnostic technologies

Intervention Studies

- Study must have evaluated a treatment for OA of the hips or knees
- Study must have been a prospective, randomized or nonrandomized comparative trial with an independent, concurrent control group
- Crossover trials were considered only if data from the first treatment period were reported separately
- Study must have enrolled ≥ 25 patients per treatment arm
- The study must report data on at least one of the included outcomes
- Study must have followed patients for at least four weeks
- All subjective outcomes (e.g., pain, aspects of patient function) must be measured using validated instruments

Referral Studies

- Study must have enrolled ≥ 10 patients
- Study must have been a clinical study (comparative or not) that investigated indications for referring patients with OA of the hips or knees for total/partial joint replacement surgery
- Expert opinion papers were not considered as evidence addressing the referral questions
- Study must have reported on the outcomes associated with indications

Additional Criteria for Key Question 18

- Study must have enrolled at least 100 patients
- Study excluded if it only considered non-modifiable patient risk factors, such as gender or age
- Study excluded if outcomes of pain and function are measured prior to six months follow-up

Search Strategy

MeSH, EMTREE, and Keywords

The search strategies employed combinations of free text keywords as well as controlled vocabulary terms including (but not limited to) the concepts shown in the Topic-specific Search Terms table.

The strategies below are presented in OVID syntax; the searches were simultaneously conducted across EMBASE and Medline. Similar strategies were used to search the databases comprising PubMed, and the Cochrane Library (See Tables A-3 through A-12 below). Search sets were structured to address specific key questions and/or groups of key questions (i.e., diagnosis/evaluation, pharmacologic management, non-pharmacologic management, complementary and alternative medicine, and referrals). These search results were further refined to capture specific patient outcomes, study designs and publication types.

Table A-3. Topic-specific Search Terms

Concept	Controlled Vocabulary	Keywords
Patient Population		
Osteoarthritis	**MEDLINE (MeSH)** osteoarthritis/ osteoarthritis, knee/ osteoarthritis, hip/ **EMBASE (EMTREE)** osteoarthritis/ knee osteoarthritis/ hip osteoarthritis/	arthrit$ degenerative joint disease$ osteoarthrit$
Knee	**MEDLINE (MeSH)** exp knee/ exp knee joint/ exp knee injuries/ **EMBASE (EMTREE)** exp knee/ exp knee injury/	ACL anterior cruciate ligament iliotibial knee knees menisc$ patellofemor$ patell$
Hip	**MEDLINE (MeSH)** exp hip/ exp hip joint/ exp hip injuries/ hip fractures/ **EMBASE (EMTREE)** exp hip/ exp hip injury/	coxa coxas hip hips
Terms for Diagnostic/Evaluation Questions		
Imaging *(Note that the same terms were used for the Referrals Question that involved imaging)*	**MEDLINE (MeSH)** exp *diagnostic imaging/ *tomography scanners, x-ray computed/ **EMBASE (EMTREE)** exp diagnostic imaging equipment/ exp "imaging and display"/ exp radiodiagnosis/ exp echography/	absorptiometry arthrography computed tomography CT DEXA dGEMRIC diffusion tensor image$ imaging magnetic resonance MR MRI neuroimaging NMR

Concept	Controlled Vocabulary	Keywords
		PET phonoarthrography positron emission tomography radiodiagnos$ radiograph$ ultrasonography ultrasound PET Scan scans scanning scintigraph$ sonograph$ SPECT spectroscopy Tc-99m technetium tomosynthesis ultrasonography ultrasound$ x ray$ xray$
Laboratory Tests (including synovial fluid analysis)	**MEDLINE (MeSH)** exp clinical laboratory techniques/ exp hematologic tests/ c-reactive protein/ synovial fluid/ rheumatoid factor/ exp serologic tests/ exp blood cell count/ **EMBASE (EMTREE)** exp laboratory diagnosis/ exp blood examination/ C reactive protein/ synovial fluid/ rheumatoid factor/ exp serology/	articular fluid blood c-reactive protein c reactive protein hematology hematologic joint fluid lab laboratory rheumatoid factor sera serum serology synovial fluid synovium
Terms for Pharmacologic Management Questions		
Acetaminophen	**MEDLINE (MeSH)** acetaminophen/ **EMBASE (EMTREE)** paracetamol/	acetaminophen$ paracetamol tylenol anacin acetaco datril panadol acamol algotropyl acetamidophenol
Corticosteroids	**MEDLINE (MeSH)** exp adrenal cortex hormones/ **EMBASE (EMTREE)**	Adrenal cortex hormones betamethasone corticosteroid$

Concept	Controlled Vocabulary	Keywords
	exp corticosteroid/	corticoid$ Dexamethasone cortisone$ glucocorticoid$ hydroxycorticosteroid$ hydrocortisone Methylprednisolone prednisolone prednisone steroid$
Injection Therapy *(Note that the same terms were used for the Referrals Question that involved injections)*	**MEDLINE (MeSH)** injections/ exp injections, intra-articular/ viscosupplementation/ **EMBASE (EMTREE)** intraarticular drug administration/ injection/ viscosupplementation/	inject$ intra-articular inject$ Intra articular inject$ Intraarticular inject$ IACI viscosupplement$
Intra-articular hyaluronates	**MEDLINE (MeSH)** viscosupplementation/ hyaluronic acid/ hyaluronic acid/tu **EMBASE (EMTREE)** viscosupplementation/ hyaluronic acid/ hyaluronic acid/dt	Adant Amvisc Arthrease Arthrum H Artz Biolon BioHy Durolane Etamucine Euflexxa Fermathron "gel-one" Healon Hyalgan Hyaluronan hyaluronate$ hyaluronic Hyaluronidate "hylan gf-20" Hyruan Hyvisc Luronit nuflexxa Orthovisc Ostenil Replasyn SLM-10 supartz Suplasyn Synject synvisc viscosupplement$ vitrax

Concept	Controlled Vocabulary	Keywords
Nonsteroidal anti-inflammatory drugs	**MEDLINE (MeSH)** exp anti-inflammatory agents, non-steroidal/ exp cyclooxygenase inhibitors/ exp cyclooxygenase 2 Inhibitors/ **EMBASE (EMTREE)** exp nonsteroid antiinflammatory agent/ exp prostaglandin synthase inhibitor/ exp cyclooxygenase 2 inhibitor/	aleve aspirin celecoxib Celebrex (Cox$ OR Cyclooxygenase$ OR Cyclo-oxygenase$) AND inhibit$ coxib$ diclofenac ibuprofen motrin naproxen nonsteroidal anti-inflammatory NSAID$ rofecoxib salicylate$ vioxx **Topical NSAIDS** "Deep Relief" "Fenbid Gel" Ibugel Ibuleve Ibumousse Ibuspray optifen pennsaid Powergel sulidin Traxam voltaran voltarol
Oral Administration	**MEDLINE (MeSH)** exp administration oral/ **EMBASE (EMTREE)** oral drug administration/	buccal "by mouth" oral "p.o." sublingual
Placebos	**MEDLINE (MeSH)** placebos/ **EMBASE (EMTREE)** placebo/	dummy Inactive no intervention no treatment placebo$ sham$
Topical Therapy	**MEDLINE (MeSH)** administration, topical/ administration, cutaneous/ **EMBASE (EMTREE)** topical treatment/ transdermal drug administration/	aerosol balm cream creme cutaneous dermal embrocation emulsion epicutaneous foam

Concept	Controlled Vocabulary	Keywords
		gel lotion liniment massage mousse oil ointment patch percutaneous plaster rub salve skin spray topical$ transcutaneous transdermal
Terms for Non-pharmacologic Management Questions		
Aquatic therapy	**MEDLINE (MeSH)** pools, swimming/ swimming/ **EMBASE (EMTREE)** aquatic exercise/ swimming/ swimming pool/	aquarobic$ aquatic aquatics hydrotherapy pool based pool therapy swim$ water
Land-based strengthening exercises	**MEDLINE (MeSH)** exp exercise/ exp exercise movement techniques/ exp exercise therapy/ physical fitness/ **EMBASE (EMTREE)** exp exercise/ fitness/ exp kinesiotherapy/ exp physical activity/	active stretching aerobic activity aerobic conditioning aerobics dance dancing endurance training exercise$ fitness hip school kinesiotherapy land based motion therapy muscle strengthening physical activity physical conditioning plyometric training resistance training strength training tai chi walk$ weight lifting yoga
Manual physical therapy	**MEDLINE (MeSH)** exp musculoskeletal manipulations/	manipulation$ manipulative

Concept	Controlled Vocabulary	Keywords
	[note: includes massage] physical therapists/ physical therapy modalities/ physical therapy department, hospital/ physical therapy specialty/ **EMBASE (EMTREE)** manipulative medicine/ massage/ muscle training/ orthopedic manipulation/ physiotherapist/ exp physiotherapy/ stretching/	manual techniques manual therapy massage mobilization mobilisation muscle stretching physical therapy physiotherap$ rehabilitation stretching
Walking aids or devices	**MEDLINE (MeSH)** canes/ crutches/ orthotic devices/ walkers/ **EMBASE (EMTREE)** orthopedic shoe/ exp orthosis/ orthotics/ exp walking aid/	brace$ bracing cane canes crutch crutches footwear inshoe$ joint supports orthotic orthotics orthoses orthosis orthopedic shoe$ taping splint splints walker$ walking aid$ walking device$ walking stick$ wedge$
Terms for Complementary and Alternative Medicine Questions		
Acupuncture	**MEDLINE (MeSH)** acupressure/ acupuncture/ exp acupuncture therapy/ **EMBASE (EMTREE)** exp acupuncture/	acupoint acupressure acupuncture$ acustimulation acu stimulation electroacupoint electroacupuncture electroacustimulation
Chiropractic care	**MEDLINE (MeSH)** chiropractic/ manipulation, chiropractic/ manipulation, osteopathic/ **EMBASE (EMTREE)** chiropractic/ chiropractic practice/	adjustment$ chiropractic$ chiropractor$ manipulation$ manipulative

Concept	Controlled Vocabulary	Keywords
	chiropractor/	
Nutritional Supplements	**MEDLINE (MeSH)** exp dietary supplements/ exp glucosamine/ exp chondroitin/ capsaicin/ exp plants, medicinal/ **EMBASE (EMTREE)** nutraceutical/ diet supplementation/ vitamin supplementation/ exp plant medicinal product/ exp glucosamine/ chondroitin/	alliums black cohosh capsaicin$ Capsaicine chondroitin Cimicifuga Creatine curcuma curcumin Cyperus devils claw Dietary supplement eazmov Feverfew Fraxinus garlic ginger Gitadyl glucosamine Guaiacum harpagophytum herb medicinal Methylsulfonylmethane milfoil Nettle$ nutraceutical$ nutritional supplement omega-3 Phytodolor Picrorhiza Picrorrhiza plant Poplar populus quercetin remedy Reumalex Rose hip S-adenosylmethionine Sarsaparilla saussurea Smilax solidago supplement tanacetum parthenium Tinospora Turmeric uncaria willow

Concept	Controlled Vocabulary	Keywords
		zingiber
Terms for Referral questions		
Joint Replacement Surgery	**MEDLINE (MeSH)** exp arthroplasty/ **EMBASE (EMTREE)** exp arthroplasty/	arthroplast$ replace replacement$ resurfac$ surgical surgery
Outcomes	**MEDLINE (MeSH)** prognosis/ treatment outcome/ exp postoperative complications/ survival rate/ outcome assessment/ "outcome assessment (health care)"/ exp "quality of life"/ mortality.fs. reoperation/ adverse effects.fs. recovery of function/ comorbidity/ mortality/ morbidity/ **EMBASE (EMTREE)** prognosis/ treatment outcome/ reoperation/ exp postoperative complication/ mortality/ morbidity/ complication.fs. convalescence/	appropriate appropriateness comorbid comorbidity complication$ morbidity mortality prognosis prognostic QOL "quality of life" survival*
Referral	**MEDLINE (MeSH)** "referral and consultation"/ decision making/ patient selection/ "severity of illness index"/ risk factors/ disability evaluation/ risk assessment/ decision trees/ patient care planning/ **EMBASE (EMTREE)** decision making/ patient selection/ risk assessment/ patient referral/ patient care planning/ risk factor/ exp disability/ exp disease severity/	consult consultation contraindicate criteria decide decision indication patient selection patient characteristics predict risk "red flag" referral refer serious surgeon specialist urgent warning

OVID Conventions:

$ or * = truncation character (wildcard)
.ab. = limit to abstract
ADJ*n* = search terms within a specified number (*n*) of words from each other in any order
exp/ = "explodes" controlled vocabulary term (e.g., expands search to all more specific related terms in the vocabulary's hierarchy)
.de. = limit controlled vocabulary heading
.fs. = floating subheading
.hw. = limit to heading word
.mp. = combined search fields (default if no fields are specified)
.pt. = publication type
.ti. = limit to title
.tw. = limit to title and abstract fields

Table A-4. Search Strategy for Diagnosis/Evaluation Key Question 1 (imaging strategies)

Set #	Concept	Search Statement
1	Osteoarthritis of specific joints	osteoarthritis, knee/ OR osteoarthritis, hip/ OR hip osteoarthritis/ OR knee osteoarthritis/
2	Osteoarthritis	osteoarthritis/ OR (arthrit$ OR osteoarthrit$ OR degenerative joint).ti.
3	Knee	exp knee/ OR exp knee joint/ OR exp knee injuries/ OR exp knee injury/ OR (knee OR knees OR menisc$ OR patellofemor$ OR patell$ OR iliotibial OR ACL OR anterior cruciate ligament).ti.
4	Hip	exp hip/ OR exp hip joint/ OR exp hip injuries/ OR exp hip fractures/ OR exp hip injury/ OR (hip OR hips).ti.
5	Combine sets	2 AND (3 OR 4)
6		1 OR 5
7	Diagnostic imaging Controlled vocabulary	Exp *diagnostic imaging equipment/ OR exp *"imaging and display"/ OR exp *radiodiagnosis/ OR exp *echography/ OR exp *diagnostic imaging/ OR *tomography scanners, x-ray computed/
8	Diagnostic imaging Keywords	(absorptiometry OR arthrography OR computed tomography OR CT OR DEXA OR dGEMRIC OR diffusion tensor OR image$ OR imaging OR magnetic resonance OR MR OR MRI OR neuroimaging OR NMR OR PET OR phonoarthrography OR positron emission tomography OR radiodiagnos$ OR radiograph$ OR scan OR scans OR scanning OR scintigraph$ OR sonograph$ OR SPECT OR spectroscopy OR Tc-99m OR technetium OR tomosynthesis OR ultrasonography OR ultrasound$ OR x-ray$ OR xray$).ti.
9	Combine sets	6 AND (7 OR 8)
10	Exclude publications that are outside of scope	9 NOT (spine OR spinal OR vertebr$ OR lumbar$ OR cervic$ OR thorac$ OR surgery OR surgical OR psoriatic OR rheumatoid OR rheumatic OR inflammatory OR juvenile OR "JRA" OR arthroplast$ OR replace$ OR reconstruct$ OR arthroscop$ OR biomarker$ OR implant$ OR injection$ OR marker$ OR osteotom$ OR resurfac$ OR sepsis OR septic OR therapeutic ultrasound OR TKA OR ultrasound therapy OR urinary).ti.
11	Exclude unwanted publications	10 NOT (book/ OR edited book/ OR case report/ OR case reports/ OR comment/ OR conference abstract/ OR conference paper/ OR conference review/ OR editorial/ OR letter/ OR news/ OR note/ OR proceeding/ OR (book OR edited book OR case report OR case reports OR comment OR conference OR editorial OR letter OR news OR note OR proceeding).pt.)

Set #	Concept	Search Statement
12	Keep case series	10 AND (case series OR case control)
13	Combine	11 OR 12
14	Limit to humans	limit 13 to humans
15	Limit to english language	limit 14 to english language
16	Limit by publication date	limit 15 to yr="2002 -Current"
17	Limit to comparative studies and systematic reviews	16 AND (comparative study/ OR control groups/ OR controlled clinical trial/ OR controlled study/ OR cross-over studies/ OR double-blind method/ OR random allocation/ OR randomized controlled trial/ OR sham procedure/ OR single-blind method/ OR (compar$ OR versus OR vs).ti. OR (blind$ OR (control ADJ group$) OR controlled study OR controlled trial OR crossover OR cross over OR latin square OR mask$ OR matched controls OR pooled OR research synthesis OR sham OR ACTRN$ OR ISRTCN$ OR (NCT$ NOT NCT)).ti,ab. OR meta-analysis/ OR systematic review/ OR (evidence ADJ base$).ti. OR (meta-analysis OR methodologic$ OR pooled OR search$ OR systematic literature review OR systematic review).ti,ab.)
18	Limit to studies that address management or outcomes	16 AND (disease course/ OR disease progression/ OR exp disease management/ OR exp "outcome assessment (health care)"/ OR predictive value/ OR "predictive value of tests"/ OR prognosis/ OR treatment outcome/ OR (adverse OR function$ OR harm$ OR pain OR outcome$ OR utility).ti,ab. OR clinical.ti. OR adverse effects.fs. OR disease management.fs.)
19	Combine sets	17 OR 18
20	**Eliminate overlap**	**Remove duplicates from 19**

Table A-5. Search Strategy for Diagnosis/Evaluation Key Questions 2 and 3 (laboratory tests and synovial fluid analysis)

Set #	Concept	Search Statement
1	Knee or Hip osteoarthritis	osteoarthritis, knee/ OR osteoarthritis, hip/ OR hip osteoarthritis/ OR knee osteoarthritis/
2	Osteoarthritis keywords	osteoarthritis/ OR arthrit$.ti. OR osteoarthrit$.ti. OR degenerative joint.ti.
3	Knee joint	exp knee/ OR exp knee joint/ OR exp knee injuries/ OR exp knee injury/ OR knee.ti. OR knees.ti. OR menisc$.ti. OR patellofemor$.ti. OR patell$.ti. OR iliotibial.ti. OR ACL.ti. OR anterior cruciate ligament.ti.
4	Hip	exp hip/ OR exp hip joint/ OR exp hip injuries/ OR exp hip fractures/ OR exp hip injury/ OR hip.ti. OR hips.ti.
5	Combine population sets	1 OR (2 AND (3 OR 4))
6	Laboratory tests	exp clinical laboratory techniques/ OR exp hematologic tests/ OR c-reactive protein/ OR synovial fluid/ OR rheumatoid factor/ OR exp serologic tests/ OR exp blood cell count/ OR exp laboratory diagnosis/ OR exp blood examination/ OR C reactive protein/ OR exp serology/
7	Laboratory tests (keywords)	"c-reactive protein".ti. OR "c reactive protein".ti. OR ((joint OR articular OR synovial OR synovium AND fluid) OR (rheumatoid ADJ factor)).ti. OR lab.ti. OR laboratory.ti. OR labs.ti. OR blood.ti. OR hematol$.ti. OR sera.ti. OR serum.ti. OR serolog$.ti.

Set #	Concept	Search Statement
11	Diagnostic test hedge	exp diagnosis/ OR di.fs. OR receiver operating characteristic/ OR ROC curve/ OR "sensitivity and specificity"/ OR accuracy/ OR diagnostic accuracy/ OR precision OR exp "prediction and forecasting"/ OR likelihood OR ((false OR true) adj (positive OR negative)) OR predictive value of tests/ OR exp diagnostic errors/ OR exp diagnostic error/ OR diagnostic accuracy/ OR positive predictive value OR PPV OR diagnosis.ti. OR diagnostic$.ti. OR diagnose$.ti. OR evaluat$.ti. OR assess$.ti. OR test.ti. OR testing.ti. OR tests.ti.
12	Combine sets	5 AND (6 OR 7) AND 11
13	Limit to english language	limit 12 to english language
14	Limit to Human studies	limit 13 to humans
15	Exclude unwanted publication types	14 NOT (book/ OR edited book/ OR case report/ OR case reports/ OR comment/ OR conference abstract/ OR conference paper/ OR conference review/ OR editorial/ OR letter/ OR news/ OR note/ OR proceeding/ OR book OR edited book OR case report OR case reports OR comment OR conference OR editorial OR letter OR news OR note OR proceeding.pt.)
16	Include case series	14 AND (case series OR case control)
17	Combine sets	15 OR 16
18	Limit by publication date	limit 17 to yr="2002-Current"
19	**Eliminate overlap**	**Remove duplicates from 18**

Table A-6. Search Strategy for Pharmacologic Management Key Questions 4, 5, 6, 7, and 8

Set #	Concept	Search Statement
1	Knee or Hip osteoarthritis	osteoarthritis, knee/ OR osteoarthritis, hip/ OR hip osteoarthritis/ OR knee osteoarthritis/
2	Osteoarthritis keywords	osteoarthritis/ OR arthrit$.ti. OR osteoarthrit$.ti. OR degenerative joint.ti.
3	Knee joint	exp knee/ OR exp knee joint/ OR exp knee injuries/ OR exp knee injury/ OR knee.ti. OR knees.ti. OR menisc$.ti. OR patellofemor$.ti. OR patell$.ti. OR iliotibial.ti. OR ACL.ti. OR anterior cruciate ligament.ti.
4	Hip	exp hip/ OR exp hip joint/ OR exp hip injuries/ OR exp hip fractures/ OR exp hip injury/ OR hip.ti. OR hips.ti.
5	Combine population sets	1 OR (2 AND (3 OR 4))
6	Intervention - Acetaminophen	Acetaminophen/ OR Paracetamol/ OR Acetaminophen$ OR paracetamol$ OR tylenol OR anacin OR acetaco OR datril OR panadol OR acamol OR algotropyl OR acetamidophenol
7	Intervention - Placebo	placebos/ OR placebo/ OR placebo$ OR sham$ OR dummy OR inactive OR (no ADJ2 intervention) OR (no ADJ2 treatment$)
8	Intervention – corticosteroids	exp adrenal cortex hormones/ OR exp corticosteroid OR "Adrenal cortex hormones" OR corticosteroid$ OR corticoid$ OR steroid$ OR glucocorticoid$ OR hydroxycorticosteroid$ OR cortisone$ OR hydrocortisone OR Dexamethasone OR prednisolone OR prednisone OR hydrocortisone OR betamethasone OR Methylprednisolone

Set #	Concept	Search Statement
9	Intervention - NSAIDS	exp Anti-Inflammatory Agents, Non-Steroidal/ OR exp cyclooxygenase inhibitors/ OR exp cyclooxygenase 2 Inhibitors/ OR exp nonsteroid antiinflammatory agent/ OR exp prostaglandin synthase inhibitor/ OR exp cyclooxygenase 2 inhibitor/ OR aleve OR aspirin OR diclofenac OR naproxen OR NSAID$ OR celecoxib OR Celebrex OR ((Cox$ OR Cyclooxygenase$ OR Cyclo-oxygenase$) AND inhibit$) OR coxib$ OR ibuprofen OR motrin OR naproxen OR (Nonsteroidal ADJ anti-inflammator$) OR (Non-steroidal ADJ anti-inflammator$) OR (Non-steroidal ADJ antiinflammatory) OR rofecoxib OR salicylate$ OR vioxx
10	Intervention – Topical NSAIDS	Traxam OR "Deep Relief" OR "Fenbid Gel" OR Ibugel OR Ibuleve OR Ibumousse OR Ibuspray OR Powergel OR voltaran OR voltarol OR pennsaid OR sulidin OR optifen
11	Intervention - Hyaluronates	Viscosupplementation/ OR Hyaluronic Acid/ OR Adant OR Amvisc OR Arthrease OR Arthrum H OR Artz OR Biolon OR BioHy OR Durolane OR Etamucine OR Euflexxa OR Fermathron OR "gel-one" OR Healon OR Hyalgan OR Hyaluronan OR hyaluronate$ OR hyaluronic OR Hyaluronidate OR "hylan gf-20" OR Hyruan OR Hyvisc OR Luronit OR nuflexxa OR Orthovisc OR Ostenil OR Replasyn OR SLM-10 OR supartz OR Suplasyn OR Synject OR synvisc OR viscosupplement$ OR vitrax
12	Intervention - Hyaluronates (controlled terms for therapy)	hyaluronic acid/tu OR hyaluronic acid/dt
13	Administration - Injections	injections/ OR exp injections, intra-articular/ OR viscosupplementation/ OR intraarticular drug administration/ OR injection/ OR viscosupplement$.mp. OR inject$.mp. OR intraarticular OR intra-articular OR (intra ADJ articular) OR "IACI"
14	Administration - Oral	exp administration oral/ OR oral drug administration/ OR oral OR buccal OR sublingual OR "p.o." OR "by mouth"
15	Administration – Topical	administration, topical/ OR administration, cutaneous/ OR topical treatment/ OR transdermal drug administration/ OR topical OR cutaneous OR transcutaneous OR topical$ OR dermal OR transcutaneous OR transdermal OR percutaneous OR skin OR massage OR embrocation OR gel OR ointment OR aerosol OR cream OR creme OR lotion OR mousse OR foam OR liniment OR spray OR rub OR balm OR salve OR emulsion OR oil OR patch OR plaster OR epicutaneous
16	Combine sets – key question 4: acetaminophen compared to placebo	5 AND 6 AND 7
17	Combine sets – key question 5: intra-articular corticosteroids compared to intra-articular hyaluronates	5 AND (8 AND 13) AND ((11 AND 13) OR 12)
18	Combine sets – key question 6: intra-articular hyaluronates compared to sham injections	5 AND ((11 AND 13) OR 12) AND 7

Set #	Concept	Search Statement
19	Combine sets – key question 7: joint injections compared to oral NSAIDS	5 AND 13 AND 9
20	Combine sets- key question 8: topical NSAIDS compared to oral NSAIDS	5 AND (10 OR (9 AND 15)) AND (9 AND 14)
21	Combine sets for key questions	16 OR 17 OR 18 OR 19 OR 20
22	Limit to humans	limit 21 to humans
23	Limit to english language	limit 22 to english language
24	Exclude unwanted publication types	23 NOT (book/ OR edited book/ OR case report/ OR case reports/ OR comment/ OR conference abstract/ OR conference paper/ OR conference review/ OR editorial/ OR letter/ OR news/ OR note/ OR proceeding/ OR (book OR edited book OR case report OR case reports OR comment OR conference OR editorial OR letter OR news OR note OR proceeding).pt.)
25	Keep case series	23 AND (case series OR case control)
26	Combine sets	24 OR 25
27	Limit by publication date	Limit 26 to yr="2002-Current"
28	**Eliminate overlap**	**Remove duplicates from 27**

Table A-7. Search Strategy for Non-pharmacologic Management Key Questions 9, 10, 11, and 12

Set #	Concept	Search Statement
1	Osteoarthritis of specific joints	osteoarthritis, knee/ OR osteoarthritis, hip/ OR hip osteoarthritis/ OR knee osteoarthritis/
2	Osteoarthritis	osteoarthritis/ OR (arthrit$ OR osteoarthrit$ OR degenerative joint).ti.
3	Knee	exp knee/ OR exp knee joint/ OR exp knee injuries/ OR exp knee injury/ OR (knee OR knees OR menisc$ OR patellofemor$ OR patell$ OR iliotibial OR ACL OR anterior cruciate ligament).ti.
4	Hip	exp hip/ OR exp hip joint/ OR exp hip injuries/ OR exp hip fractures/ OR exp hip injury/ OR (hip OR hips).ti.
5	Combine sets	2 AND (3 OR 4)
6		1 OR 5
7	Land-based exercise Controlled vocabulary	exp exercise/ OR exp exercise movement techniques/ OR exp exercise therapy/ OR fitness/ OR kinesiotherapy/ OR exp physical activity/ OR physical fitness/
8	Land-based exercise Keywords	active stretching OR aerobic activity OR aerobic conditioning OR aerobics OR apos$ OR dance OR dancing OR endurance training OR exercise$ OR fitness OR kinesiotherapy OR land based OR motion therapy OR muscle strengthening OR physical activity OR physical conditioning OR plyometric training OR resistance training OR strength training OR tai chi OR walk$ OR weight lifting OR yoga
9	Aquatic exercise Controlled vocabulary	aquatic exercise/ OR pools, swimming/ OR swimming/ OR swimming pool/

Set #	Concept	Search Statement
10	Aquatic exercise Keywords	aquarobic$ OR (aquatic AND (exercise$ OR rehabilitation OR therapy OR training)) OR aquatics OR hydrotherapy OR pool based OR pool therapy OR swim$ OR (water AND (aerobics$ OR exercise$ OR therapy))
11	Manual physical therapy Controlled vocabulary	manipulative medicine/ OR massage/ OR muscle training/ OR exp musculoskeletal manipulations/ OR orthopedic manipulation/ OR physical therapists/ OR physical therapy modalities/ OR physical therapy department, hospital/ OR physical therapy specialty/ OR physiotherapist/ OR exp physiotherapy/ OR stretching/
12	Manual physical therapy Keywords	manipulation$ OR manipulative OR manual techniques OR manual therapy OR massage OR mobilisation OR mobilization OR muscle stretching OR physical therapy OR physiotherapies OR physiotherapy OR rehabilitation.ti. OR stretching
13	Walking aids or Devices Controlled vocabulary	canes/ OR crutches/ OR orthopedic shoe/ OR exp orthosis/ OR orthotic devices/ OR orthotics/ OR walkers/ OR exp walking aid/
14	Walking aids or devices Keywords	brace OR braces OR bracing OR cane OR canes OR crutch OR crutches OR footwear OR inshoe$ OR joint supports OR orthotic OR orthotics OR orthoses OR orthosis OR (orthopedic ADJ shoe$) OR taping OR splint OR splints OR walker$ OR (walking ADJ (aid OR aids OR device$ OR stick$)) OR wedge$
15	Land-based strengthening exercises vs. aquatic therapy	6 AND (7 OR 8) AND (9 OR 10)
16	Land-based strengthening exercises vs. manual physical therapy	6 AND (7 OR 8) AND (11 OR 12)
17	Aquatic therapy vs. manual physical therapy	6 AND (9 OR 10) AND (11 OR 12)
18	Walking aids or devices	6 AND (13 OR 14)
19	Combine sets	15 OR 16 OR 17 OR 18
20	Exclude unwanted publications	19 NOT (book/ OR edited book/ OR case report/ OR case reports/ OR comment/ OR conference abstract/ OR conference paper/ OR conference review/ OR editorial/ OR letter/ OR news/ OR note/ OR proceeding/ OR (book OR edited book OR case report OR case reports OR comment OR conference OR editorial OR letter OR news OR note OR proceeding).pt.)
21	Limit to humans	limit 20 to humans
22	Limit to english language	limit 21 to english language
23	Limit by publication date	limit 22 to yr="2002-Current"

Set #	Concept	Search Statement
24	Limit to comparative studies and systematic reviews	23 AND (comparative study/ OR control groups/ OR controlled clinical trial/ OR controlled study/ OR cross-over studies/ OR double-blind method/ OR placebo/ OR placebos/ OR random allocation/ OR randomized controlled trial/ OR sham procedure/ OR single-blind method/ OR (compar* OR versus OR vs).ti. OR (blind$ OR (control ADJ group*) OR controlled study OR controlled trial OR crossover OR cross over OR latin square OR mask$ OR matched controls OR placebo$ OR pooled OR research synthesis OR sham OR ACTRN$ OR ISRTCN$ OR (NCT$ NOT NCT)).ti,ab. OR meta-analysis/ OR systematic review/ OR (evidence ADJ base$).ti. OR (meta-analysis OR methodologic$ OR pooled OR search$ OR systematic literature review OR systematic review).ti,ab.)
25	**Eliminate overlap**	**Remove duplicates from 24**

Table A-8. Search Strategy for Complementary and Alternative Medicine Questions 13 and 14 (chiropractic care and acupuncture)

Set #	Concept	Search Statement
1	Osteoarthritis of specific joints	osteoarthritis, knee/ OR osteoarthritis, hip/ OR hip osteoarthritis/ OR knee osteoarthritis/
2	Osteoarthritis	osteoarthritis/ OR (arthrit$ OR osteoarthrit$ OR degenerative joint).ti.
3	Knee	exp knee/ OR exp knee joint/ OR exp knee injuries/ OR exp knee injury/ OR (knee OR knees OR menisc$ OR patellofemor$ OR patell$ OR iliotibial OR ACL OR anterior cruciate ligament).ti.
4	Hip	exp hip/ OR exp hip joint/ OR exp hip injuries/ OR exp hip fractures/ OR exp hip injury/ OR (hip OR hips).ti.
5	Combine sets	2 AND (3 OR 4)
6		1 OR 5
7	Chiropractic care Controlled vocabulary	chiropractic/ OR chiropractic practice/ OR chiropractor/ OR manipulation, chiropractic/ OR manipulation, osteopathic/
8	Chiropractic care Keywords	adjustment$ OR chiropractic$ OR chiropractor$ OR manipulation$ OR manipulative
9	Acupuncture Controlled vocabulary	acupressure/ OR exp acupuncture/ OR exp acupuncture therapy/
10	Acupuncture Keywords	((acupoint OR electroacupoint) ADJ stimulation) OR acupressure OR acupunctur$ OR acustimulation OR acu stimulation OR electroacupuncture OR electroacustimulation
11	Chiropractic care	6 AND (7 OR 8)
12	Acupuncture	6 AND (9 OR 10)
13	Combine sets	11 OR 12
14	Exclude unwanted publications	13 NOT (book/ OR edited book/ OR case report/ OR case reports/ OR comment/ OR conference abstract/ OR conference paper/ OR conference review/ OR editorial/ OR letter/ OR news/ OR note/ OR proceeding/ OR (book OR edited book OR case report OR case reports OR comment OR conference OR editorial OR letter OR news OR note OR proceeding).pt.)
15	Limit to humans	limit 14 to humans
16	Limit to english language	limit 15 to english language
17	Limit by publication date	limit 16 to yr="2002-Current"

Set #	Concept	Search Statement
18	Limit to comparative studies and systematic reviews	17 AND (comparative study/ OR control groups/ OR controlled clinical trial/ OR controlled study/ OR cross-over studies/ OR double-blind method/ OR placebo/ OR placebos/ OR random allocation/ OR randomized controlled trial/ OR sham procedure/ OR single-blind method/ OR (compar* OR versus OR vs).ti. OR (blind$ OR (control ADJ group*) OR controlled study OR controlled trial OR crossover OR cross over OR latin square OR mask$ OR matched controls OR placebo$ OR pooled OR research synthesis OR sham OR ACTRN$ OR ISRTCN$ OR (NCT$ NOT NCT)).ti,ab. OR meta-analysis/ OR systematic review/ OR (evidence ADJ base$).ti. OR (meta-analysis OR methodologic$ OR pooled OR search$ OR systematic literature review OR systematic review).ti,ab.)
19	**Eliminate overlap**	**Remove duplicates from 18**

Table A-9. Search Strategy for Complementary and Alternative Medicine Key Question 15 (nutritional supplements)

Set #	Concept	Search Statement
1	Knee or Hip osteoarthritis	osteoarthritis, knee/ OR osteoarthritis, hip/ OR hip osteoarthritis/ OR knee osteoarthritis/
2	Osteoarthritis keywords	osteoarthritis/ OR arthrit$.ti. OR osteoarthrit$.ti. OR degenerative joint.ti.
3	Knee joint	exp knee/ OR exp knee joint/ OR exp knee injuries/ OR exp knee injury/ OR knee.ti. OR knees.ti. OR menisc$.ti. OR patellofemor$.ti. OR patell$.ti. OR iliotibial.ti. OR ACL.ti. OR anterior cruciate ligament.ti.
4	Hip	exp hip/ OR exp hip joint/ OR exp hip injuries/ OR exp hip fractures/ OR exp hip injury/ OR hip.ti. OR hips.ti.
5	Combine population sets	1 OR (2 AND (3 OR 4))
6	Nutritional supplements (controlled terms)	exp dietary supplements/ OR exp glucosamine/ OR exp chondroitin/ OR capsaicin/ OR plants, medicinal/ OR nutraceutical/ OR diet supplementation/ OR vitamin supplementation/ OR exp plant medicinal product/ OR exp glucosamine/ OR chondroitin/
7	Nutritional supplements (keywords)	((dietary OR nutritional OR herb$ OR plant$)AND (supplement$ OR remedy OR remedies OR medicinal)) OR nutraceutical$ OR glucosamine OR chondroitin OR capsaicin$ OR Capsaicine OR S-adenosylmethionine OR Methylsulfonylmethane OR Turmeric OR curcuma OR curcumin OR (Devils ADJ claw) OR Harpagophytum OR uncaria OR Eazmov OR Cyperus OR Tinospora OR Saussurea OR Picrorrhiza OR picrorhiza OR Ginger OR Zingiber OR nettle OR nettles OR Willow OR Gitadyl OR feverfew OR (tanacetum ADJ parthenium) OR milfoil OR Phytodolor OR Populus OR Fraxinus OR Solidago OR Reumalex OR Guaiacum OR (black ADJ cohosh) OR Cimicifuga OR Sarsaparilla OR Smilax OR Poplar OR (Rose ADJ hip$) OR alliums OR garlic OR omega-3 OR quercetin OR creatine
8	Combine sets –	5 AND (6 OR 7)
9	Limit to humans	Limit 8 to humans
10	Limit to english language	limit 9 to english language
11	Exclude unwanted publication types	10 NOT (book/ OR edited book/ OR case report/ OR case reports/ OR comment/ OR conference abstract/ OR conference paper/ OR conference review/ OR editorial/ OR letter/ OR news/ OR note/ OR proceeding/ OR (book OR edited book OR case report OR case reports OR comment OR conference OR editorial OR letter OR news OR note OR proceeding).pt.)

Set #	Concept	Search Statement
12	Limit to controlled studies	11 AND (randomized controlled trial/ OR random allocation/ OR double-blind method/ OR single-blind method/ OR placebos/ OR cross-over studies/ OR crossover procedure/ OR cross over studies/ OR double blind procedure/ OR single blind procedure/ OR placebo/ OR latin square design/ OR crossover design/ OR double-blind studies/ OR single-blind studies/ OR triple-blind studies/ OR random assignment/ OR exp controlled study/ OR exp clinical trial/ OR exp comparative study/ OR cohort analysis OR follow-up studies/ OR intermethod comparison/ OR parallel design/ OR control group/ OR prospective study/ OR retrospective study/ OR case control study/ OR major clinical study/ OR evaluation studies/ OR follow-up studies/ OR random$.hw. OR random$.ti. OR placebo$.mp. OR ((singl$ OR doubl$ OR tripl$ OR trebl$) and (dummy OR blind OR sham)).mp. OR latin square.mp. OR ISRCTN$.mp. OR ACTRN$.mp. OR (NCT$ not NCT).mp.)
13	Limit to guidelines	11 AND (st.fs. OR guideline.pt. OR consensus.pt. OR practice parameter OR position statement OR position paper OR policy statement OR standard$.ti. OR guideline$.ti. OR white paper OR clinical pathway OR practice guidelines/ OR exp practice guideline/ OR consensus development/)
14	Limit to systematic reviews	11 AND (systematic review/ OR meta-analysis/ OR meta-analysis/ OR pooled OR meta-analysis.pt. OR "systematic review" OR search$.ab.)
15	Combine sets	12 OR 13 OR 14
16	Limit by publication date	Limit 15 to yr="2002-Current"
17	Eliminate overlap	Remove duplicates from 16

Table A-10. Search Strategy for Referral Key Question 16 (imaging findings)

Set #	Concept	Search Statement
1	Osteoarthritis of specific joints	osteoarthritis, knee/ OR osteoarthritis, hip/ OR hip osteoarthritis/ OR knee osteoarthritis/
2	Osteoarthritis	osteoarthritis/ OR (arthrit$ OR osteoarthrit$ OR degenerative joint).ti.
3	Knee	exp knee/ OR exp knee joint/ OR exp knee injuries/ OR exp knee injury/ OR (knee OR knees OR menisc$ OR patellofemor$ OR patell$ OR iliotibial OR ACL OR anterior cruciate ligament).ti.
4	Hip	exp hip/ OR exp hip joint/ OR exp hip injuries/ OR exp hip fractures/ OR exp hip injury/ OR (hip OR hips).ti.
5	Combine sets	2 AND (3 OR 4)
6		1 OR 5
7	Diagnostic imaging Controlled vocabulary	exp *diagnostic imaging equipment/ OR exp *"imaging and display"/ OR exp *radiodiagnosis/ OR exp *echography/ OR exp *diagnostic imaging/ OR *tomography scanners, x-ray computed/
8	Diagnostic imaging Keywords	(absorptiometry OR arthrography OR computed tomography OR CT OR DEXA OR dGEMRIC OR diffusion tensor OR image$ OR imaging OR magnetic resonance OR MR OR MRI OR neuroimaging OR NMR OR PET OR phonoarthrography OR positron emission tomography OR radiodiagnos$ OR radiograph$ OR scan OR scans OR scanning OR scintigraph$ OR sonograph$ OR SPECT OR spectroscopy OR Tc-99m OR technetium OR tomosynthesis OR ultrasonography OR ultrasound$ OR x-ray$ OR xray$).ti.
9	Combine sets	6 AND (7 OR 8)
10	Arthroplasty	exp arthroplasty/ OR (arthroplast$ OR hemiarthroplast$ OR replace OR replacement$ OR resurfacing OR surgery OR surgical).ti.

Set #	Concept	Search Statement
11	Combine sets	9 AND 10
12	Referral Controlled terms	decision making/ OR decision trees/ OR exp disability/ OR disability evaluation/ OR exp disease severity/ OR patient care planning/ OR patient referral OR patient selection/ OR "referral and consultation"/ OR risk assessment/ OR risk factor/ OR risk factors/ OR severity of illness index/
13	Referral Keywords	(consultation$ OR consult OR contraindicat$ OR criteria OR decision OR decide$ OR indication$ OR (patient ADJ2 characteristic$) OR (patient ADJ2 selection) OR predict$ OR "red flag" OR referral OR refer OR risk$ OR serious OR specialist OR surgeon OR urgent OR warning).ti.
14	Outcomes Controlled vocabulary	adverse effects.fs. OR comorbidity/ OR complication.fs. OR convalescence/ OR morbidity/ OR mortality/ OR mortality.fs. OR outcome assessment/ OR "outcome assessment (health care)"/ OR exp postoperative complication/ OR exp postoperative complications/ OR prognosis/ OR quality of life/ OR recovery of function/ OR reoperation/ OR survival rate/ OR treatment outcome/
15	Outcomes Keywords	(appropriate$ OR comorbid$ OR complication$ OR morbidity OR mortality OR outcome$ OR prognos$ OR survival$ OR "quality of life" OR QOL).ti.
16	Combine sets	11 AND (12 OR 13) AND (14 OR 15)
17	Exclude unwanted publications	16 NOT (book/ OR edited book/ OR case report/ OR case reports/ OR comment/ OR conference abstract/ OR conference paper/ OR conference review/ OR editorial/ OR letter/ OR news/ OR note/ OR proceeding/ OR (book OR edited book OR case report OR case reports OR comment OR conference OR editorial OR letter OR news OR note OR proceeding).pt.)
18	Keep case series	16 AND (case series OR case control)
19	Combine	17 OR 18
20	Limit to humans	limit 19 to humans
21	Limit to english language	limit 20 to english language
22	Limit by publication date	limit 21 to yr="2002 -Current"
23	Eliminate overlap	Remove duplicates from 22
24	Retain relevant records	from 23 keep 1-4, 7-9, 14, 16, 21, 27
25	Examine combination of sets without limiting to those with outcomes	11 AND (12 OR 13 OR selection.ti.)
26	Exclude previously identified results	25 NOT 16
27	Exclude unwanted publications	26 NOT (book/ OR edited book/ OR case report/ OR case reports/ OR comment/ OR conference abstract/ OR conference paper/ OR conference review/ OR editorial/ OR letter/ OR news/ OR note/ OR proceeding/ OR (book OR edited book OR case report OR case reports OR comment OR conference OR editorial OR letter OR news OR note OR proceeding).pt.)
28	Keep case series	26 AND (case series OR case control).mp.
29	Combine	limit 27 to humans
30	Limit to humans	limit 29 to english language
31	Limit to english language	limit 30 to yr="2002 –Current"

Set #	Concept	Search Statement
32	Limit by publication date	remove duplicates from 31
33	Retain relevant records	from 32 keep 7-8, 10, 12-14, 16, 18-24, 27
34	Combine sets	24 OR 33
35	Eliminate overlap	remove duplicates from 34

Table A-11. Search Strategy for Referral Key Questions 17 and 18 (patient signs/symptoms and patient-centered risk factors)

Set #	Concept	Search Statement
1	Knee or Hip osteoarthritis	osteoarthritis, knee/ OR osteoarthritis, hip/ OR hip osteoarthritis/ OR knee osteoarthritis/
2	Osteoarthritis keywords	osteoarthritis/ OR arthrit$.ti. OR osteoarthrit$.ti. OR degenerative joint.ti.
3	Knee joint	exp knee/ OR exp knee joint/ OR exp knee injuries/ OR exp knee injury/ OR knee.ti. OR knees.ti. OR menisc$.ti. OR patellofemor$.ti. OR patell$.ti. OR iliotibial.ti. OR ACL.ti. OR anterior cruciate ligament.ti.
4	Hip	exp hip/ OR exp hip joint/ OR exp hip injuries/ OR exp hip fractures/ OR exp hip injury/ OR hip.ti. OR hips.ti.
5	Combine population sets (osteoarthritis)	1 OR (2 AND (3 OR 4))
6	Arthroplasty	exp arthroplasty/ OR arthroplast$.ti. OR replace.ti. OR replacement$.ti. OR surgery.ti. OR surgical.ti. OR resurfac$.ti.
7	Referral – controlled terms	"referral and consultation"/ OR decision making/ OR patient selection/ OR "severity of illness index"/ OR risk factors/ OR disability evaluation/ OR risk assessment/ OR decision trees/ OR patient referral/ OR patient care planning/ OR risk factor/ OR exp disability/ OR exp disease severity/
8	Referral - keywords	(referral OR refer OR criteria OR indication$ OR contraindicat$ OR predict$ OR risk$ OR consultation$ OR consult OR decision OR decide$ OR (patient adj2 selection) OR (patient adj2 characteristic$) OR warning OR "red flag" OR urgent OR serious OR surgeon OR specialist).ti.
9	Outcomes - controlled terms	prognosis/ OR treatment outcome/ OR exp postoperative complications/ OR survival rate/ OR outcome assessment/ OR "Outcome Assessment (Health Care)"/ OR exp "quality of life"/ OR mortality.fs. OR reoperation/ OR adverse effects.fs. OR recovery of function/ OR comorbidity/ OR exp postoperative complication/ OR mortality/ OR morbidity/ OR complication.fs. OR convalescence/
10	Outcomes - keywords	(appropriate$ OR prognos$ OR outcome$ OR morbidity OR mortality OR comorbid$ OR complication$ OR survival* OR "quality of life" OR QOL).ti.
11	Combine sets - Referral	7 OR 8
12	Combine sets- Outcomes	9 OR 10
13	Combine sets key questions 17 and 18	5 AND 6 AND 11 AND 12
14	Limit to english language	limit 13 to english language
15	Limit to Human studies	limit 14 to humans

Set #	Concept	Search Statement
16	Exclude unwanted publication types	15 NOT (book/ OR edited book/ OR case report/ OR case reports/ OR comment/ OR conference abstract/ OR conference paper/ OR conference review/ OR editorial/ OR letter/ OR news/ OR note/ OR proceeding/ OR book OR edited book OR case report OR case reports OR comment OR conference OR editorial OR letter OR news OR note OR proceeding.pt. OR conference abstract.pt.)
17	Include case series	15 AND (case series OR case control)
18	Combine sets	16 OR 17
19	Limit by publication date	Limit 18 to yr="2002-Current"
20	Eliminate overlap	Remove duplicates from 20

Table A-12. Search Strategy for Referral Key Question 19 (trial of injection therapy)

Set #	Concept	Search Statement
1	Osteoarthritis of specific joints	osteoarthritis, knee/ OR osteoarthritis, hip/ OR hip osteoarthritis/ OR knee osteoarthritis/
2	Osteoarthritis	osteoarthritis/ OR (arthrit$ OR osteoarthrit$ OR degenerative joint).ti.
3	Knee	exp knee/ OR exp knee joint/ OR exp knee injuries/ OR exp knee injury/ OR (knee OR knees OR menisc$ OR patellofemor$ OR patell$ OR iliotibial OR ACL OR anterior cruciate ligament).ti.
4	Hip	exp hip/ OR exp hip joint/ OR exp hip injuries/ OR exp hip fractures/ OR exp hip injury/ OR (hip OR hips).ti.
5	Combine sets	2 AND (3 OR 4)
6		1 OR 5
7	Hyaluronates Controlled terms for therapy	hyaluronic acid/ AND (ad OR dt OR tu).fs.
8	Hyaluronates	viscosupplementation/ OR hyaluronic acid/ OR adant OR amvisc OR arthrease OR arthrum h OR artz OR biolon OR biohy OR durolane OR etamucine OR euflexxa OR fermathron OR "gel-one" OR healon OR hyalgan OR hyaluronan OR hyaluronate$ OR hyaluronic OR hyaluronidate OR "hylan gf-20" OR hyruan OR hyvisc OR luronit OR nuflexxa OR orthovisc OR ostenil OR replasyn OR SLM-10 OR supartz OR suplasyn OR synject OR synvisc OR viscosupplement$ OR vitrax
9	Corticosteroids	exp adrenal cortex hormones/ OR exp corticosteroid/ OR "adrenal cortex hormones" OR betamethasone OR corticoid$ OR corticosteroid$ OR cortisone$ OR dexamethasone OR glucocorticoid$ OR hydrocortisone OR hydroxycorticosteroid$ OR methylprednisolone OR prednisolone OR prednisone OR steroid$
10	Administration by injections	Injection/ OR injections/ OR exp injections, intra-articular/ OR intraarticular drug administration/ OR viscosupplementation/ OR (inject$ OR intraarticular OR intra-articular OR (intra ADJ articular) OR "IACI" OR viscosupplement$).mp.
11	Combine sets	7 OR ((8 OR 9) AND 10)
12	Combine sets	6 AND 11
13	Arthroplasty	exp arthroplasty/ OR (arthroplast$ OR hemiarthroplast$ OR replace OR replacement$ OR resurfacing OR surgery OR surgical).ti,ab.
14	Effect / Influence / Relationship	Treatment failure/ OR alternative$ OR avoid$ OR cancel$ OR delay$ OR eligib$ OR repeated cycles OR repeated doses OR (repeat$ ADJ treatment$) OR postpone$ OR second course
15	Combine sets	12 AND 13 AND 14

Set #	Concept	Search Statement
16	Exclude unwanted publications	15 NOT (book/ OR edited book/ OR case report/ OR case reports/ OR comment/ OR conference abstract/ OR conference paper/ OR conference review/ OR editorial/ OR letter/ OR news/ OR note/ OR proceeding/ OR (book OR edited book OR case report OR case reports OR comment OR conference OR editorial OR letter OR news OR note OR proceeding).pt.)
17	Keep case series	15 AND (case series OR case control)
18	Combine	16 OR 17
19	Limit to humans	limit 18 to humans
20	Limit to english language	limit 19 to english language
21	Limit by publication date	limit 20 to yr="2002 -Current"
22	Eliminate overlap	Remove duplicates from 21

Search Results

Extensive literature searches identified 6,872 citations potentially addressing the key questions of interest to this evidence review. Of those, 5,315 were excluded upon title review for clearly not meeting inclusion criteria (e.g., not pertinent to the topic, published prior to 2002). Overall, 1,557 abstracts were reviewed with 735 of those being excluded for the following reasons: not a systematic review or clinical study, clearly did not address a Key Question of interest to this review, clearly did not report outcomes of interest to this review, or published prior to 2002 for clinical studies or 2008 for systematic reviews. A total of 822 full-length articles were reviewed. Of those, 459 were excluded at a first pass review for not addressing a key question (mainly because the study did not address a comparison of interest), not reporting on outcomes of interest to the review, not being a full-length systematic review or clinical study, not including the required number of patients, or being a duplicate. A total of 363 full-length articles were thought to address one or more key questions and were further reviewed. Of these, 208 were ultimately excluded. Reasons for their exclusion are presented in Figure A-1 below.

Overall, 155 studies addressed one or more of the Key Questions and were considered as evidence in this review. Table A-13 indicates the number of studies that addressed each of the questions.

Figure A-1. PRISMA Diagram of Literature Search Results

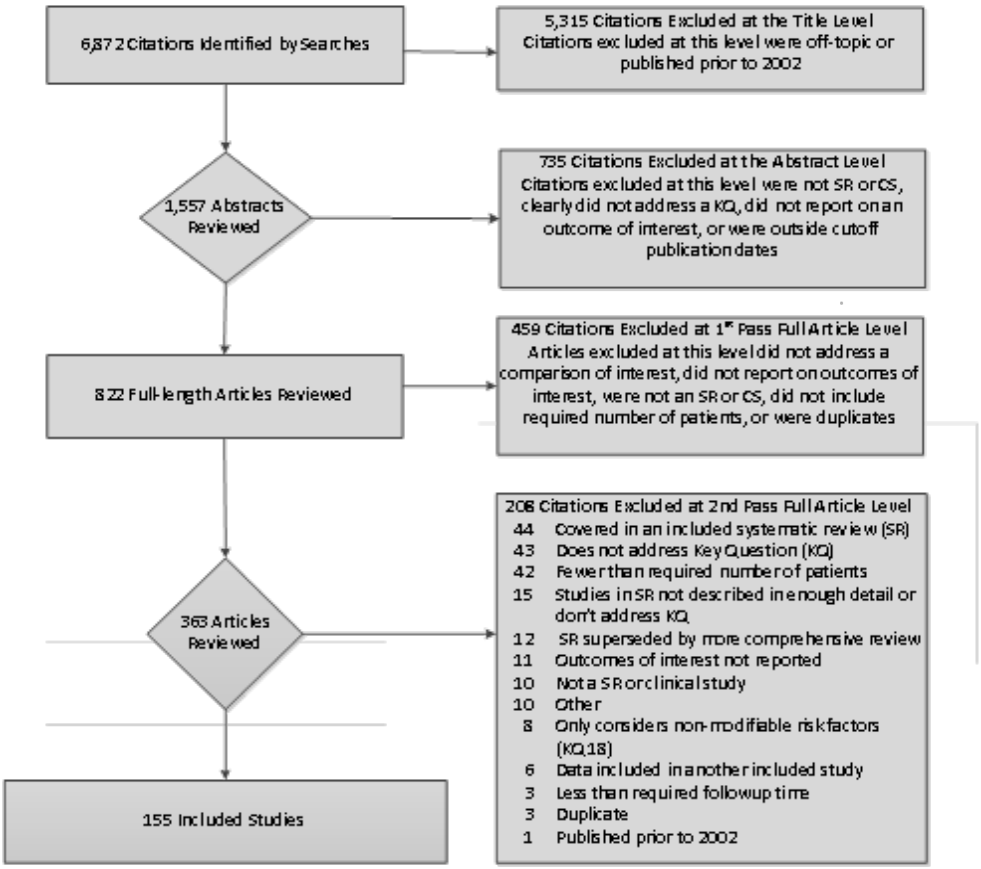


Table A-13. Evidence Base for Key Questions

Key Question	# of Studies
Diagnostic Questions:	
1. In adults with clinical symptoms and signs consistent with OA of the hips or knees, which imaging strategies, including plain radiograph, MRI, and CT contribute to improved clinical outcomes?	3
2. In adults with clinical symptoms and signs consistent with OA of the hips or knees, do laboratory tests contribute to improved clinical outcomes?	Searches did not identify any studies that met inclusion criteria
3. In adults with clinical symptoms and signs consistent with OA of the knees, does synovial fluid analysis contribute to improved clinical outcomes?	Searches did not identify any studies that met inclusion criteria
Intervention Questions:	
4. In adults with OA of the hips or knees, what is the comparative effectiveness of acetaminophen to placebo with respect to pain, improved function, and harms?	4
5. In adults with OA of the hips or knees, what is the comparative effectiveness of intra-articular corticosteroids to intra-articular hyaluronates with respect to pain, improved function, and harms?	7
6. In adults with OA of the hips or knees, what is the comparative effectiveness of intra-articular hyaluronates to sham injections with respect to pain, improved function, and harms?	6
7. In adults with OA of the hips or knees, what is the comparative effectiveness of joint injections to oral NSAIDs (selective or non-selective) with respect to pain, improved function, and harms?	Searches did not identify any studies that met inclusion criteria
8. In adults with OA of the hips or knees, what is the comparative effectiveness of topical NSAIDs to oral NSAIDs (selective or non-selective) with respect to pain, improved function, and harms?	5
9. In adults with OA of the hips or knees, what is the comparative effectiveness of traditional land-based strengthening exercises to aquatic therapy with respect to pain, improved function, and harms?	6
10. In adults with OA of the hips or knees, what is the comparative effectiveness of traditional land-based strengthening exercises to manual physical therapy with respect to pain, improved function, and harms?	3
11. In adults with OA of the hips or knees, what is the comparative effectiveness of aquatic therapy to manual therapy with respect to pain, improved function, and harms?	Searches did not identify any studies that met inclusion criteria
12. What is the comparative effectiveness of walking aids or devices (e.g., cane ambulation to OA unloader braces for the knees) used to treat OA of the hips or knees with respect to pain, improved function, and harms?	4
13. In adults with OA of the hips or knees, what is the comparative effectiveness of chiropractic care to usual therapy with respect to pain, improved function, and harms?	1
14. In adults with OA of the hips or knees, what is the comparative effectiveness of acupuncture to usual therapy with respect to pain, improved function, and harms?	5
15. In adults with OA of the hips or knees, what is the comparative effectiveness of nutritional supplements (e.g., glucosamine) to usual therapy with respect to pain, improved function, and harms?	37
Referral Questions:	
16. In patients with clinical symptoms and signs consistent with OA, what imaging findings indicate that referral for total/partial joint replacement surgery is the best option for achieving optimal clinical outcomes?	7
17. For adults with OA of the hips or knees, what patient symptoms or signs (e.g., level of pain and/or disability) indicate that referral for total/partial joint replacement surgery is the best option for achieving optimal clinical outcomes?	13
18. In adults with OA of the hips or knees, what patient-centered risk factors would preclude referral for surgery?	50
19. For adults with OA of the hips or knees, should a trial of injection therapy (corticosteroids or viscosupplementation) be attempted before referral for total/partial joint replacement surgery?	5

Assessing the Quality of the Evidence

The strength of the evidence supporting findings for the outcomes of interest under each key question was assessed using the categories listed in Table A-14. We considered the evidence for each outcome according to four core domains, as follows: study quality (internal validity), consistency, directness, and precision. Our methods for judging the quality of individual studies are described above. Consistency is the similarity in effect sizes or direction of an effect of different studies in an evidence base. An inconsistent evidence base is one in which the studies report conflicting results. Consistency cannot be assessed when a body of evidence has only a single study (consistency is unknown). Directness refers to whether there is a direct link between the intervention and the ultimate health outcome. An ultimate health outcome (e.g., improved pain) is typically more clinically meaningful than an indirect outcome, and a direct link between outcome and intervention is strongest in head-to-head comparisons. Precision is a measure of the degree of certainty around a single outcome's effect size. In this report, we define a "precise" result as one in which the data were informative (e.g., the confidence interval [CI] around the effect size clearly indicated there was a difference between groups) and an "imprecise" result as one in which the data were not informative (e.g., the CI was sufficiently wide that an estimate is consistent with either benefit or no benefit in comparison to another intervention).

Table A-14. Assessment of Evidence Base

Evidence Category	Definition	Example of Assessment of Evidence
Study Quality (Internal Validity or Risk of Bias)	Study Quality takes into account the overall risk of bias rating of all the studies included in the evidence base.	Example: The overall risk of bias was fair. A couple of studies were rated as poor because they did not blind the patients or outcome assessors and did not report the method used to randomize patients.
Consistency of Results	Consistency of Results considers if the studies demonstrated similar positive or negative results (an inconsistent rating would indicate that the findings across studies were mixed).	Example: The majority of studies (20 out of 25) indicated a statistically positive effect of acetaminophen over placebo in reducing pain and improving function. In five studies, the results were not significant.
Directness of Evidence	Directness of Evidence considers the link between the interventions and patient outcomes (head-to-head comparisons provide the most direct evidence).	Example: The evidence linking the effects of acetaminophen to patient outcomes of pain and function was direct as it came primarily from head-to-head comparisons of acetaminophen to placebo.
Precision of Results	Precision estimates the degree of certainty around an outcome's effect size.	Example: The 95% confidence interval around the between-group difference in pain scores was wide enough to allow the possibility that the treatments were equivalent, treatment A is more effective than treatment B, or treatment B is more effective than treatment A.

Final Evidence Report

The evidence review team at ECRI Institute synthesized the results of the systematic review and provided a detailed analysis of relevant information for each key question. Some of the key elements discussed in the report include the quality of the evidence base and the magnitude of effect of specific interventions. Furthermore, the synthesis report contained critical information on potential limitations of certain studies, allowing for a better understanding of the certainty of the evidence. The review team produced a comprehensive evidence review report and distributed it to the Champions and Work Group members approximately two weeks prior to the face-to-face meeting.

Face-to-Face Meeting

In consultation with the Contracting Officer Representative, the Champions, and the Work Group, the Lewin Team convened a three and a half day face-to-face meeting of the CPG Champions and Work Group members in May 2013. These experts were gathered in order to review the evidence, develop recommendations, and grade the recommendations in accordance with the U.S. Preventive Services Task Force (USPSTF) methods for assessing and grading the evidence.

Developing Recommendations

During the face-to-face meeting, and under the direction of the Champions, the Work Group members were charged with interpreting the results of the evidence review, and asked to review initial recommendations and/or develop new recommendations. In order to accomplish this task, the experts were divided into four smaller subgroups, each of which was led by a Champion. In addition, Work Group members were responsible for assessing the overall strength of evidence for each recommendation, by determining the magnitude and certainty of net benefit.

Grading Recommendations

The graded recommendations are based on two main dimensions: 1) **net benefit of** an intervention and 2) **certainty** of evidence associated with that net benefit.

Net benefit (or impact) refers to the benefit minus the harm of an intervention. As shown in Table A-15, the four categories of net benefit are: Substantial, Moderate, Small, and Zero/Negative. For example, a Substantial benefit could result from high benefit and minimal harm. These categories only reflect the order of magnitude of net benefit, they do *not* reflect *how certain* we are of that magnitude of net benefit.

Table A-15. USPSTF Recommendations – Net Benefit [5,150]

Substantial	More than a small relative impact on a frequent condition with a substantial burden of suffering; or A large impact on an infrequent condition with a significant impact on the individual patient level.
Moderate	A small relative impact on a frequent condition with a substantial burden of suffering; or A moderate impact on an infrequent condition with a significant impact on the individual patient level.
Small	A negligible relative impact on a frequent condition with a substantial burden of suffering; or A small impact on an infrequent condition with a significant impact on the individual patient level.
Zero or Negative	Negative impact on patients; or No relative impact on either a frequent condition with a substantial burden of suffering, or an infrequent condition with a significant impact on the individual patient level.

Certainty refers to the level of certainty that is associated with a net benefit. The level of certainty is greater with stronger evidence (i.e., from a greater number of well-designed and well-conducted studies). As shown in Table A-16, the three levels of certainty are High, Medium, and Low. Higher

certainty suggests that the observed net benefit (regardless of its magnitude as described in Fig. 2) is correct. For any given magnitude of net benefit (whether it is Substantial or Zero), the certainty can range from High to Low.

When considering what grade should accompany a recommendation, it may help to consider these two dimensions separately before arriving at a grade. That is, based on the health outcomes in the available evidence, "How big is the net benefit here?" Then, based on the strength of that available evidence, "How certain are we that this net benefit (no matter its size) is real?"

Table A-16. USPSTF Recommendations – Certainty [5]

Level of Certainty*	Description
High	The available evidence usually includes consistent results from well-designed, well-conducted studies in representative primary care populations. These studies assess the effects of the preventive service on health outcomes. This conclusion is therefore unlikely to be strongly affected by the results of future studies.
Moderate	The available evidence is sufficient to determine the effects of the preventive service on health outcomes, but confidence in the estimate is constrained by such factors as: The number, size, or quality of individual studies. • Inconsistency of findings across individual studies. • Limited generalizability of findings to routine primary care practice. • Lack of coherence in the chain of evidence. As more information becomes available, the magnitude or direction of the observed effect could change, and this change may be large enough to alter the conclusion.
Low	The available evidence is insufficient to assess effects on health outcomes. Evidence is insufficient because of: • The limited number or size of studies. • Important flaws in study design or methods. • Inconsistency of findings across individual studies. • Gaps in the chain of evidence. • Findings not generalizable to routine primary care practice. • Lack of information on important health outcomes. More information may allow estimation of effects on health outcomes.

*The USPSTF defines certainty as "likelihood that the USPSTF assessment of the net benefit of a preventive service is correct." The net benefit is defined as benefit minus harm of the preventive service as implemented in a general, primary care population. The USPSTF assigns a certainty level based on the nature of the overall evidence available to assess the net benefit of a preventive service.

The **grade of recommendation** is based on a framework that combines the two dimensions, as shown in Table A-17. As described above, the grade depends on both net benefit and certainty. For example, in the USPSTF grading scheme, a grade of A is assigned to a recommendation that is based on a High certainty of a Substantial net benefit. Three combinations of certainty and net benefit can yield a grade of B. Note that, in the USPSTF framework, any recommendation associated with Low certainty of net benefit results in a recommendation of I, regardless of the magnitude of net benefit.

Given: 1) the level of certainty that a net benefit exists and 2) the magnitude of that net benefit, what grade of recommendation do we assign?

Table A-17. USPSTF Recommendations – Grade [5]

Certainty of Net Benefit	Magnitude of Net Benefit			
	Substantial	**Moderate**	**Small**	**Zero/Negative**
High	A	B	C	D
Moderate	B	B	C	D
Low	Insufficient			

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.

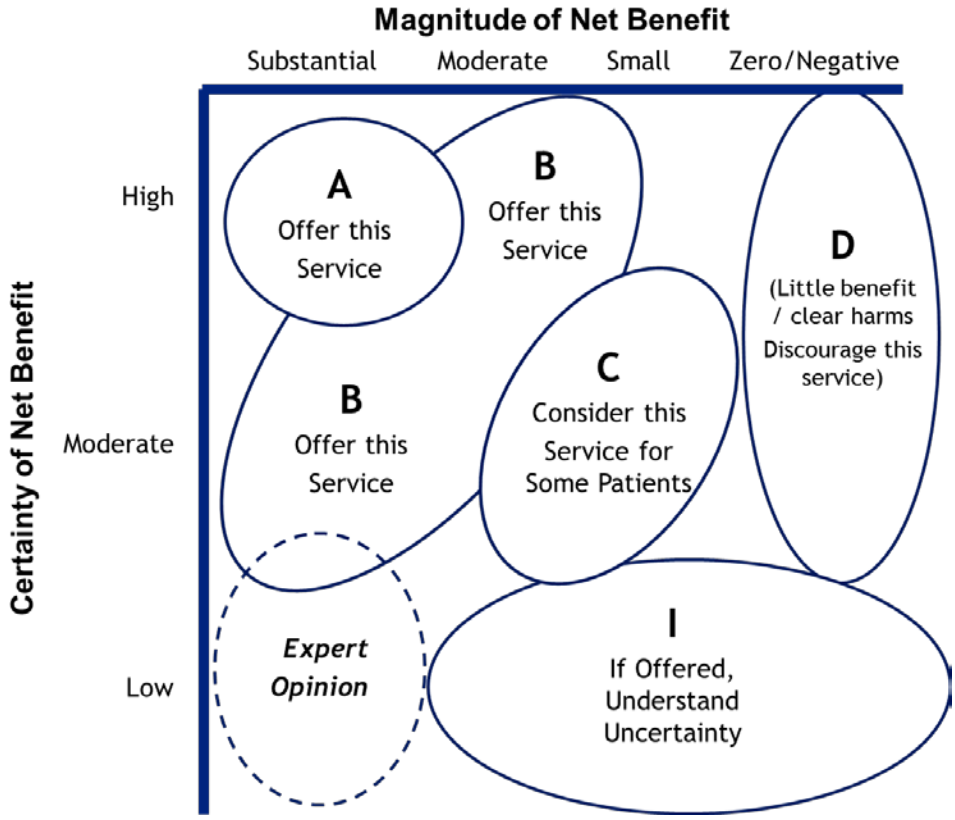
Grade C indicates that the certainty of the evidence is either high or moderate and that the magnitude of net benefits is small.

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).

Figure A-2 is a framework that incorporates Expert Opinion. The dimensions of Net Benefit of an intervention and Certainty of evidence still correspond to the USPSTF framework, and grades of recommendation (A, B, C, D, I) are the same, except for the use of E in place of I in one sector of the framework. We made slight modifications in this framework to make the cross-walk from USPSTF more clear and better reflect the sense of our work group discussions.

Figure A-2. Framework with Expert Opinion



Final Evidence-Based Clinical Practice Guideline for the Management of OA

Following the face-to-face meeting in May, the OA CPG Champions and Work Group developed several drafts of the Guideline, submitting the final document to the VA/DoD Evidence-Based Practice Working Group in August 2014.

Appendix B: Evidence Table

No.	Recommendation	Sources of Evidence	Certainty of Net Benefit	Magnitude of Net Benefit	Strength of Recommendation
Diagnosis and Evaluation					
1	Clinicians should conduct a history and physical examination for all patients, with an emphasis on the musculoskeletal examination.	[7] [27]	Low	Moderate	EO
2	Clinicians may use plain radiography to confirm the clinical diagnosis of hip and knee osteoarthritis.	[26]	Moderate	Small	C
3	Clinicians should not use magnetic resonance imaging (MRI) as an evaluative tool to diagnose, confirm, or manage the treatment of osteoarthritis.	[28] [143] [144]	Low	Zero	D
4	Clinicians should avoid routine use of laboratory examinations or synovial fluid analysis to diagnose osteoarthritis of the hip and/or knee.	[25]	Low	Substantial	EO
Core Non-Surgical Treatment Principles					
5	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.	Expert consensus	Low	Moderate	EO
6	For patients with osteoarthritis of the hip and/or knee, clinicians should attempt the core non-surgical therapies prior to referral to surgery.	[154]	Moderate	Small	C
7	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.	[31] [32] [33] [39] [37] [38] [40] [41] [42]	Moderate	Moderate	B
8	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.	[35] [36]	Moderate	Moderate	C
9	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.	Expert consensus	Low	Substantial	EO
Physical Therapy Approaches					
10	For patients with osteoarthritis of the knee, the addition of manual physical therapy	[31]	Moderate	Moderate	B

No.	Recommendation	Sources of Evidence	Certainty of Net Benefit	Magnitude of Net Benefit	Strength of Recommendation
	as an adjunct to traditional physical therapy and supervised exercise can improve pain, function, and walking distance.				
11	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.	[32] [33]	Moderate	Moderate	B
12	For adults with osteoarthritis of the knee who do not tolerate land-based therapeutic exercise, clinicians should consider adjunctive aquatic physical therapy.	[39] [37] [38] [40] [41] [42]	Moderate	Small	C
13	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.	Expert Opinion	Low	Substantial	EO
Pharmacologic Therapies					
14	In patients with no contraindications to pharmacologic therapy, clinicians should consider acetaminophen or oral non-steroidal anti-inflammatory drugs (NSAIDs) as first line treatment.	[64] [67] [69] [68] [70] [71] [72] [74]	Moderate	Moderate	B
15	Clinicians should ensure that patients receive no more than four grams of acetaminophen daily from all sources of prescribed and non-prescribed medications.	[65] [66]	High	Substantial	A
16	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.	[84] [85] [86]	High	Substantial	A
17	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.	[87] [88] [83] [95] [96]	Moderate	Substantial	B
18	In patients with mild to moderate pain associated with osteoarthritis of the knee, topical capsaicin can be considered as first line or adjunctive therapy.	[105] [102]	Moderate	Small	C

No.	Recommendation	Sources of Evidence	Certainty of Net Benefit	Magnitude of Net Benefit	Strength of Recommendation
		[103] [104]			
19	There is insufficient evidence to recommend for or against the use of topical capsaicin for the hip as first line or adjunctive therapy.	[104]	Low	Small	I
20	For patients with persistent moderate or moderately severe osteoarthritis pain, clinicians may offer duloxetine or tramadol as an alternative or adjunct to oral NSAIDs.	[133] [107] [108] [136] [155] [156] [157] [158] [159] [160] [161] [162] [163] [164] [165] [166] [167] [168] [169] [170] [171] [172]	High	Moderate	B
21	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.	[173] [174] [175] [166] [111] [176]	Moderate	Small	C
22	For patients with symptomatic osteoarthritis of the knee, clinicians may consider consider intra-articular corticosteroid injection.	[177] [178] [119-121]	Moderate	Small	C

No.	Recommendation	Sources of Evidence	Certainty of Net Benefit	Magnitude of Net Benefit	Strength of Recommendation
23	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.	[179,180] [181] [182]	Moderate	None	I
24	For patients with moderate to severe osteoarthritis of the hip, clinicians may consider imaging/ultrasound directed corticosteroid injection to reduce pain.	[117]	Low	Moderate	C
25	Intra-articular injection of hyaluronate/hylan is not recommended for patients with osteoarthritis of the hip.	Expert consensus	Low	Substantial	EO
Complementary and Alternative Therapies					
26	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.	[183] [184] [185] [186] [187]	Low	Small	I
27	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.	[126] [127] [133] [128] [129] [130] [131] [132]	Moderate	None	D
28	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 chiropractice therapy for relief of pain and improved function.	[134] [135] [136] [138] [137]	Low	Small	I
Referrals for Surgical Consultation					
29	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.	[142] [140] [188]	Moderate	Moderate	B

No.	Recommendation	Sources of Evidence	Certainty of Net Benefit	Magnitude of Net Benefit	Strength of Recommendation
30	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.	[189] [190] [142] [191] [192]	Moderate	Moderate	B
31	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.	Expert Consensus	Low	Substantial	EO

Appendix C: Patient History and Physical Examination

Knee History

Patients with knee OA may present with either localized or diffuse knee pain that is activity related. Occasionally, patients with hip OA present with knee pain. It is imperative to examine both the hip and knee in patients with either knee or hip pain. A patient with an abnormal hip examination may result in early detection of hip OA.

Patients with knee osteoarthritis may have a prior history of knee injury or surgery. Prior anterior cruciate ligament (ACL) injury and/or reconstruction as well as prior meniscectomy or patellar dislocation should increase suspicion of early knee OA.

Knee Physical Examination

Gait and Alignment: The most common pattern for knee OA is primarily medial compartment degeneration with progressive development of genu varum (bow legged). Less commonly patients may display genu valgum (knock knee) or primary lateral compartment degeneration. Patients with some form of mechanical malalignment are at higher risk to develop osteoarthritis. It is important for the health care provider to record overall knee alignment as well as gait patterns. Patients with knee OA may ambulate with an antalgic gait favoring the involved knee or walk with a stiff and semi-flexed involved knee.

Knee Effusion and Range of Motion: Patients with OA occasionally may have an effusion that can be detected on physical examination. Furthermore, stiffness and limitations in range of motion are often found in OA, especially, lack of terminal extension or flexion contracture.

Joint Line Tenderness and Crepitus: Although non-specific, patients with symptomatic osteoarthritis may have localized or more diffuse knee tenderness. Crepitus, especially involving the patellofemoral joint can be appreciated during passive knee range of motion testing.

Hip History

The pain related to the hip osteoarthritis occurs in different locations including the groin, thigh, buttocks, or knee. Although the classic complaint of patients with hip OA is groin pain, the patients will often 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.” The pain experienced by the patient can be stabbing, sharp, or dull. Similarly to osteoarthritis of the knee, the hip becomes increasingly stiff as the disease progresses. Ultimately the patient will experience a sense of grinding in the joint and can lose range of motion. At this point walking and performing routine activities of daily living can become difficult.

Hip Physical Examination

Gait and stance: Patients with a painful hip will often stand with a slightly flexed hip and knee to relax the hip joint capsule. Furthermore, while seated, they may feel more comfortable shifting their weight to the contralateral hemi pelvis and slouching to avoid excessive flexion or internal rotation of the involved hip.

When ambulating, they may walk with an abductor lurch while standing on the involved hip. During the stance phase the patient will shift their center of mass over the involved hip. This serves to relax the hip abductors (gluteus medius and gluteus minimus) thereby decreasing the joint reactive forces about the hip.

Range of Motion: Hip OA often results in loss of motion as well as pain at the extremes of motion. Flexion is best measured with the patient supine and the contralateral hip in full extension to stabilize the pelvis. Likewise, in order to assess for a flexion contracture (lack of full extension) the contralateral hip should be maximally flexed to see if the involved hip can extend to touch the exam table. Internal and external rotation can be easily measured with the hip and knee flexed to 90 degrees. Loss of internal rotation is frequently seen in hip osteoarthritis.

Special Tests: A passive straight leg raise can help to differentiate nerve root tension signs from true intra-capsular hip pathology. The Patrick or Faber test (flexion, abduction, external rotation) stresses the femeroacetabular as well as the sacroiliac joint. The passive log roll is the most specific test for hip pathology as only the femoral head is moving in relation to the acetabulum; however, it is not very sensitive. More sensitive special tests include the anterior "impingement test" where the hip is brought into maximal flexion, adduction and internal rotation. Additionally, a resisted straight leg raise or Stinchfield reproducing groin pain is sensitive at identifying intra-articular pathology. This maneuver works by generating more force than walking across the hip joint.

Appendix D: Pharmacologic Therapies

Tramadol

The adverse event profile of tramadol is the main reason for recommending that tramadol be considered after trials of non-opioids and before advancing to trials of more potent opioids. Although classified as an opioid, tramadol is considered safer than other opioids because it is associated with lower risks of respiratory depression and constipation, and is not a controlled substance. Tramadol abuse and addiction are less problematic than with conventional opioids. [193-198] Some patients may develop physical dependence with regular use and experience withdrawal symptoms typical of opioid withdrawal if tramadol therapy is stopped too quickly. Atypical withdrawal symptoms that may be related to the SNRI effects (e.g., hallucinations, paranoia, extreme anxiety, panic attacks, confusion and unusual sensory experiences such as numbness and tingling in the extremities) may also occur. [199,200] If tramadol is discontinued, the dose should be slowly tapered off to avoid withdrawal symptoms.

The main safety concern with tramadol is development of seizures. Tramadol should be avoided or used with caution in patients with a history or risk of seizures or those who are taking drugs that reduce the seizure threshold, such as antidepressants, anorectics, SSRIs, SNRIs, tricyclic antidepressants, tricyclic compounds (such as cyclobenzaprine, promethazine), other opioids, monoamine oxidase inhibitors (MAOIs), and neuroleptics.

Careful attention should be given to recommended dosage adjustments and maximal dosage limits in at-risk populations (e.g., the elderly and patients with renal or hepatic impairment). This is of particular

importance in the typical elderly patient population with OA. Maximal recommended doses are 400 mg per day for the IR formulation and 300 mg per day for the ER formulation in patients with normal renal function. The dosage of tramadol should be reduced in patients:

- With creatinine clearances of less than 30 ml/min (maximum 200 mg per day and extension of dosing intervals to 12 hours with the IR form of tramadol; avoid ER form);
- In the presence of cirrhosis (usual dose is 50 mg every 12 hours of the IR form; avoid the ER form in Child-Pugh class C / severe hepatic impairment); and
- older than 75 years (maximum 300 mg per day of tramadol IR).

The incidences of adverse events are dose-related. [201] Tolerability with tramadol IR can be improved by using a low initial dose and slowly titrating doses over a period of 10 to 16 days. Incremental titration of the ER form of tramadol is also suggested. More studies are needed to determine whether the ER formulation can be titrated up faster than the IR product while maintaining tolerability. [202] Although differences in adverse events have been observed between IR and ER formulations in one OA study, [201] overall the ER formulations of tramadol, dosed once daily or twice daily, are similar in efficacy and safety to the IR formulations. [203,204] The main advantage of the ER formulation seems to be the convenience of less frequent dosing for the patient.

Tramadol as an Alternative Monotherapy

There is fair quality, consistent evidence that tramadol, mainly as an extended release (ER) formulation, in treatment courses of up to three months long are effective in improving pain, physical function, and sleep in patients with OA of the knee or hip; however, the effects are small. [155-163] Results of a meta-analysis of 11 clinical trials published up to 2005 (N = 1939) showed that pain improved by 12 percent and physical function improved by 8.5 percent. The NNT was six relative to placebo for at least moderate improvement on patient global assessment. [155]

Although effect sizes for analgesia with tramadol ER have been small, patients have gained clinically meaningful improvements in physical function, [161] health status [161] and sleep disturbances. [162] One post hoc analysis of a 12-week clinical trial by the manufacturer showed that reductions in OA pain by only 15 percent to 29 percent (in contrast to cutoffs of 30 percent and 50 percent in mixed chronic pain conditions) were clinically meaningful. [161] Improvement in pain was not associated with improvement in OA related tiredness or fatigue. [161]

Higher doses improve the effect size slightly and doses of 300 mg per day or more of tramadol ER worsened the risk of adverse events and did not improve efficacy. [159,160] Whereas the recommended maximum dose of tramadol immediate-release (IR) is 400 mg per day, for ER formulations the maximum dose is 300 mg per day because the risk of seizures was shown to be increased at 400 mg per day. [164]

Tramadol was also poorly tolerated when the dose was not titrated up slowly. The NNT for treatment discontinuations due to adverse events in fixed-dose studies was eight, which is close to the NNT for benefit, suggesting a narrow benefit–risk margin without slow upward dosage titration. Studies using

slow dosage titration reduced the risk of treatment discontinuations due to adverse events, with an NNT of 33. [155]

Tramadol Compared with Alternative Therapies

The relative efficacy of tramadol is uncertain because of the limited number of active-control trials.

Tramadol versus Acetaminophen

Tramadol IR 150 mg per day was shown to be better than acetaminophen 1500 mg per day in a small (N = 20), seven-day randomized trial included in a meta-analysis. [155] The mean difference between treatments in pain reduction was 20 (95% CI 1.36–38.64) on a 0–100 mm visual analogue scale. [205]

Tramadol versus NSAIDs

In comparative clinical trials, tramadol was similar to NSAIDs in improving pain, physical function, and sleep. Relative to diclofenac IR, tramadol IR had a similar risk of treatment discontinuations due to adverse events, although was more likely to cause minor adverse events, with an NNT for minor adverse events of six versus diclofenac. [155] Using titrated doses, tramadol ER (200–400 mg once daily) was shown to be similar to diclofenac ER (75–100 mg once daily) in pain, physical function and sleep, as well as incidences of adverse events and treatment discontinuations due to adverse events; however, improvements in efficacy measures were small (16 percent or less) for both treatments. [165]

Tramadol versus Duloxetine

In a meta-analysis that included indirect comparisons of duloxetine (three trials; N = 383) and tramadol (five trials; N = 1507), the two agents were shown to be similar in improving normalized Western Ontario and McMaster Universities Osteoarthritis Index (WOMAC) total scores (reflecting pain, stiffness and function). [166] When adjustment was made for baseline pain scores in a Bayesian analysis, duloxetine was statistically better than tramadol, but the magnitude of difference was of questionable clinical relevance (4.92; 95% CI 1.51 to 8.34 on a 0–100 scale).

Tramadol versus Other Weak Opioids

In indirect comparisons from a meta-analysis, tramadol was associated with a larger decrease in OA pain intensity than dihydrocodeine or pentazocine, and a higher likelihood of global impression of at least moderate improvement than pentazocine (by 150 percent). [155] Tramadol was less likely to cause minor adverse events relative to pentazocine (NNT = four in favor of tramadol). Tramadol was similar to pentazocine in treatment discontinuations due to adverse events.

A 12-week, open-label, non-inferiority, randomized trial (N = 134) showed that, in patients with moderate to severe OA of the hip or knee, twice daily tramadol ER (75, 100, 150, or 200 mg per day, maximum 400 mg per day) and once daily low-dose transdermal buprenorphine (5, 10 or 20 mcg/hour) were similar in pain reduction. [167] Transdermal buprenorphine was non-inferior to twice daily tramadol ER therapy. The incidences of adverse events were similar for both treatments but the risk of treatment discontinuations due to adverse events was higher on tramadol (29.2 percent versus 14.5 percent). A once daily buprenorphine transdermal patch was preferred over a twice daily tramadol therapy by 70 percent of patients in each treatment group.

Tramadol as Add-On Therapy

The addition of tramadol to acetaminophen therapy is often thought to enhance analgesia by complementary mechanisms of action. Whereas additional benefit was shown with IR tramadol/acetaminophen over the individual agents alone in acute, post-operative dental pain, [206] there is insufficient evidence to make conclusions for OA pain. Tramadol and tramadol/acetaminophen showed similar efficacy and safety in indirect comparisons, suggesting that there was little additional benefit from the addition of tramadol to acetaminophen in patients with OA pain. However, these observations were based on only two RCTs included in a meta-analysis. [155]

There is more evidence available for the addition of tramadol or tramadol/acetaminophen to NSAIDs with some potential caveats to consider. The addition of tramadol IR for breakthrough OA pain during daily NSAID therapy was inconsistently beneficial in a short-term (13-day) trial. [168] The results of another trial suggested that NSAID responders may be more likely than NSAID non-responders to obtain additional relief from add-on tramadol therapy. [169] Tramadol/acetaminophen as add-on therapy to NSAIDs including COX-2 inhibitors was shown to improve pain to only a small extent, [155,170,171] although in one trial [172] the small reduction in pain was accompanied by significant improvement in physical function.

The addition of tramadol to duloxetine therapy has not been evaluated in OA clinical trials. Concomitant use of tramadol with duloxetine is not a contraindication; however, exercise caution and consider potential patient risk factors (e.g., increasing age or renal impairment) if using tramadol in combination with duloxetine. Concomitant use of tramadol and duloxetine may result in additive serotonergic effects and increase the risk for serotonin syndrome. Duloxetine co-therapy may increase tramadol plasma concentrations because it is a moderate CYP2D6 inhibitor and increase the risk for seizures.

Non-Tramadol Opioids

Non-tramadol Opioids as Alternative Monotherapy

A Cochrane meta-analysis of ten trials (N = 2268) involving oxycodone (four trials), codeine (three trials), oxymorphone (two trials), transdermal fentanyl and oral morphine (one trial each) showed small to moderate improvements relative to placebo in pain (for at least 50 percent improvement, NNT = 8; 95% CI 7 to 11) and physical function (NNT = 10; 95% CI 8 to 15). [173] These benefits were outweighed by large increases in the risk of treatment discontinuations due to adverse events relative to placebo (NNT = 19; 95% CI 13 to 29). More potent opioids did not seem to be substantially better than less potent opioids. The authors concluded that non-tramadol opioids should not be used routinely even if OA pain is severe. The results reflect short-term treatment courses (median, four weeks) using morphine equivalent doses ranging from 13 to 160 mg per day (median, 51 mg per day).

An investigational formulation of hydromorphone ER showed inconsistent benefit in OA pain depending on the imputation method of data analysis. [174]

In patients with OA with uncontrolled persistent pain who were receiving or could not tolerate standard therapy with NSAIDS, acetaminophen, or short-acting opioids, a 90-day course of treatment

with oxycodone ER (20 mg per day) was efficacious in improving pain, physical function and sleep. [175]

Non-tramadol Opioids Compared with Non-opioid Therapies

In meta-analytic indirect comparisons using Bayesian analyses, oxycodone was similar to duloxetine in WOMAC total score change from baseline. [166]

Tapentadol Compared with Non-tramadol Opioids

In a ten-day major safety and efficacy clinical trial to support an acute pain indication, every four to six hour dosing regimens of tapentadol IR (50 or 75 mg) were shown to be non-inferior to oxycodone IR (10 mg every four to six hours) in 666 patients whose pain was not controlled by current therapy and who were surgical candidates for hip or knee replacement because of end-stage OA. [111] Compared with oxycodone, tapentadol therapy was associated with significantly lower incidences of nausea, vomiting and constipation.

Opioid Rotation to Tapentadol ER

Patients already on opioids for OA pain may be considered for rotation to tapentadol ER. In a small, manufacturer-sponsored, 12-week open-label study which was terminated early because of slow enrollment and drug shortages, the rotation of World Health Organization (WHO) step III opioids to tapentadol ER led to improvements in efficacy and safety. [176] In patients who responded but were not tolerating WHO step III opioid therapy for severe OA knee pain, rotation to tapentadol ER reduced total WOMAC scores over a 12-week period, reflecting improvements in pain, stiffness and physical function, and in sleep disturbances. Although the intent was to maintain the same level of pain control, after the switch to tapentadol there were at least ten percent decreases in the percentages of patients experiencing nausea, constipation, dry mouth and fatigue. These four adverse events and dizziness were the main reasons for switching to tapentadol ER.

Non-tramadol Opioids as Add-on Therapy

No studies evaluating non-tramadol opioids as add-on therapy in OA were found. The evidence to support add-on therapy is inferred from monotherapy studies.

Corticosteroids versus Placebo

Intra-articular corticosteroids are commonly used to reduce pain in patients with OA of the knee and less commonly of the hip. Available evidence provides support for reducing pain in patients with OA of the knee but evidence is limited for hip OA. In the majority of studies, samples sizes were small and the severity of OA was stated to range from mild to severe.

Knee

Three systematic reviews/meta-analyses were identified in which intra-articular steroids were compared to placebo in patients with OA of the knee. A fourth meta-analysis, examining the effect of various pharmacologic interventions (including intra-articular steroids) compared to placebo for knee OA was also included. In the review by Arroll, et al., [207] ten trials met the inclusion criteria and six of the trials provided data on improvement of OA symptoms. There was a statistically significant difference in favor of steroid injections versus placebo for improvement in OA symptoms (RR 1.66,

95% CI 1.37-2.01, NNT 1.3-3.5). Symptoms were improved up to two weeks after injection but one study, using a higher steroid dose (40 mg triamcinolone), reported a prolonged duration of reduced symptoms. [207] Godwin, et al., included five randomized trials involving 312 patients. From their review, patients receiving corticosteroid joint injections reported reduced pain at one week and through three to four weeks when compared to placebo. No differences were reported in pain scores between groups by week six in any of the included studies. Adverse events resulting from the steroid injection were not reported in any of the five included trials. [208] The third systematic review was conducted by the Cochrane Collaboration and included a comparison of intra-articular knee injection with corticosteroids versus placebo or hyaluronates/hylan. For the comparison to placebo, intra-articular injection with steroids improved pain (weighted mean difference [WMD] -21.91, 95% CI -29.93 to -13.89) and patient global assessment (RR 1.44, 95% CI 1.13-1.82) at one week after injection (NNT 3-4). Pain was significantly reduced in the steroid group between two and three weeks post injection (RR 1.81, 95% CI 1.09-3, RR 3.11, 95% CI 1.61-6.01, respectively). No differences were noted in pain between 4 and 24 weeks post injection. There were no statistical differences reported for improvement in function between groups. [177]

Hip

There was one review of the use of intra-articular corticosteroids in patients with OA of the hip as a therapeutic intervention. [209] In this review, the authors identified eight trials, in which only four were randomized, placebo-controlled trials and included a total of 268 patients. In each of the studies, joint injection was performed using fluoroscopic or ultrasound guidance. Benefit of the steroid injection was noted in reducing pain, stiffness and increasing function and/or range of motion. An improvement in symptoms was reported up to three months, but in one study was limited to 28 days. There were no serious adverse events that were reported in any of the trials. [209]

Another use of intra-articular steroid injection of the hip is to assist in the differential diagnosis to help distinguish pain arising from the hip (intra-articular), the spine or other extra-articular origin in those patients presenting with atypical lower extremity or hip pain. This diagnostic tool may be helpful in determining whether total hip replacement (THR) will resolve painful symptoms. In a retrospective assessment of 204 consecutive diagnostic hip injections, investigators found hip injection with a steroid and local anesthetic to have a sensitivity of 91.5 percent, specificity and positive predictive value of 100 percent and a negative predictive value of 84.6 percent for a favorable response to THR. [210]

Hyaluronate/Hylan (HA)

There were a large number of published studies investigating the effect of intra-articular HA injections versus placebo in patients with OA of the knee. Many of these studies have been deemed of lower quality as many are small and have flawed study methodology and data analysis. Furthermore in the process of conducting meta-analyses, negative results from unpublished trials have led to concerns of publication bias in this area. [179] With regard to intra-articular HA in patients with OA of the hip, limited published data are available. In these studies, pain improvement was measured using the VAS, WOMAC, and Osteoarthritis Research Society International (OARSI) 2004 criteria. Physical function

was assessed by the OARSI 2004 criteria, Patient Global Assessment (PGA), and WOMAC. Adverse events were classified as serious or non-serious events in five studies.

Knee

There were eight published systematic reviews with meta-analyses examining the benefit of intra-articular HA/hylan to placebo in patients with OA of the knee; two of which were published in 2012. [179,180] Of the meta-analyses published prior to 2010 (n=six), four reported at least a modest benefit in comparison to placebo. [118,211-213] While the remaining two studies found minimal to no benefit, [214,215] Rutjes et al., reported an overall effect size of HA on pain improved compared to placebo as -0.37 (95% CI -0.46 to -0.28). [179] While this is a typically considered as a moderate effect size, it was deemed to be minimally clinically significant by the authors. Additionally, when reanalyzed to include only those data from larger studies, there was an even a smaller effect size (-0.16, 95% CI -0.26 to -0.07), which was statistically different from placebo but did not reach the pre-specified minimal clinically important difference. Overall, the effect size for improved function was moderate (-0.33, 95% CI -0.43 to -0.22). However, when only data from larger studies were analyzed, differences in physical function were no longer significant. In the meta-analysis by Colen et al., the authors noted a change in WMD of -10.20 (95% CI -15.97 to -4.42) in visual analogue scale from baseline to three months, after taking into account the placebo response observed with intra-articular saline. [180]

Treatment related adverse events were fairly consistent across all studies and intra-articular HAs were not associated with an increased risk of overall adverse events in comparison to placebo. In the meta-analysis by Rutjes et al., a higher rate of serious adverse events were reported in the group receiving hyaluronates but the authors acknowledge that the causal nature of those serious events is not known. [179]

Hip

Two published studies [216,217] met our inclusion criteria and included 186 patients. In the study by Richette et al., [216] intra-articular HA was administered using fluoroscopic guidance versus placebo. The authors did not observe any differences between groups in pain assessed by VAS, WOMAC sub scores for pain, stiffness or disability, differences in physician global assessment or any other outcome measured. Rates of adverse events were consistent in both studies and were not different between HA and placebo. [216,217]

There were two published systematic reviews of intra-articular injection of HA in patients with OA of hip. Both authors concluded that the available evidence is limited and of lower quality and therefore additional studies are recommended prior to make conclusive recommendations regarding its use in hip OA. [218,219]

The effect of hyaluronic acid intra-articular hip injections on the need for total hip replacement surgery was examined in two studies. One of the studies was a non-randomized comparative trial comparing three different HA formulations [181] and was of fair quality. The second study, Migliore et al., [182] was a retrospective cohort study, and was of Fair quality. In the study, 82 percent of patients avoided total hip arthroplasty at 48 months following HA injections every six months. [182] Survival analysis of

the 2008 study indicated that 51 percent of patients had not undergone surgery at three years and adverse events (none serious) ranged from 10 to 30 percent. [181] Both studies showed reduction of pain and increase in function following the HA injections. However, no placebo or non-intervention comparative group was considered

Corticosteroids versus Hyaluronate/Hylan

Seven studies comparing corticosteroids to HA in patients with OA were identified. These studies compared corticosteroid to hyaluronate injections and include one systematic review and six randomized controlled trials (RCTs) involving a total of 1436 enrolled patients. The systematic review and four of the six RCTs evaluated patients with OA of both the knees and hips while the remaining RCTs enrolled only patients with OA of the hips. The mean patient age ranged from 39 to 83 years and all studies included more females than males. The type of intra-articular hyaluronates (HA) and corticosteroid used as well as the doses used varied across the studies. Pain improvement was measured using the Visual Analog Scale (VAS), WOMAC pain sub-scores, the Knee Society clinical rating, and the Lequesne score, the blinded clinical observer global assessment (COGA), the patient global assessment, and the total arthritis index. Physical function was assessed by the WOMAC physical function subscales and the Knee Society clinical rating. Five of the seven studies reported adverse events that were classified as serious.

Knee

The systematic review [178] included seven RCTs and 606 patients. Of note, five of the seven RCTs included in this review were deemed low quality trials and two were rated as high quality. Pain scores at week two favored corticosteroids, at week four there was equal efficacy and at weeks 8, 12 and 26, pain scores favored HA. Three RCTs, [119-121] not included in the systematic review, consisted of 181 patients. In these three studies, no statistically significant difference between agents in pain scores at any follow up interval (which ranged from five weeks to six months) was observed. [119-121]

Outcomes related to physical function were reported in two studies. Caborn et al. found a statistically significant difference between groups at week 12 and week 26 favoring HA utilizing the WOMAC domain C score. [122] However, Skwara et al. did not find a significant between group differences at any follow up time point. [120] Overall, adverse events were fairly consistent across all studies and there was no significant difference in overall incidence of adverse events in the corticosteroid groups versus the HA groups.

Hip

Two RCTs [217,220] included 406 patients showed consistent outcomes related to pain as there was no significant difference in pain improvement scores at any follow up time point between patients who received intra-articular HA versus corticosteroid. Spitzer et al. reported improvement in physical function at four weeks that was statistically significant favoring the corticosteroid group; however, this difference disappeared by week 26. [220] In these two studies, comparable rates of adverse events were noted and included hip infection, pain flares and joint stiffness. [217,220]

Corticosteroid Injection prior to Hip or Knee Arthroplasty

Although infection is a known complication arising from both joint injection and arthroplasty, there are limited data showing an increased risk of deep joint infection in patients who have undergone intra-articular corticosteroid injection prior to joint arthroplasty (e.g., knee or hip). Patient factors that may increase the risk for deep joint infection following joint arthroplasty including prior open surgical procedure, immunosuppressive therapy, poor nutrition, hypokalemia, diabetes, obesity and history of smoking. [221] Joint injections with corticosteroids are used to reduce pain in an attempt to delay joint arthroplasty or in those patients that are not appropriate surgical candidates and are also used as a diagnostic aide to identify the origin of joint pain and discomfort (e.g., intrinsic hip pain versus extrinsic pain arising from the spine or referred pain from the hip to the knee). Therapeutic corticosteroid joint injections are more commonly used prior to knee replacement since accessing the hip joint poses an increased technical challenge without the use of fluoroscopy or ultrasound guidance. The available evidence pertaining to the risk of deep joint infection after joint arthroplasty is in the form of retrospective or case-control studies. A literature review by McMahon, et al., included data from twelve studies in which the rates of superficial and deep joint infections (n=2068) in cohorts of patients who did receive or did not receive a corticosteroid joint injection and who underwent hip or knee arthroplasty were analyzed. From their review, the authors concluded that steroid injection prior to joint replacement (either hip or knee) did not statistically increase the risk for superficial or deep joint infection. [222]

Knee

One retrospective [223] and two retrospective, case-control studies [224,225] were identified in patients having total knee replacement (TKR) surgery. In the study by Papavasailliou, 231 patients having undergone TKR over a period of 2.5 years were reviewed and 144 evaluated after exclusion criteria were applied. In those patients having received a steroid joint injection (n=54) in an 11-month period before surgery, three deep infections were identified versus none in patients who did not receive a joint injection (n=90). Five other patients having received an injection prior to surgery underwent further examination for possible deep joint infection because of ongoing swelling or pain. It was not noted whether these patients were later diagnosed with a deep infection. The number of superficial infections did not differ between those who did and did not receive an injection prior to TKR. The authors concluded that the decision to administer an intra-articular steroid injection in a potential candidate for TKR requires careful consideration. [223] In the study by Joshy et al., 32 patients with deep joint infection following TKR were compared with 32 control patients with no infection. There was no significant difference in numbers of patients who had steroid joint injections prior to TKR between groups (p=one). [225] In the second study by Desai et al., 440 patients had TKR replacements and only 90 patients had an intra-articular steroid injection prior to surgery. Half of those patients received the injection within one year before surgery. A group of 180 patients, who did not have a steroid injection, served as the control. Two cases of superficial infection were found in the injection and five in the control group (NS). No deep infections were noted in any of the case or control patients (p=one). [224]

Hip

There have been nine published retrospective and case-control trials conducted to determine if the risk of deep infection is increased in patients having received intra-articular steroid injection prior to total hip replacements (THR). One of the case-control studies found an increased risk of deep joint infection in patients having hip joint injections and is the study that is responsible for raising these concerns. In their study, 40 patients having received a steroid joint injection prior to THR was compared to 40 patients having THR without receiving an injection. Five joint revisions were necessary, four of which were done because of deep infection versus none in the non-injection group. Six other patients experienced ongoing problems with their new hip in the injection group versus one in the control group. The authors noted that deep infection required joint revision in 10 percent of the injection patients (4/40) versus none in the control group. Overall, hip joint revision rates in the injection patients was 12.5 percent versus 1.02 percent of 979 THR performed during the same study period. The authors conclude that due to the potential complications from steroid joint injection prior to THR, their use should be contraindicated in possible candidates for THR. [226] In another case-control study, 224 patients having primary THR within one year of intra-articular steroid injection were compared with 224 patients having THR without steroid injection. In the injection group, there were three deep infections and 11 superficial infections versus one deep infection and eight superficial infections in the non-injection group; neither of these differences was statistically significant. Two of the four patients that developed a deep infection had a chronic comorbid condition. Of note, the average time to injection and THR was 112 days. However, in the patients that developed deep infections, the average time between the steroid injection and THR was 44 days (standard deviation 23 days). [227] Of the remaining seven retrospective/case-control studies, none of them found an increased risk for deep joint infection in patients receiving intra-articular steroid injections in the operative joint. Many of the authors cited potential reasons for an increased rate of deep infections in the Kaspar, et al. study including concern regarding administration of intra-articular hip injections outside of a controlled, low-infection environment, such as an operating room and adhering to strict aseptic techniques. [228-234]

Table D-1. List of Pharmacologic Agents and their Selected Characteristics

List of Pharmaceuticals for treatment of Osteoarthritis*+						
Generic Name	Brand	Formulations	Usual Starting Dose	Max Single Dose	Frequency	Notes
COX-2 selective NSAIDs:[a]						
Celecoxib	CELEBREX	C	100-200 mg	200 mg	once or twice daily	Max 200 mg/day for OA
Partially selective NSAIDs:[a]						
Etodolac	generic only/XR	C, T; C (XR)	200 mg	400 mg	2-4 times daily	XR up to 1200/daily
Meloxicam	MOBIC/generics	T, Susp	7.5 mg	15 mg	once daily	Max dose is 15 mg daily
Nabumetone	generic only	T	1000 mg	2000 mg	once daily	May divide twice daily. Max dose is 2000 mg daily
Non-aspirin, nonselective NSAIDs:[a]						
Diclofenac potassium/sodium	generics	several	50 mg	75 mg	2-3 times daily	Max total daily dose is 150 mg. May divide up to 3 times daily
Diclofenac sodium	VOLTAREN XR	T	100 mg	100 mg	once daily	Max dose is 100 mg daily
Diflunisal	generic only	T	250 mg	750 mg	twice daily	Max dose is 1500 mg daily
Fenoprofen	NALFON/generics	C, T	300 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	several	400 mg	800 mg	3-4 times daily	Max dose in chronic pain is 2400 mg daily
Indomethacin	INDOCIN/SR/generics	C, 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	generic only	C; OTC T	50 mg	75 mg	3 or 4 times daily	Max dose is 300 mg daily
Ketoprofen ER	generic only	C	200 mg		once daily	
Meclofenamate sodium	generic only	C	50 mg	100 mg	4 times daily	May give 3 times daily. Max dose is 400 mg daily
Naproxen/-EC	NAPROSYN/generics	T, susp	250 mg	500 mg	twice daily	Max dose in chronic pain is 1000 mg daily
Naproxen Sodium	ANAPROX/generics	T	275 mg	550 mg	twice daily	Max dose in chronic pain is 1100 mg daily
Oxaprozin	DAYPRO/generics	T	1200 mg	1800 mg	once daily	Max dose is 26 mg/kg up to 1800 mg, whichever is lower

List of Pharmaceuticals for treatment of Osteoarthritis*+						
Generic Name	Brand	Formulations	Usual Starting Dose	Max Single Dose	Frequency	Notes
Piroxicam	FELDENE/generics	C	10 mg	20 mg	once daily	Max dose is 20 mg daily. May divide twice daily
Sulindac	CLINORIL/generics	T	150 mg	200 mg	twice daily	Max dose is 400 mg daily
Tolmetin	generic only	T, C	400-600 mg	600 mg	3 times daily	Max dose is 1800 mg daily
Aspirin and Salsalate:						
Aspirin	several	T, Supp	1000 mg	1000 mg	3 times daily	May increase to 4 times daily Max dose is 4000 mg daily
Salsalate	several	T	500 mg-750 mg	1000 mg	2-3 times daily	May increase to 3 times daily Max dose is 3000 mg daily
Acetaminophen and Supplements						
Acetaminophen	several	several	650 mg	1300 mg	3-4 times daily (Max dose 2-4 grams daily, depending upon the patient)	Max 3000-4000 mg/day Consider lower total daily doses (e.g., 2-3 grams) in elderly patients or in those with heavy use of alcohol The total daily dose of acetaminophen from all sources (single and multiple ingredient products) must not exceed 4000 mg/day
Chondroitin	several	several	400 mg		3 times daily	Large variation in delivered dose Not recommended due to lack of evidence showing benefit
Glucosamine	several	several	500 mg		3 times daily	Large variation in delivered dose Not recommended due to lack of evidence showing benefit
Topical Therapies						

List of Pharmaceuticals for treatment of Osteoarthritis*+						
Generic Name	Brand	Formulations	Usual Starting Dose	Max Single Dose	Frequency	Notes
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	Pennsaid	Soln 1.5 and 2%	40 drops	40 drops	4 times daily	Local skin irritation
Diclofenac	Flector	Patch 1.3%	1 patch (180 mg)	1 patch (180mg)	twice daily	Not FDA approved for OA Local skin irritation
Diclofenac	Solaraze	Gel 3%	--	--	twice daily	Local skin irritation
Other Therapies						
Duloxetine	Cymbalta/generics	Delayed release C	30 mg for 1 week, increase to 60 mg conce 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, warnings and precautions and adverse events.

List of Pharmaceuticals for treatment of Osteoarthritis*+						
Generic Name	Brand	Formulations	Usual Starting Dose	Max Single Dose	Frequency	Notes
Tramadol (IR)	generics	T, several	25-50 mg	100 mg	Every 4-6 hours Max daily dose 400 mg	For patients not requiring rapid onset of pain relief, initiate dosing at 25 mg 4 times daily, increasing by 25 mg every 3 days until reaching 25 mg 4 times daily, and so on. When combined with certain drugs or in those patients with a history of seizure disorder, tramadol may increase the risk of seizures.

Hyaluronate/Hylan Injections: Treatment Course (Each injection is given at weekly intervals)			
Hyaluronate/Hylan	**Frequency**	**Volume**	**Notes**
Euflexxa	3 weekly; repeat approved	2.0 ml	---
Gel-One	Single injection	3.0 ml	Caution in those with avian allergy
Hyalgan	3 or 5 weekly	2.0 ml	Caution in those with avian allergy
Orthovisc	3 to 4 weekly	2.0 ml	---
Supartz	3 or 5 weekly	2.5 ml	Caution in those with avian allergy
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

*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. +For additional details on warnings and precautions, drug-drug interactions, etc., refer to the prescribing information for the individual agents of interest.

[a]All NSAIDs have the potential to increase the risk for cardiovascular (CV) events and therefore should be used at the lowest effective dose for the shortest possible duration. Naproxen has a neutral or lowest risk for adverse CV events. 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, known cardiovascular disease, patients receiving anticoagulants, etc.

Appendix E: Nutraceuticals and Dietary Supplements

Table E-1. Key Findings from Studies on Nutraceuticals/Dietary Supplements

Dietary Supplement	Summary of Study Characteristics	Key Findings	Additional Comments
Ayurvedic formulations (components: Shunthi and Guduchi)	One RCT rated as Good quality; 5 Ayurvedic formulations were compared to placebo and glucosamine sulfate; total n = 245 Chopra et al. 2011 [235]	No statistically significant improvements in pain or function for any group.	Paracetamol rescue medication was permitted; participants were allowed to continue established physical therapy routines.
Boiogito (Sinomenium Stem)	One RCT (unblinded) rated as fair compared Boiogito with loxoprofen vs. loxoprefen alone; n = 50 Majima et al. 2012 [236]	Both groups experienced improvements in pain from baseline and physical function.	
Collagen Derivatives (Indentured Collagen; Gelatin; Collagen Hydrolysate)	One systematic review of 8 trials included 6 RCTs, 1 quasi-RCT, and 1 crossover design study, total n = 1187. The review was rated as Good quality, but the studies included were low to moderate in quality. VanVijven et al. 2012 [237]	For both pain and function, Collagen (various forms) did not appear to be more effective than placebo, based on meta-analysis of 3 trials.	Use of rescue medication was not clearly described. Harms were poorly reported.
Curcuma (domestica and longa)	Two RCT's, both rated as Fair quality (lack of blinding); compared curcuma to placebo plus rescue medication or curcuma to ibuprofen. Madhu et al. 2012 [238] Kuptniratsaikul et al. 2009 [239]	One trial found statistically significant improvements in pain and function for patients treated with curcuma vs placebo; [238] the other did not.	Rescue medication used significantly less often in the curcuma group. [238]
Derris Scandens	One RCT rated as Fair for lack of blinding; compared Derris Sandens to naproxen, n=107. Kuptniratsaikul et al. 2011 [240]	No statistically significant findings by treatment group in mean pain reduction or for function.	Harms for Derris Scandens was not significantly different from naproxen.
Duhuo Jisheng Wan	One RCT rated as Good, n =200, compared	No statistically significant difference	No other medications were permitted.

Dietary Supplement	Summary of Study Characteristics	Key Findings	Additional Comments
	Duhuo Jisheng Wan to diclofenac. Teekachunhatean et al. 2004 [241]	in measures of pain or function seen between groups.	
Eggshell membrane	One RCT rated as Good quality, n =60, compared eggshell membrane to placebo. Ruff et al. 2009 [242]	Eggshell group showed a statistically significant but not clinically meaningful reduction in pain compared to placebo; there was no statistically significant improvement in function.	Acetaminophen as rescue medication. No difference in harms (self-reported).
Flavocoxid ("Limbrel" proprietary product)	One RCT with a quality rating of Good, n=223; compared product to naproxen. Levy et al. 2010 [243]	There were no between group differences in pain or function.	Harms (self-report, clinical exam, lab) were statistically significantly different, with those on naproxen reporting more edema and dyspepsia, and more flatulence with Librel.
Ginger	One Good quality systematic narrative review and one Good quality RCT. Leach et al. 2008 [243] Zakeri et al. 2011 [244]	Within the Leach review, 3 trials compared ginger to placebo; one trial found a statistically significant improvement in pain in the ginger group. In the Leach review, 2 trials compared ginger to ibuprofen; there was no statistically significant difference between groups. Improvements in function favored ibuprofen only.	Harms for ginger included bad taste, heartburn, dyspepsia, nausea, stool changes and skin allergy, but there was no statistically significant differences in harms between ginger and placebo. For ginger and ibuprofen, reported harms were similar and were not different between groups.
MESACA (Methylsulfonylmethane and Boswellia Acid Combination)	One RCT of Good quality compared MESACA to placebo (total n = 30). Notarnicola et al. 2012	Both groups experienced statistically significant improvements in pain	Paracetamol, pyroxicam or diclofenac were permitted as rescue

Dietary Supplement	Summary of Study Characteristics	Key Findings	Additional Comments
	[245]	from baseline, but the between group difference favored placebo; however, the MESACA group used significantly less rescue medication than at baseline. There was no statistically significant difference in measures of function between groups.	meds. No side effects were reported (harms were self-report).
Phytalgic (proprietary blend of fish oil; vitamin E; uritica dioica)	One RCT rated as Good quality compared Phytalgic to placebo (total n = 81). Jacquet et al. 2009 [246]	There was a statistically significant reduction in pain and improved function for the Phytalgic group compared to placebo.	Various harms reported with Phytalgic included eructations smelling of fish, pain outside OA, infection; not reported as to significant difference in harms between Phytalgic and placebo.
Pycnogenol	One RCT rated as Good quality compared Pycnogenol to placebo (total n = 100). Cisar et al. 2008 [247]	There was no statistically significant difference between Pycnogenol and placebo for pain or daily activities; patients on Pycnogenol were able to decrease their analgesic doses, but statistical significance was not reported. Total WOMAC score was improved significantly for the Pycnogenol group.	Patients were permitted to use any medications taken pre-enrollment or to change medications if desired. Harms were self-report and by lab value; no changes in biochemical parameters, unclear if reported harms differed between groups but were generally few.
SKI 306X (Clematis Radix, Trichosanthes Root, Prunella Spike)	N – 249, OA of the knee, patients aged 35-75 years; SK1306X with placebo, administered 200 mg 3 x/d for 4 weeks, vs 100 mg dicolfenac 100 mg/d plus placebo.	Statistically significant difference vbetween groups in favor of diclofenac for function; no between group difference for pain.	Patients permitted to exercise and receive massage.

Dietary Supplement	Summary of Study Characteristics	Key Findings	Additional Comments
	Jung et al. 2001 [248]		
SAMe	A systematic review was rated as Good, but included trials of low quality rating; trials compared SAMe to placebo. One recently published RCT was considered Good quality and compared SAMe to nabumetone. Rutjes et al. 2009 [249] Kim et al. 2009 [250]	Rutjes et al. performed a meta-analysis of 2 RCTs and found no between group difference in pain reduction or improved function. In the RCT by Kim, there was no statistically significant difference for pain or function between groups.	Kim et al. reported adverse events for SAMe at 35.8% and for nabumetone at 31.3%, but did not report if there was a statistically significant difference.
Sierrasil	One RCT with a Good quality rating compared high dose Sierrasil, low dose Sierrasil and placebo (total n = 107). Miller et al. 2003 [251]	There was no statistically significant between group difference for pain scores; all groups improved from baseline for measures of function, but it was not stated if groups differed in the improvement.	Patients were allowed to take paracetamol, but no other rescue medications or supplements. Harms were reported as self-report and laboratory values; authors state that changes in lab values were not indicative of adverse response to study medications.
Siriraj Wattama Recipe (proprietary blend of 15 herbs)	One RCT of Fair quality with unblinded design compared the supplement to diclofenac (total n = 60). Pengkhum et al. 2012 [252]	No statistically significant between group difference for pain score or function.	Marginally higher levels of AST and eosinophils with supplement. Adverse events for supplement (n=2) compared to diclofenac (n=3).

The literature review included intervention studies with at least 25 patients per treatment arm in a prospective, randomized or nonrandomized comparative trial with an independent, concurrent control group. Alternately, recent systematic reviews were included. These inclusion criteria limited the number of studies included; for many dietary supplements, only one study meeting these criteria was located.

There were six dietary supplements for which more than one study met the inclusion criteria and indicated some effect on pain and function for patients with hip and/or knee OA: glucosamine or chondroitin sulfate or the combination (one meta-analysis, 20 RCTs); avocado-soybean

unsaponifiables (one meta-analysis rated as good, included four RCTs); Boswellia Serrata (one good and one fair quality RCT); Methysufonylmehtane (MSM) (one good quality systematic review on two RCTs); Rosa Canina (Rose hips) (one good quality systematic review on one RCT and two crossover trials).

Meta-analysis by Christensen et al. compared avocado-soybean unsaponifiables to placebo, and included four double-blind RCTs and a total of 664 patients (427 female) with a mean age of 64.1 years. [183] Two of the RCTs included hip and knee OA; one was knee OA only; one was hip OA only. The product used in all trials was Piascledine, and all trials were manufacturer funded. In the study, participants self-reported the pain using the VAS pain scale. Use of rescue medications was not reported. The meta-analysis of the four RCTs found a statistically significant and clinically meaningful reduction in pain compared to placebo (effect size 0.39, 95% confidence interval 0.01-0.76, p =0.042) but heterogeneity was high. Two trials clearly favored the avocado-soybean preparation; two trials did not favor the supplement over placebo. A meta-regression analysis showed that patients with knee OA can expect a larger clinical effect than patients with hip OA. Meta-analysis for improved function found significantly greater improvement in the avocado-soybean group than in placebo (effect size 0.45, 95% CI 0.21-0.70; p =0.0003) but heterogeneity was high. The three trials including knee OA patients favored avocado-soybean treatment. Measurement of harms was not reported in the RCTs; no evidence of significant adverse events was found per the meta-analysis authors.

There were three RCTs evaluating the effectiveness of Boswellia Serrata for treatment of OA pain and improvements in function. A good quality RCT by Vishal et al. compared the Boswellia Serrata preparation Alfapin (n=30) to placebo (n=29). [184] The Alfapin group showed a statistically significant reduction in pain and statistically significant improvements in function. There were no major differences in harms between the Alfapin and placebo groups. Sengupta et al. compared two dose levels of five-Loxin (a Botswellia Serrata preparation; 250 mg, n=23; 100 mg, n=24) to placebo (n=23) in a RCT of good quality. [186] Both five-Loxin groups showed statistically significant improvements in pain and function. There were no statistically significant differences in harms among the three groups. A fair quality RCT by Sontakke et al. showed a statistically significant reduction in pain compared to valecoxib; the author's note that valecoxib had a faster onset of action by month one, but that there was no end of treatment data reported. At final follow up, the authors found a statistically significant improvement in daily activities score compared to valecoxib. The Sontakke study was rated as fair quality because of unblinded study design. [185]

A good quality systematic review by Brien et al. was conducted on Methylsulfonylmethane (MSM); it included two RCTs and included a total of 168 patients (101 female) and a mean age range from 50-55.6 between the two studies. The study designs did not allow for meta-analysis, as one trial compared MSM to placebo and the other compared MSM to glucosamine. Both trials found MSM to be superior for pain reduction (p=0.001) and one trial found statistically significant improvements in physical function compared to placebo. Harms included GI discomfort and diarrhea, but were not broken down by group. [187]

Appendix F: Participants List

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