
Anil Krishnamurthy, MBBS; Adam Edward Lang, PharmD; Sanjog Pangarkar, MD; Jess Edison, MD; John Cody, MD; and James Sall, PhD, FNP-BC

Abstract

In July 2020, the US Department of Veterans Affairs (VA) and US Department of Defense (DoD) approved a new joint clinical practice guideline for the non-surgical management of hip and knee osteoarthritis. This synopsis highlights some of the recommendations. In February 2019, the VA/DoD Evidence-Based Practice Work Group convened a joint VA/DoD guideline development effort that included clinical stakeholders and conformed to the National Academy of Medicine’s tenets for trustworthy clinical practice guidelines. The guideline panel developed key questions, systematically searched (ie, Cochrane Database of Systematic Reviews, EMBASE, MEDLINE PreMEDLINE, PubMed, and the Agency for Healthcare Research and Quality website) and evaluated the literature, created a simple 1-page algorithm, and advanced 19 recommendations using the Grading of Recommendations Assessment, Development, and Evaluation system. This synopsis summarizes key recommendations in all 6 topics covered in the guideline. These topics are diagnosis, self-management, physical therapy, pharmacotherapy, orthobiologics, and complementary and integrative health.

Osteoarthritis (OA) is one of the most common chronic medical conditions worldwide and in the United States. According to the Centers for Disease Control and Prevention, OA affects more than 30 million Americans,1 with prevalence estimates of 13.9% in adults 25 years and older and 33.6% in adults 65 years and older.2 Risk factors for OA may be broadly categorized as patient-level or joint-related factors. Patient-level risk factors include older age, female sex, overweight and obesity, genetics, race, and engagement in certain work or recreational activities. Heavy work activities (eg, farming and construction work) or work that requires frequent kneeling, heavy lifting, or repetitive use of joints are associated with the development of OA.3 The activities that place patients at higher risk for OA are an integral part of the daily duties of many who serve or have served in the US military.4 Studies also report a strong association between high-impact sports (eg, football, hockey, and sky diving) and the development of OA.5,6

GUIDELINE DEVELOPMENT PROCESS

To develop these recommendations, the US Department of Veterans Affairs/US Department of Defense (VA/DoD) followed a process developed by the VA/DoD Evidence-Based Practice work group that adheres to the standards described for trustworthy guidelines.7 The group selected 3 guideline panel co-chairs, 1 from the VA and 2 from the DoD. The co-chairs, in conjunction with VA and DoD leadership, selected a multidisciplinary panel of practicing clinician stakeholders with specialists from various disciplines including orthopedics, rheumatology, pain medicine, radiology,
Diagnosis

Radiological examinations are frequently ordered in the primary care setting to make or confirm the diagnosis of OA of the knee and/or hip. However, the most recent evidence, consisting of 2 diagnostic cohort studies by Xu et al. and Segal et al., did not indicate a clear benefit of magnetic resonance imaging (MRI) over plain radiography for the diagnosis of OA of the knee and/or hip. Magnetic resonance imaging can reveal articular cartilage loss as well as injury to intra-articular and extra-articular soft tissue structures; however, it should not be used routinely to diagnose or work-up OA. As a result, we recommend against the routine use of MRI in patients with known or suspected OA. Magnetic resonance imaging is a
costly alternative for diagnosis without proven benefit over plain radiography.

Self-management
Exercise of various types (eg, land, aquatic, strengthening, and aerobic) has been found to be effective in reducing pain and improving function in those with OA of the hip or knee.16-19

Weight loss may help to reduce cumulative loading to the lower extremity joints.20 The studies on weight loss evaluated pain, physical function, mobility, and mental quality of life. For overweight and obese patients with OA of the knee, weight loss may improve pain, quality of life (physical domain), physical function, and mobility. There are limited studies on the harms and benefits of weight loss in OA of the hip in overweight and obese patients.

Bracing with soft braces (defined by study authors as a nonelastic, nonadhesive material) or either valgus or varus knee braces may improve pain and self-reported physical function in the knee.21,22 For bracing, although the evidence did not specifically identify harms associated with the use of bracing, the work group recognized that bracing can lead to atrophy and functional loss if appropriate exercise is also not undertaken.

On the basis of the evidence found, we suggest a self-management program that includes exercise and weight loss for OA of the hip and, additionally, bracing for OA of the knee.

Physical Therapy
The evidence supporting the use of physical therapy as a core treatment in the

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**TABLE 1. Key Questions and Evidence Base**

<table>
<thead>
<tr>
<th>Question no.</th>
<th>Question</th>
<th>No. of studies and type of studies</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>What are the benefits and harms of FDA-approved oral pharmacotherapy for the treatment of OA of the hip and knee?</td>
<td>7 SRs and 2 RCTs</td>
</tr>
<tr>
<td>2</td>
<td>What are the benefits and harms and comparative effectiveness of FDA-approved intra-articular injections of pharmacotherapy agents for the treatment of moderate-to-severe OA of the hip and knee?</td>
<td>7 SRs and 8 RCTs</td>
</tr>
<tr>
<td>3</td>
<td>What are the benefits and harms of intra-articular orthobiologics regenerative medicine (stem cell injections or others [eg, platelet-rich plasma, amniotic fluid, and amniotic membrane]) for the treatment of OA of the hip and knee?</td>
<td>4 SRs and 25 RCTs</td>
</tr>
<tr>
<td>4</td>
<td>What are the comparative benefits and harms of topical pharmacotherapy agents vs oral pharmacotherapy for the treatment of OA of the hip and knee?</td>
<td>6 SRs</td>
</tr>
<tr>
<td>5</td>
<td>What are the benefits and harms of tramadol and other opioids as an alternative to or adjunct to nonopioid pharmacotherapies for managing moderately severe-to-severe OA of the hip and knee?</td>
<td>3 SRs and 3 RCTs</td>
</tr>
<tr>
<td>6</td>
<td>What are the benefits and harms of dietary supplements and nutraceuticals for the treatment of OA of the hip and knee?</td>
<td>9 SRs and 8 RCTs</td>
</tr>
<tr>
<td>7</td>
<td>What are the benefits and harms of CIH treatments of OA of the hip and knee as either monotherapy or adjunctive therapy?</td>
<td>6 SRs and 9 RCTs</td>
</tr>
<tr>
<td>8</td>
<td>What diagnostic testing is needed to confirm the diagnosis of OA?</td>
<td>2 diagnostic cohort studies</td>
</tr>
<tr>
<td>9</td>
<td>What are the benefits and harms of electrostimulation devices for hip and knee OA?</td>
<td>1 SR and 4 RCTs</td>
</tr>
<tr>
<td>10</td>
<td>What are the benefits and harms of weight loss on short-term and long-term complications and outcomes of hip and knee OA?</td>
<td>2 SRs and 2 RCTs</td>
</tr>
<tr>
<td>11</td>
<td>What is the comparative effectiveness of physical therapy for OA of the hip and knee?</td>
<td>3 SRs and 13 RCTs</td>
</tr>
<tr>
<td>12</td>
<td>What are the benefits and harms of various self-management interventions for OA of the hip and knee?</td>
<td>6 SRs and 1 RCT</td>
</tr>
</tbody>
</table>

Total evidence base: 131 studies

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

From the 2020 VA/DoD Clinical Practice Guideline for the Non-Surgical Management of Hip & Knee Osteoarthritis,8 with permission.
<table>
<thead>
<tr>
<th>Topic</th>
<th>Sub topic</th>
<th>S. no.</th>
<th>Recommendation</th>
<th>Strength</th>
<th>Category</th>
</tr>
</thead>
<tbody>
<tr>
<td>Diagnosis</td>
<td></td>
<td>1.</td>
<td>We suggest against obtaining magnetic resonance imaging for the diagnosis of osteoarthritis of the hip and knee.</td>
<td>Weak against</td>
<td>Reviewed, new-replaced</td>
</tr>
<tr>
<td>Self-management</td>
<td></td>
<td>2.</td>
<td>We suggest a self-management program, including exercise and weight loss for osteoarthritis of the hip and knee, and bracing for osteoarthritis of the knee.</td>
<td>Weak for</td>
<td>Reviewed, new-replaced</td>
</tr>
<tr>
<td>Physical therapy</td>
<td></td>
<td>3.</td>
<td>We suggest offering physical therapy as part of a comprehensive management plan for patients with osteoarthritis of the hip or knee.</td>
<td>Weak for</td>
<td>Reviewed, amended</td>
</tr>
<tr>
<td>Pharmacotherapy</td>
<td>aa. Topical pharmacotherapy</td>
<td>4.</td>
<td>We recommend offering topical nonsteroidal anti-inflammatory drugs for patients with pain associated with osteoarthritis of the knee.</td>
<td>Strong for</td>
<td>Reviewed, new-added</td>
</tr>
<tr>
<td></td>
<td></td>
<td>5.</td>
<td>There is insufficient evidence to recommend for or against the use of topical nonsteroidal anti-inflammatory drugs for patients with pain associated with osteoarthritis of the hip.</td>
<td>Neither for nor against</td>
<td>Reviewed, new-added</td>
</tr>
<tr>
<td></td>
<td></td>
<td>6.</td>
<td>We suggest offering topical capsaicin for patients with pain associated with osteoarthritis of the knee.</td>
<td>Weak for</td>
<td>Reviewed, amended</td>
</tr>
<tr>
<td></td>
<td></td>
<td>7.</td>
<td>There is insufficient evidence to recommend for or against the use of topical capsaicin for patients with pain associated with osteoarthritis of the hip.</td>
<td>Neither for nor against</td>
<td>Reviewed, amended</td>
</tr>
<tr>
<td></td>
<td>bb. Oral pharmacotherapy</td>
<td>8.</td>
<td>We suggest offering acetaminophen and/or oral nonsteroidal anti-inflammatory drugs for pain associated with osteoarthritis of the hip and knee.</td>
<td>Weak for</td>
<td>Reviewed, new-replaced</td>
</tr>
<tr>
<td></td>
<td>b. Oral Pharmacotherapy</td>
<td>9.</td>
<td>We suggest offering duloxetine as an alternative or adjunctive therapy for patients with an inadequate response or contraindications to acetaminophen or nonsteroidal anti-inflammatory drugs for pain associated with osteoarthritis of the knee.</td>
<td>Weak for</td>
<td>Reviewed, new-replaced</td>
</tr>
<tr>
<td></td>
<td></td>
<td>10.</td>
<td>We suggest against initiating opioids (including tramadol) for pain associated with osteoarthritis of the hip and knee. For patients already on long-term opioid therapy, refer to the current VA/DoD Clinical Practice Guideline for the Management of Opioid Therapy for Chronic Pain.</td>
<td>Weak against</td>
<td>Reviewed, new-replaced</td>
</tr>
<tr>
<td></td>
<td></td>
<td>11.</td>
<td>We suggest offering an intra-articular corticosteroid injection for patients with persistent pain due to osteoarthritis of the knee inadequately relieved by other interventions.</td>
<td>Weak for</td>
<td>Reviewed, new-replaced</td>
</tr>
<tr>
<td></td>
<td>c. Intra-articular injections</td>
<td>12.</td>
<td></td>
<td>Weak for</td>
<td>Reviewed, new-replaced</td>
</tr>
</tbody>
</table>

Continued on next page
<table>
<thead>
<tr>
<th>Topic</th>
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<th>S. no.</th>
<th>Recommendation</th>
<th>Strength</th>
<th>Category</th>
</tr>
</thead>
<tbody>
<tr>
<td>We suggest offering an intra-articular image-guided corticosteroid injection for patients with persistent pain due to osteoarthritis of the hip inadequately relieved by other interventions.</td>
<td></td>
<td>13.</td>
<td>We suggest offering intra-articular viscosupplementation injection(s) for patients with persistent pain due to osteoarthritis of the knee inadequately relieved by other interventions.</td>
<td>Weak for</td>
<td>Reviewed, new-replaced</td>
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<tr>
<td>We suggest against the use of intra-articular viscosupplementation injection(s) of the hip.</td>
<td></td>
<td>14.</td>
<td></td>
<td>Weak against</td>
<td>Reviewed, new-replaced</td>
</tr>
<tr>
<td>Orthobiologics</td>
<td></td>
<td>15.</td>
<td>There is insufficient evidence to recommend for or against platelet-rich plasma injections for the treatment of osteoarthritis of the hip or knee.</td>
<td>Neither for nor against</td>
<td>Reviewed, new-added</td>
</tr>
<tr>
<td>We suggest against stem cell injections (eg, mesenchymal, adipose-derived, and bone marrow-derived) for the treatment of osteoarthritis of the knee.</td>
<td></td>
<td>16.</td>
<td></td>
<td>Weak against</td>
<td>Reviewed, new-added</td>
</tr>
<tr>
<td>Complementary and Integrative Health, Dietary Supplements, and Nutraceuticals</td>
<td></td>
<td>17.</td>
<td>There is insufficient evidence to recommend for or against the use of the following dietary supplements or nutraceuticals for the treatment of osteoarthritis of the hip or knee:</td>
<td>Neither for nor against</td>
<td>Reviewed, new-replaced</td>
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<tr>
<td>- Avocado and soybean extract</td>
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<td>- Boswellia serrata</td>
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<td>- Cannabidiol (CBD oil)</td>
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<td>- Chondroitin</td>
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<tr>
<td>- Curcumin (active component of turmeric)</td>
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<td>- Collagen</td>
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<td>- Glucosamine</td>
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<tr>
<td>- Glucosamine plus chondroitin</td>
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<tr>
<td>- Methylsulfonylmethane</td>
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<td>- Omega-3 fatty acid</td>
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<tr>
<td>- Pycnogenol (pine bark)</td>
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<td></td>
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<tr>
<td>- Rosehip</td>
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<tr>
<td>- Traditional Chinese medicine</td>
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<tr>
<td>- Vitamin D</td>
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<tr>
<td>- Vitamin E</td>
<td></td>
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<td></td>
<td></td>
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<tr>
<td>- Willow bark extract</td>
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</tbody>
</table>
management of patients with OA of the hip and knee is extensive. A randomized controlled trial (RCT) by Deyle et al.\(^{23}\) compared physical therapy to glucocorticoid injections in the US Military Health System and the results favored the physical therapy group on both primary and secondary outcome measures at 1 year. Individualized physical therapy management plans have been found to reduce pain and improve function in patients with hip or knee OA and should augment medical and pharmacological approaches.\(^{17,18,24}\)

Although physical therapy for knee and hip OA has traditionally been delivered via individual in-person appointments, alternative delivery models of care such as group visits, Internet-based, and telephone-based approaches are increasingly used without any loss of effectiveness.\(^{25-28}\) After reviewing this evidence, it was clear that physical therapy is an important part of a comprehensive management plan for patients with OA of the hip or knee.

**Pharmacotherapy**

**Topical Agents**

Nonsteroidal Anti-inflammatory Drugs. The pain-relieving benefits of oral nonsteroidal anti-inflammatory drugs (NSAIDs) are well known; however, topical NSAIDs can also have a valuable role in managing OA pain in the knee. Diclofenac is the only commercially manufactured topical NSAID currently available in the United States and comes in various formulations. A systematic review (SR) by Derry et al.\(^{29}\) reported topical diclofenac to be superior to placebo and equivalent to oral diclofenac at reducing pain associated with OA of the knee. Treatment with topical NSAIDs was associated with markedly fewer gastrointestinal adverse events but had substantially more local adverse events than with oral NSAIDs.\(^{29,30}\) Safety data are largely limited to 12-week follow-up; however, 2 open-label studies in Derry et al.\(^{29}\) found the safety profile of topical diclofenac at 1 year to be consistent with results at 12 weeks, helping us come to a “strong for” recommendation in patients with knee OA pain.
Capsaicin. Topical capsaicin has also been used for pain management, including mild-to-moderate pain associated with OA of the knee. Capsaicin, which is obtained from chili peppers, works by depleting substance P (SP) in a reversible fashion. Substance P, a neuropeptide, plays a role in pain pathogenesis and intensity. When applied capsaicin can cause pain and a burning feeling to the local area as it spurs SP release, but continued utilization results in SP depletion and a reduction in pain. Because of this, capsaicin may need to be used continuously for 2 to 4 weeks before a therapeutic effect is experienced. Adverse events occur at the site of application and may include burning or stinging. An SR by Laslett and Jones included 5 RCTs comparing topical capsaicin 0.025% to 0.075% with placebo. Evidence from the SR supports at least a moderate effect of capsaicin (standard mean difference, 0.44) in reducing moderate knee pain associated with OA. In these SRs, nearly all the patients were treated for knee OA pain; therefore, we suggest offering capsaicin to patients in this population.

Our evidence review did not find sufficient evidence that evaluated the effect of topical pharmacotherapy on pain associated with OA of the hip. Given the depth of the hip joint, it is unlikely a topical agent would provide much benefit; however, given the lack of evidence, we are unable to recommend for or against the use of either topical NSAIDs or capsaicin for hip OA.

Oral Agents

Acetaminophen. Acetaminophen is an analgesic and antipyretic without substantial anti-inflammatory activity. Some prescribers may prefer it for patients with more mild disease or mild-to-moderate symptoms of OA or with contraindications to NSAID therapy. A network meta-analysis by da Costa et al and an SR by Leopoldino et al revealed clinically insignificant differences for acetaminophen vs placebo in reducing pain and improving function in patients with OA of the hip and/or knee. In a second SR network meta-analysis in patients with knee OA only, Jung et al noted substantial benefits of acetaminophen in reducing pain in patients with mild-to-moderate pain. In this SR, the benefit of acetaminophen ranked higher than that of some NSAIDs in patients with mild-to-moderate pain associated with knee OA.

Oral NSAIDs. Oral NSAIDs are frequently used to manage OA pain and patients usually tolerate them well. Three SRs with network meta-analyses for effectiveness and 2 SRs
with meta-analyses focusing on safety support the recommendation to consider NSAID therapy.\textsuperscript{32,34-37} Nonsteroidal anti-inflammatory drugs have also exhibited superiority to acetaminophen in those with moderate-to-severe OA pain.\textsuperscript{34}

On the basis of the evidence, we suggest offering acetaminophen and/or oral NSAIDs for pain associated with OA of the hip and knee.

**Duloxetine.** Duloxetine is a selective serotonin and norepinephrine reuptake inhibitor that is commonly used to treat depression, anxiety, and pain. An SR by Chen et al\textsuperscript{38} evaluated 6 RCTs and found that duloxetine achieved significant reductions in pain outcomes for patients with OA. The same SR found a statistically significant improvement in physical function for patients taking duloxetine. As a result, we suggest the use of duloxetine in treating patients with OA.

Patients should be educated that duloxetine is to be taken daily (not as needed) and discontinued only after consultation with their prescribing provider. When discontinuing, duloxetine should be tapered over at least 2 to 4 weeks for those treated with therapy longer than 3 weeks.\textsuperscript{39} Duloxetine should be initiated at doses 30 mg/d or more and increased to a goal of 60 mg/d.

**Opioids.** Current evidence does not support using opioids, including tramadol, to manage pain associated with OA of the hip and knee. Systematic reviews by da Costa et al, Fuggle et al, and Toupin et al and RCTs by Banerjee et al, Rauk et al, and Spierings et al compared various opioids (ie, codeine, transdermal fentanyl, hydromorphone, morphine, oxycodone, oxymorphone, tramadol, tapentadol) with no treatment, placebo, or active control for the treatment of hip or knee OA.\textsuperscript{40-45} Although opioid treatment led to a statistically significant reduction in pain intensity, the reduction did not reach the benchmark for clinical significance set by da Costa et al\textsuperscript{45} (standard mean difference, 0.37, corresponding to 0.9 cm reduction on a 10-cm visual analog scale). Treatment with all opioids, except for tapentadol, also improved physical function more than placebo, but these improvements were relatively small.\textsuperscript{40-45}

The opioids mentioned above all led to a higher risk for adverse events than did placebo (relative risk, 1.28-1.69).\textsuperscript{40-45} Studies also assessed other safety outcomes including withdrawal symptoms, study withdrawal due to adverse events, and serious adverse events. These safety outcomes were all significantly worse in the opioid treatment groups vs placebo. As a result of finding limited benefit with a high risk of adverse effects, the work group recommends against using opioids, including tramadol, to manage OA pain.
Injection Therapies

Corticosteroids. Intra-articular corticosteroids have been found to reduce joint pain and improve function in OA-related knee pain. Methylprednisolone, when compared with placebo, improved knee pain and function at 4 and 24 weeks, whereas triamcinolone improved pain and function at 6 weeks but not 12 weeks. These effects are time limited without long-term improvement at 2-year follow-up. Comparably, intra-articular corticosteroid injections (CSIs) for patients with persistent OA-related hip pain were also found to be beneficial. However, because of joint depth and proximity to vascular and neural structures, hip injections require image guidance to ensure safety but knee injections do not. Few adverse events were reported from either knee or hip CSIs when compared with placebo at 6 months; however, providers must take into account the potential long-term negative effects on bone health, joint structure, and meniscal thickness associated with repeat intra-articular corticosteroid administration.

We suggest offering CSIs in patients with persistent knee and/or hip OA pain, with hip injections being image guided.

This CPG’s systematic evidence review did not identify any new SRs or RCTs examining whether CSI should be avoided in the 3 months before joint replacement surgery of the knee. Although joint injection and arthroplasty can both be complicated by infection, there are limited data describing an elevated risk of deep joint infection when intra-articular CSI is given before joint (eg, knee and hip) arthroplasty.

Hyaluronic Acid. Viscosupplementation injections (VSIs) are designed as synthetic

### TABLE 4. Second-line and Combination Pharmacotherapy

<table>
<thead>
<tr>
<th>Second-line or combination treatments:</th>
</tr>
</thead>
<tbody>
<tr>
<td>● Consider combining 2 initial treatments (see Table 3)</td>
</tr>
<tr>
<td>● Consider intra-articular CSI for knee and hip OA:</td>
</tr>
<tr>
<td>○ Corticosteroid injection should be avoided for 3 mo preceding joint replacement surgery</td>
</tr>
<tr>
<td>○ Corticosteroid injection for the hip should be image guided</td>
</tr>
<tr>
<td>● Duloxetine: consider adding duloxetine as an alternative or adjunct to initial treatments (see Table 3)</td>
</tr>
<tr>
<td>● Consider intra-articular VSI in patients with inadequately controlled knee pain with core pharmacological and nonpharmacological treatments</td>
</tr>
</tbody>
</table>

CSI, corticosteroid injection; OA, osteoarthritis; VSI, viscosupplementation injection.

From the 2020 VA/DoD Clinical Practice Guideline for the Non-Surgical Management of Hip & Knee Osteoarthritis, with permission.

### TABLE 5. Pharmacotherapy Considerations

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

CKD, chronic kidney disease; COX-2, cyclooxygenase 2; CVD, cardiovascular disease; DoD, Department of Defense; eGFR, estimated glomerular filtration rate; NSAID, nonsteroidal anti-inflammatory drug; PPI, proton pump inhibitor; UGI, upper gastrointestinal tract; VA, Department of Veterans Affairs.

From the 2020 VA/DoD Clinical Practice Guideline for the Non-Surgical Management of Hip & Knee Osteoarthritis, with permission.
hyaluronic acid to provide lubrication in the setting of OA. They are typically indicated when analgesic agents and nonpharmacological treatments have failed to improve symptoms of OA. For patients with pain related to OA of the knee, the use of VSIs may improve pain and function. Recent evidence comparing VSIs with CSIs found that CSIs provided longer-term pain relief at 6, 9, and 12 months with similar risk profiles. This pattern was reported again in an RCT by Trueba Davallillo et al. However, 2 RCTs, Campos et al and Siddharth and Harleen, reported no difference in pain relief or function at 1 and 6 months comparing VSI with CSI. For pain related to OA of the hip, an SR by Leite et al evaluated 4 RCTs comparing VSI with placebo and found no difference in pain relief at all time points. As such, the work group recommended offering intra-articular VSIs for persistent pain related to knee OA, but not for OA-related hip pain.

Orthobiologics

Platelet-rich Plasma. Platelet-rich plasma (PRP) is a novel regenerative medicine treatment option with a physiological mechanism of action that is hypothesized to involve direct delivery of multiple growth factors implicated in soft tissue repair. The studies evaluating the use of PRP in the treatment of knee OA had mixed results. Our evidence review found 1 SR of 15 trials and 7 additional RCTs. Some of the studies reported no benefit, whereas others reported small benefits from PRP. In addition, there were no serious adverse effects reported in the studies. As for the treatment of hip OA, there is limited research on the use of PRP. Ye et al found that PRP led to statistically significant reductions in pain compared with hyaluronic acid at 2 months but not at 6 and 12 months. The clinical importance of this statistically significant difference is unclear. Additionally, the SR did not find any difference in function between PRP and hyaluronic acid at all follow-up periods. Because the results of the studies were inconsistent, we were unable to recommend for or against the use of PRP for hip or knee OA.

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

Research in this area is in its infancy. This CPG’s systematic evidence review identified 1 SR and 8 RCTs that addressed the benefits and harms of cell therapy intra-articular injections in patients with knee OA; however, it did not identify relevant evidence on cell therapy in patients with hip OA. The studies revealed statistically significant improvements in pain and function; however, it was unclear whether these results were clinically significant. At least one of the studies did not find significant differences in MRI evaluations between the joints that had been injected and the controls. The body of evidence had limitations, including serious inconsistency and imprecision with study designs and outcome measures. We were concerned about blinding, incomplete outcome data collection, selective reporting, other biases, and unclear randomization and allocation concealment methods. Limitations of the evidence base also included a lack of studies in patients with hip OA, limited evidence for interventions in patients with severe knee OA, lack of reporting on radiography-related outcomes, and no studies comparing interventions with CSIs. As a result of these limitations, we found that the current evidence base does not support the use of cell therapy injections for the treatment of OA of the knee and we suggest against their use.

Complementary and Integrative Health

There is insufficient evidence to recommend for or against the use of the any complementary and integrative health interventions that we reviewed, to include dietary supplements.
or nutraceuticals, for the treatment of OA of the hip or knee. A list of the interventions for which evidence was reviewed can be found in recommendations 17, 18, and 19 (Table 2). Concerning dietary supplements and nutraceutical agents, the evidence is lacking in methodological rigor and clear protocol implementation. For these products to be viable, consistent, and trusted therapeutic options that can be measured and evaluated, clarity is needed in product content and dosage and assurance is needed in purity and quality.

CONCLUSION
Clinical practice guidelines were developed jointly by the VA and DoD to address the nonoperative treatment of OA of the hip and knee, focusing on imaging for diagnosis, physical therapy, pharmacotherapy, injection-based therapy, and orthobiologics. The group strongly advocates against the use of MRI for the diagnosis of hip and knee OA. There is clear evidence to support the use of a self-management program as well as physical therapy in the treatment of OA of the hip and knee. The work group looked at multiple pharmacotherapies and found evidence to support the use of topical NSAIDs and capsaicin for knee OA pain and oral NSAIDs, acetaminophen, and duloxetine for either knee or hip OA pain. The group recommends against the use of opioids or tramadol in the management of pain in hip and knee OA. The work group also found evidence to support the use of intra-articular corticosteroids in the management of OA of the hip and knee and the use of hyaluronic acid in the management of knee OA. There was insufficient evidence to support the use of PRP injections in the treatment of knee OA, but we suggest against the use of stem cell injections in the treatment of hip and knee OA. Lastly, there was insufficient evidence to recommend for or against any complementary or integrative health intervention included in our review.

We acknowledge that there is a lack of quality evidence regarding this topic and have included the following as research priorities: long-term effectiveness and safety studies longer than 12 weeks, comparative effectiveness research of both pharmacological and nonpharmacological options, optimal timing for the delivery of physical therapy services within disease progression, and further safety and efficacy trials for orthobiologics and other emerging biologic treatments. By providing these guidelines, we aim to provide the primary care team with the most up-to-date resources. This will help the team more efficiently assess the patient’s condition and determine optimal treatments, improve quality of life and health outcomes, and keep preventable complications and morbidity to a minimum, all while highlighting the use of patient-centered care.8

Abbreviations and Acronyms: CPG, clinical practice guideline; CSI, corticosteroid injection; DoD, US Department of Defense; MRI, magnetic resonance imaging; NSAID, nonsteroidal anti-inflammatory drug; OA, osteoarthritis; PRP, platelet-rich plasma; RCT, randomized controlled trial; SP, substance P; SR, systematic review; VA, US Department of Veterans Affairs; VSI, viscosupplementation injection

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Correspondence: Address to Adam Edward Lang, PharmD, Department of Primary Care, McDonald Army Health Center, 576 Jefferson Ave, Office L028B, Fort Eustis, VA 23604 (a.edward.lang@gmail.com; Twitter: @AdamEdwardLang).

ORCID
Adam Edward Lang: https://orcid.org/0000-0002-4347-6514; Jess Edison: https://orcid.org/0000-0002-5260-0273

REFERENCES
6. Vigeon RL, Nepple JJ, Eftekhary N, Viggiani C. What is the association of elite sporting activities with the

www.mayoclinicproceedings.org
44. Banerjee M, Mondal S, Sarkar R, Mondal H, Bhattacharya K. Comparative study of efficacy and safety of tapentadol versus