Washington State Health Care Authority

FINAL Key Questions and Background

Hyaluronic acid/viscosupplementation, platelet-rich plasma injections for knee or hip osteoarthritis

Background

Osteoarthritis (OA) is one of the most common disabilities affecting people in the United States, with roughly 32.5 million Americans currently affected.[1] This number is projected to grow in the coming years, with estimates as high as 29.5% of US adults over the age of 45 by 2032.[2] Osteoarthritis, which most commonly occurs in the knee and hip, often causes pain, fatigue, disability, and general limitations to daily life activities that impact physical, mental, and emotional wellbeing.[1] There is no cure for this condition and, as such, treatment can become considerably expensive long term. Healthcare cost due to osteoarthritis in the United States is estimated at $45.4 billion per year, with affected individuals paying an additional $1778 per year in healthcare costs on average.[3] Reduced ability to work results in additional wage loss of $1114 per year, more than double that of those without osteoarthritis ($517).[3]

Osteoarthritis is a progressive disease that may often lead to joint failure requiring total joint replacement. Given the generally slow rate of progression of the disease, however, care in the interim before eligibility or need for replacement surgery is of the utmost importance. Conservative management of osteoarthritis commonly includes exercise and physical therapy, use of non-steroidal anti-inflammatory drugs (NSAIDs) or acetaminophen, use of supportive devices, weight loss, corticosteroid injections and may include hyaluronic acid (HA, viscosupplementation) and intra-articular platelet-rich plasma (PRP).[4] Exercise and physical therapy are currently considered front-line treatments for knee and hip osteoarthritis and provide considerable benefit both for pain relief and maintenance of functionality, but may be difficult to begin for overweight or obese individuals and time commitments and costs may present challenges to some.[5] Pain medications such as NSAIDs and acetaminophen are commonly recommended or prescribed for relief of pain and inflammation caused by osteoarthritis. These medications are generally easy to access and carry relatively low cost, but long-term use increases risk of potentially serious adverse events such as stomach, kidney, and liver damage, heart attack, and stroke.[6,7] Supportive devices are commonly used by osteoarthritis patients, with between 40% and 76% of patients utilizing an assisted walking device such as a cane, walker, or crutches.[8] Evidence on the efficacy of these devices for pain reduction and slowing of disease progression, however, is limited and contradictory to professional consensus.[8,9] Weight loss has shown to be effective at reducing pain and increasing functionality in osteoarthritis patients, but this benefit is only available to overweight and obese individuals and there may be significant barriers to achieving weight loss, including pain and reduced functionality from the disease itself.[10] Less commonly, conservative care may include use of opiate medications, acupuncture, and supplements such as turmeric or glucosamine chondroitin.

Intra-articular corticosteroid injections may be effective at reducing pain in knee and hip osteoarthritis patients in short- and medium-term settings, but carry risk of adverse events such as pain flare and rapid destructive osteoarthritis of the joint[11,12] as well as increased risk of post-operative surgical infection months following injection, transient increases in blood sugar and hypertension and transient decrease in immune response. Viscosupplementation is an increasingly popular treatment for knee and hip osteoarthritis over the last twenty years. Viscosupplementation with intra-articular hyaluronic acid (IAHA) is most commonly provided to individuals who are unable to utilize or do not respond well to other front-line or preferred treatments; it may provide anti-inflammatory, analgesic, and

chondroprotective effects.[13] Hyaluronic acid products require approval from the Food and Drug Administration (FDA), which notes numerous mild to moderate adverse events such as swelling, pain, and edema at injection site and lack of sufficient evidence for non-knee indications.[14] PRP also shows promise for improving osteoarthritis symptoms for longer intervals than similar intra-articular treatments with a similar adverse event risk profile, particularly in younger patients, but the overall evidence base utilized for many reviews and recommendations may be outdated.[15]

While IAHA and PRP are not curative, they may provide some longer-term relief compared with some primary treatment modalities and may be more acceptable to some patients. Previous reviews of the effectiveness of HA and PRP report mixed results on the effectiveness of these for pain reduction and/or functional improvement. There has been a considerable increase in available evidence on the use of HA and PRP for knee and hip OA since the publication of prior reviews for the Washington State Health Technology Assessment Program in 2013 and 2016, respectively, and re-review of the evidence is therefore warranted.

Policy context

Health Technology Assessments (HTAs) on HA/viscosupplementation and PRP were performed in 2013 and 2016 respectively and reviewed by the Washington Health Technology Assessment Program (HTAP). The prior HA report (2013) focused on patients with knee OA. The prior PRP report (2016) included osteoarthritis as well as a range of other musculoskeletal conditions. The focus of this re-review will be on symptomatic adults with knee or hip OA who may be treated with HA or PRP as a primary form of treatment or in conjunction with conservative therapies. The HTAP is interested in re-evaluation of these treatments in patients with knee or hip osteoarthritis given that additional evidence has been published subsequent to the original reviews. Other musculoskeletal conditions will not be part of this re-review. Given the chronic and progressive nature of OA, the report will focus on RCTs that report on persistence of symptom relief or functional improvement one or more months post treatment.

The DRAFT Key Questions and Scope were published on the HTAP website in October 2022. Public comments were reviewed. None led to changes in the questions or scope. All citations suggested by commenters will be evaluated for inclusion based on the final questions and scope below.

Final Key Questions and Scope of this HTA

1. In adults with symptoms related to knee or hip osteoarthritis considered for treatment **with hyaluronic acid/viscosupplementation (HA)**
    a. What is the effectiveness of HA compared with placebo/sham, common conservative treatments, PRP, or no treatment in the short and longer-term?
    b. What is the evidence regarding short- and long-term harms and complications of HA compared with placebo/sham, common conservative treatments, PRP, or no treatment?
    c. Is there evidence of differential efficacy, effectiveness, or safety of HA compared with placebo/sham, commonly used conservative treatments (e.g., NSAIDs, exercise, physical therapy), PRP, or no treatment by factors such as age, race/ethnicity, gender, primary versus secondary OA, disease severity and duration, weight (body mass index), prior treatments or contraindications to common conservative care options?

d. What is the evidence of cost-effectiveness of HA compared with placebo/sham, PRP, common conservative treatments, or no treatment?

2. In adults with symptoms related to knee or hip osteoarthritis considered for treatment **with platelet-rich plasma (PRP)**

a. What is the effectiveness of PRP compared with placebo/sham, common conservative treatments, treatments other than HA, or no treatment in the short and longer-term?

b. What is the evidence regarding short- and long-term harms and complications of PRP compared placebo/sham, common conservative treatments, treatments other than HA, or no treatment?

c. Is there evidence of differential efficacy, effectiveness, or safety of PRP compared with, placebo/sham, commonly used conservative treatments (e.g., NSAIDs, exercise, physical therapy), treatments other than HA, or no treatment by factors such age, race/ethnicity, gender, primary versus secondary OA, disease severity and duration, weight (body mass index), prior treatments or contraindications to common conservative care options?

d. What is the evidence of cost-effectiveness of PRP compared with placebo/sham, common conservative treatments, or no treatment?

PICOTS/Scope:

Study Component	Inclusion	Exclusion
Population	Adults with symptomatic knee or hip osteoarthritis Subpopulations based on patient characteristics, primary or secondary OA, disease severity/duration, prior treatments, contraindications to common conservative care options	• Conditions other than knee or hip OA • Patients <18 years old • Asymptomatic individuals
Intervention	Autologous PRP injection(s) or hyaluronic acid (HA) (viscosupplementation) injection(s) used as the primary intervention or in conjunction with common conservative care options	• Non-FDA-approved HA (viscosupplementation) formulations; products undergoing phase III trials may be considered • PRP or HA used in conjunction with another intervention not listed for inclusion (e.g., open, arthroscopic or minimally invasive surgery, invasive procedures are not included) • Combinations of HA with PRP together • Other biologics (growth factor injections [., plasma rich in growth factor], "stem cell" injections, etc.)
Comparator	• Common conservative treatment(s) (e.g., NSAIDs, oral pain medications, exercise, physical therapy, weight loss) which may be included in usual care	• Combinations of HA with PRP together • Other biologics (growth factor injections [e.g., plasma rich in growth factor], bone marrow aspirate/bone marrow aspirate concentrate, blood plasma, autologous

Study Component	Inclusion	Exclusion
	• Arthroscopic lavage and/or debridement • Prolotherapy • Corticosteroid injection • Placebo or sham • No treatment	blood products [e.g., autologous conditioned serum"] medicinal signaling cells, mesenchymal stem cells, "stem cell", adipose, fat, or microfat injections); peptide injections • Ozone treatment • Non-FDA approved treatments • Herbal treatments • Acupuncture • Nerve ablation
Outcomes	**Primary** • Function • Pain • Need for secondary invasive procedures (e.g., surgery) • Adverse events or harms **Secondary** • Symptom Recurrence (e.g., persistent or increased pain, reduced function) resulting in need for additional injection of HA or PRP within 2 months after protocol completion • Quality of life • Medication use • Return to normal activities (sports, work, or activity level) **Economic** • Cost-effectiveness (e.g., cost per improved outcome), cost-utility (e.g., cost per quality adjusted life year (QALY), incremental cost effectiveness ratio (ICER) outcome	• Non-clinical outcomes • Non-validated measures (e.g., for pain, function, QOL)
Timing	Review will focus on persistence of relief 1 or more months post-treatment	
Study design	**Focus will be on studies with the least potential for bias with ≥ 1 month post treatment results** **Key Questions 1 and 2 parts a and b:** • High quality systematic reviews of RCTs will be considered if available and they address the key questions. • Randomized controlled trials (RCTs) • In the absence of RCTs, high quality non-randomized comparative studies will be	• Indirect comparisons • Comparisons with historical cohorts • Noncomparative studies (case series, single arm studies, pre-post) • Nonrandomized studies which do not control for confounding • Incomplete economic evaluations such as costing studies • Studies with fewer than 30 patients per treatment group • Case reports

Study Component	Inclusion	Exclusion
	considered in the absence of RCTs with a focus on comparative prospective studies **Key Question 1b and 2b:** • KQ2: In the absence of RCTs, high-quality non-randomized studies designed specifically to evaluate harms/adverse events that are rare or occur long-term **Key Question 1c and 2c:** • RCTs which present results for both intervention and comparator such that they are stratified on patient or other characteristics of interest and test for interaction. **Key Question 1d and 2d:** Only full, formal economic studies (i.e., cost-effectiveness, cost-utility, cost-minimization, and cost-benefit studies) will be considered.	• Studies in which <80% of patients have a condition of interest • Studies that do not report on primary outcomes or harms
Publication	• Studies published in English in peer reviewed journals or publicly available FDA reports (e.g., SSED)	• Abstracts, conference proceedings, editorials, letters • Duplicate publications of the same study which do not report on different outcomes • Single reports from multicenter trials • White papers • Narrative reviews • Articles identified as preliminary reports when results are published in later versions

Study Component	Inclusion	Exclusion
Population	Adults with symptomatic knee or hip osteoarthritis Subpopulations based on patient characteristics, primary or secondary OA, disease severity/duration, prior treatments, contraindications to common conservative care options	• Conditions other than knee or hip OA • Patients <18 years old • Asymptomatic individuals
Intervention	Autologous PRP injection(s) or hyaluronic acid (HA) (viscosupplementation) injection(s) used as the primary intervention or in conjunction with common conservative care options	• Non-FDA-approved HA (viscosupplementation) formulations; products undergoing phase III trials may be considered • PRP or HA used in conjunction with another intervention not listed for inclusion (e.g., open, arthroscopic or minimally invasive surgery, invasive procedures are not included) • Combinations of HA with PRP together

Study Component	Inclusion	Exclusion
		• Other biologics (growth factor injections [., plasma rich in growth factor], "stem cell" injections, etc.)
Comparator	• Common conservative treatment(s) (e.g., NSAIDs, oral pain medications, exercise, physical therapy, weight loss) which may be included in usual care • Arthroscopic lavage and/or debridement • Prolotherapy • Corticosteroid injection • Placebo or sham • No treatment	• Combinations of HA with PRP together • Other biologics (growth factor injections [e.g., plasma rich in growth factor], bone marrow aspirate/bone marrow aspirate concentrate, blood plasma, autologous blood products [e.g., autologous conditioned serum"] medicinal signaling cells, mesenchymal stem cells, "stem cell", adipose, fat, or microfat injections); peptide injections • Ozone treatment • Non-FDA approved treatments • Herbal treatments • Acupuncture • Nerve ablation
Outcomes	**Primary** • Function • Pain • Need for secondary invasive procedures (e.g., surgery) • Adverse events or harms **Secondary** • Symptom Recurrence (e.g., persistent or increased pain, reduced function) resulting in need for additional injection of HA or PRP within 2 months after protocol completion • Quality of life • Medication use • Return to normal activities (sports, work, or activity level) **Economic** • Cost-effectiveness (e.g., cost per improved outcome), cost-utility (e.g., cost per quality adjusted life year (QALY), incremental cost effectiveness ratio (ICER) outcome	• Non-clinical outcomes • Non-validated measures (e.g., for pain, function, QOL)
Timing	Review will focus on persistence of relief 1 or more months post-treatment	

Study Component	Inclusion	Exclusion
Study design	**Focus will be on studies with the least potential for bias with ≥ 1 month post treatment results** **Key Questions 1 and 2 parts a and b:** • High quality systematic reviews of RCTs will be considered if available and they address the key questions. • Randomized controlled trials (RCTs) • In the absence of RCTs, high quality non-randomized comparative studies will be considered in the absence of RCTs with a focus on comparative prospective studies **Key Question 1b and 2b:** • KQ2: In the absence of RCTs, high-quality non-randomized studies designed specifically to evaluate harms/adverse events that are rare or occur long-term **Key Question 1c and 2c:** • RCTs which present results for both intervention and comparator such that they are stratified on patient or other characteristics of interest and test for interaction. **Key Question 1d and 2d:** Only full, formal economic studies (i.e., cost-effectiveness, cost-utility, cost-minimization, and cost-benefit studies) will be considered.	• Indirect comparisons • Comparisons with historical cohorts • Noncomparative studies (case series, single arm studies, pre-post) • Nonrandomized studies which do not control for confounding • Incomplete economic evaluations such as costing studies • Studies with fewer than 30 patients per treatment group • Case reports • Studies in which <80% of patients have a condition of interest • Studies that do not report on primary outcomes or harms
Publication	• Studies published in English in peer reviewed journals or publicly available FDA reports (e.g., SSED)	• Abstracts, conference proceedings, editorials, letters • Duplicate publications of the same study which do not report on different outcomes • Single reports from multicenter trials • White papers • Narrative reviews • Articles identified as preliminary reports when results are published in later versions

References

1. Osteoarthritis Action Alliance, Thurston Arthritis Research Center at the University of North Carolina. OA Prevalence and Burden - Osteoarthritis Action Alliance. OA. Published 2021. Accessed September 21, 2022. https://oaaction.unc.edu/oa-module/oa-prevalence-and-burden/
2. Turkiewicz A, Petersson IF, Björk J, et al. Current and future impact of osteoarthritis on health

care: a population-based study with projections to year 2032. *Osteoarthr Cartil*. 2014;22(11):1826-1832. doi:10.1016/J.JOCA.2014.07.015
3. Zhao X, Shah D, Gandhi K, et al. Clinical, humanistic, and economic burden of osteoarthritis among noninstitutionalized adults in the United States. *Osteoarthr Cartil*. 2019;27(11):1618-1626. doi:10.1016/j.joca.2019.07.002
4. Centers for Disease Control, Prevention. Osteoarthritis (CDC). *Website*. Published online 2015:Osteoarthritis (OA). Accessed September 21, 2022. https://www.cdc.gov/arthritis/types/osteoarthritis.htm
5. Skou ST, Roos EM. Physical therapy for patients with knee and hip osteoarthritis: supervised, active treatment is current best practice. *Clin Exp Rheumatol*. 2019;37(5):112-117. Accessed September 21, 2022. https://www.clinexprheumatol.org/abstract.asp?a=14740
6. Da Costa BR, Pereira T V., Saadat P, et al. Effectiveness and safety of non-steroidal anti-inflammatory drugs and opioid treatment for knee and hip osteoarthritis: network meta-analysis. *BMJ*. 2021;375. doi:10.1136/BMJ.N2321
7. Can arthritis pain medications be harmful? - Mayo Clinic. Accessed September 21, 2022. https://www.mayoclinic.org/diseases-conditions/arthritis/expert-answers/arthritis-pain-medications/faq-20058391
8. Carbone LD, Satterfield S, Liu C, et al. Assistive Walking Device Use and Knee Osteoarthritis: the Health, Aging, and Body Composition Study (Health ABC Study). *Arch Phys Med Rehabil*. 2013;94(2):332. doi:10.1016/J.APMR.2012.09.021
9. Anandacoomarasamy A, March L. Current Evidence for Osteoarthritis Treatments. *Ther Adv Musculoskelet Dis*. 2010;2(1):17. doi:10.1177/1759720X09359889
10. Bliddal H, Leeds AR, Christensen R. Osteoarthritis, obesity and weight loss: evidence, hypotheses and horizons – a scoping review. *Obes Rev*. 2014;15(7):578. doi:10.1111/OBR.12173
11. Arroll B, Goodyear-Smith F. Corticosteroid injections for osteoarthritis of the knee: meta-analysis. *BMJ Br Med J*. 2004;328(7444):869. doi:10.1136/BMJ.38039.573970.7C
12. Choueiri M, Chevalier X, Eymard F. Intraarticular Corticosteroids for Hip Osteoarthritis: AReview. *Cartilage*. 2021;13(1 Suppl):122S. doi:10.1177/1947603520951634
13. Food and Drug Administration. Federal Register :: Intent To Consider the Appropriate Classification of Hyaluronic Acid Intra-articular Products Intended for the Treatment of Pain in Osteoarthritis of the Knee Based on Scientific Evidence. Published 2018. Accessed September 21, 2022. https://www.federalregister.gov/documents/2018/12/18/2018-27351/intent-to-consider-the-appropriate-classification-of-hyaluronic-acid-intra-articular-products
14. Margerrison E, Argentieri M, Kommala D, Schabowsky CN. Hyaluronic Acid (HA) Safety Profile Report Details Date of Submission ECRI Corporate Governance Project Manager. Published online 2021.
15. Bennell KL, Hunter DJ, Paterson KL. Platelet-Rich Plasma for the Management of Hip and Knee Osteoarthritis. *Curr Rheumatol Rep*. 2017;19(5). doi:10.1007/S11926-017-0652-X