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**CADTH RAPID RESPONSE REPORT:**
**SUMMARY WITH CRITICAL APPRAISAL**

# Viscosupplementation for Knee Osteoarthritis: A Review of Clinical and Cost-Effectiveness and Guidelines


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## Context and Policy Issues

There are more than 4.6 million people living with osteoarthritis (OA) in Canada, and this number is expected to rise over the next 30 years to more than 10 million, or more than one in four people.[1] In 2009, 29.4% of Canadians reported being diagnosed with knee OA, with prevalence rising to 48.7% in those 65 years and older.[2]

OA is a major source of pain, severely impacting health-related quality of life (QoL) and productivity for affected individuals.[1] Therapeutic goals in treatment for patients with knee OA include reducing pain, enhancing function, and improving QoL.[3]

Non-pharmacological treatments for patients with symptomatic early-stage knee OA include exercise, weight loss, shoe insoles, acupuncture, and education.[4] When these interventions are no longer effective, pharmacological treatments may be prescribed, including Paracetamol, oral and topical non-steroidal anti-inflammatory drugs (NSAIDS), opioid analgesics, and topical capsaicin.[4] As the disease progresses, intra-articular (IA) injections including corticosteroids (CS) and hyaluronic acid (HA) may be used.[4] Surgery, including arthroscopy, osteotomy, and uni-compartmental and total joint replacement is generally indicted for end-stage knee OA that is resistant to other measures.[4]

Viscosupplementation is a medical procedure during which HA, also known as hyaluronate or hyalunoran, is injected into a joint to treat the symptoms of OA.[5] HA is a large viscoelastic glycosaminoglycan molecule that is found naturally in synovial fluid and cartilage, important for shock absorption, traumatic energy dissipation, protective coating of the articular cartilage surface, and lubrication.[6] People with knee OA tend to have lower concentrations of HA.[5,6]

Several HA agents are available, with varying molecular weights, and recommended treatment course.[3] Single injection HAs, and HA agents requiring three to five injections per treatment course are available.

The purpose of this review is to evaluate the clinical and cost-effectiveness of HA relative to other knee OA interventions, and to review evidence-based guidelines for the use of IA HA for knee OA.

## Research Questions

1. What is the clinical effectiveness of viscosupplementation for the treatment of adults with osteoarthritis of the knee?
2. What is the cost-effectiveness of viscosupplementation for the treatment of adults with osteoarthritis of the knee?
3. What are the evidence-based guidelines associated with viscosupplementation for the treatment of adults with osteoarthritis of the knee?

## Key Findings

There is a substantial body of evidence investigating viscosupplementation with hyaluronic acid (HA) in adults with knee osteoarthritis (OA), but the evidence to support its efficacy is conflicting. Three meta-analyses rated by investigators as the best available evidence suggested that HA was superior to intra-articular (IA) placebo, corticosteroids (CS), and non-steroidal anti-inflammatory drugs (NSAIDs), in terms of improving knee pain and function, without increasing adverse events. However, another study reported that when only the highest-quality randomized controlled trials (RCTs) were meta-analyzed, no clinically important differences of HA treatment over IA placebo were observed. There are significant limitations reported in the HA literature, including flawed study designs and reporting, a strong placebo effect from IA injections, potential conflicts of interest due to industry funding, and variation in dose, treatment course, and molecular composition of the various HA agents under study. It has been suggested that statistical significance of effects observed in some HA studies may not have clinical significance. Limited high-quality evidence suggests that two types of HA agents are cost-effective in the treatment of knee OA compared with other interventions including NSAIDS and other analgesics, as well as other forms of conservative care such as physiotherapy, weight loss, and ambulatory aids. The majority of guidelines did not find sufficient evidence to make a recommendation for or against the use of HA for knee OA, however two guidelines recommend against its use. Some guidelines recommend HA after failure of other treatments, or in older adults with a certain OA grade.

## Methods

### Literature Search Methods

A limited literature search was conducted on key resources including PubMed, The Cochrane Library, University of York Centre for Reviews and Dissemination (CRD) databases, Canadian and major international health technology agencies, as well as a focused Internet search. No methodological filters were applied to limit retrieval by study type. Where possible, retrieval was limited to the human population. The search was also limited to English language documents published between January 1, 2012 and May 24, 2017.

Rapid Response reports are organized so that the evidence for each research question is presented separately.

### Selection Criteria and Methods

One reviewer screened citations and selected studies. In the first level of screening, titles and abstracts were reviewed and potentially relevant articles were retrieved and assessed for inclusion. The final selection of full-text articles was based on the inclusion criteria presented in Table 1.

## Table 1: Selection Criteria

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| **Population** | Adults with osteoarthritis of the knee |
| **Intervention** | Viscosupplementation |
| **Comparator** | Q1-2: Conservative treatment (non-pharmacological therapy (e.g., physiotherapy, exercising, weight management], pharmacological therapy [e.g., acetaminophen, oral and topical non-steroidal anti-inflammatory drugs (NSAIDS), intra-articular glucocorticoids, etc.); Surgical treatment<br>Q3: No comparator |
| **Outcomes** | Q1: Clinical effectiveness, clinical benefit, safety (harms, risks)<br>Q2: Cost-Effectiveness (e.g., cost per QALY increase, etc.)<br>Q3: Evidence-based guidelines |
| **Study Designs** | Systematic reviews (SRs), meta-analyses (MAs), health technology assessments (HTAs), economic evaluations, evidence-based guidelines |

### Exclusion Criteria

Articles were excluded if they did not meet the selection criteria outlined in Table 1, they were duplicate publications, or were published prior to 2012. Articles were excluded if they were captured in an included SR. Studies evaluating HA only in combination with other therapies were also excluded, as were studies that evaluated HA in other joints (e.g., hip) or related conditions (e.g., rheumatoid arthritis), in addition to knee OA. Economic evaluations were excluded if they did not provide an evaluation of benefits. Evidence-based guidelines were excluded if they were not based on a systematic search strategy.

### Critical Appraisal of Individual Studies

The included systematic reviews were critically appraised using the AMSTAR checklist,[7] economic evaluations were assessed using the Drummond checklist,[8] and guidelines were assessed with the AGREE II instrument.[9] Summary scores were not calculated for the included studies; rather, a review of the strengths and limitations of each included study were described.

## Summary of Evidence

### Quantity of Research Available

A total of 422 citations were identified in the literature search. Following screening of titles and abstracts, 391 citations were excluded and 31 potentially relevant reports from the electronic search were retrieved for full-text review. Five potentially relevant publications were retrieved from the grey literature search. Of these potentially relevant articles, 13 publications were excluded for various reasons, while 23 publications met the inclusion criteria and were included in this report. Appendix 1 describes the PRISMA flowchart of the study selection.

Additional references of potential interest are provided in Appendix 5.

## Summary of Study Characteristics

A summary of the characteristics of the included SRs and MAs, economic evaluations, and guidelines are presented below, and in Appendix 2, Tables A1, A2, and A3.

### *Study Design*

There were nine SRs,[3,4,6,10-15] with or without MA of at least some included studies, and all of these SRs included only RCTs in the analysis, except one SR[13] that included RCTs and observational studies, one SR[14] that included RCTs, SRs, and MAs, and one SR[3] that included RCTs and MAs. In addition, two additional SRs [16,17] incorporating a network meta-analysis (NMA), were identified, along with two SRs of MAs [18,19].

There were three economic evaluations (cost cost-utility analyses) identified.[20-22]. Of these, two were based on RCT evidence[21,22] and one was based on data from an observational multi-centre study.[20]

Six evidence-based guidelines[23-28] and one SR of guidelines[29] were included.

### *Country of Origin*

The included SRs were conducted by authors in China,[10,15,18] the USA,[3,12,13,16,17,19] the UK,[4,6] Iran[11], and Brazil.[14]

The included cost-utility analyses were conducted by authors from France[20] and the USA[21,22]

All guidelines, with the exception of one from the UK,[24] originated from organizations or first authors from the USA.

### *Search Methods*

All of the included SRs were based on literature searches that were conducted in multiple databases, across various time ranges from database inception through to August 16, 2016 (the search date of the most recently published study).

All of the included guidelines were based on systematic literature reviews conducted in multiple databases from various publication dates through August 2014 (the search date of the most recently published guideline).

### *Patient Population*

All included SRs and cost-studies included patients with knee OA, with a wide range of sample sizes, age groups, and sex ratio reported, in studies that included this detail. Included guidelines evaluated HA in the treatment of OA in the knee and other joints.

### *Interventions and Comparators*

Two of the included SRs[10,15] included studies that compared HA (various agents) with CS. One SR[6] compared HA with either IA placebo or CS. Two SRs[13,16] compared various HA agents against each other, or against IA or oral placebo. Five SRs [3,4,12,14,18] compared HA against IA placebo (although one of these studies[12] included two studies with usual care (undefined) as a comparator, and three studies that combined HA with an active treatment as an intervention). One SR[11] compared HA with IA platelet-rich plasma (PRP). One SR[17] compared HA with either oral or IA placebo, CS, naproxen, ibuprofen, or diclofenac, while another SR[19] compared HA with either NSAIDS, CS, or IA placebo. In most of the included

SRs a variety of HA agents were represented in the HA arm of the included studies, or the HA agent(s) utilized was not reported. In one SR,[4] the single HA agent administered was G-F 20.

One cost-utility analysis compared one HA agent consisting of three injections at one-week intervals, with NSAIDS.[20] Two of the included cost-utility analyses evaluated a single a bioengineered HA agent compared with non-HA options, including NSAIDs, analgesics, corticosteroids, physiotherapy, weight loss, ambulatory aids, and surgical options.[21,22]

The majority of guidelines did not specify a particular HA agent in their recommendations. One guideline published by NICE[24] compared several HAs to placebo or active treatments such as CS and exercise. These guidelines included both licensed and unlicensed products to generate the recommendations.[24]

### *Outcomes*

For the SRs and MAs, a range of outcomes were reported, including pain, function, and stiffness, which were most often measured using scales such as the Western Ontario and McMaster Universities Osteoarthritis Index (WOMAC), the Visual Analog Scale (VAS), the Knee Injury and Osteoarthritis Outcome Score (KOOS), or the Lequesne Index. Other outcomes included adverse events (AEs), withdrawal from the study due to AEs or knee pain, rescue medication after treatment initiation, range of motion, gait pattern, quality of life (QoL), Activities of Daily Living (ADLs), total knee replacement (TKR), and time to TKR. The investigators from two SRs of MAs utilized the Jadad scale to identify the best evidence studies.[18,19]

The outcomes included in the cost studies included quality-adjusted life years (QALYs)[21,22] prevalence of knee OA[22] and QoL measured using EuroQuol-5 Dimension (EQ-5D)[20] scores.

In the included guidelines, the outcomes used to inform recommendations included pain, QoL, and AEs.

### *Follow-Up*

Where it was reported, follow-up for the studies analyzed in the included SRs varied widely, from as little as three weeks, to 12 years.

Follow-up of the study populations in the included cost studies ranged from six months[20] to 26 weeks[21,22]

### *Study Appraisal*

A variety of appraisal methods were reported in the included SRs, including The Cochrane Risk of Bias tool, the Jadad scale, AMSTAR, QUOROM, the Newcastle-Ottawa Scale, McHarms, GRADE, the U.S. Preventive Services Task Force (USPSTF) criteria and the Critical Appraisal Skills Program Checklist.

For the included guidelines, a number of appraisal methods were used, including USPSTF, AMSTAR, Cochrane Risk of Bias, and GRADE.

## Summary of Critical Appraisal

A summary of the critical appraisal is presented below and in Appendix 3, Tables A4, A5, and A6.

### *Systematic Reviews and Meta-Analyses*

All but two of the included SRs[6,14] were rated as high quality based on application of the AMSTAR[7] criteria. One SR[14] was rated as low quality, while one other[6] was of moderate quality. In all but one included study[14] an a priori study design was provided. Duplicate study selection and data extraction was reported for all but five studies.[3,4,6,12,14] The status of publication was used as an inclusion criteria for all but four studies.[3,4,6,14] Only one study[13] provided a list of included and excluded studies. Varying details regarding population characteristics were provided for all studies**.** The scientific quality of the included studies was assessed and documented in all but one study.[14] The methods used to combine the findings of studies were appropriate for all but one study,[14] which did not attempt to combine the findings. Publication bias was assessed in only four studies.[11-13,15] A conflict of interest statement was made for all but two studies.[6,15] However, most of the SRs did not evaluate potential conflict of interest for the included studies.

### *Economic Evaluations*

The three included economic evaluations[20-22] were of high quality as rated by the Drummond checklist[8], but included only two types of HA agents. All three studies were industry funded, included a well-defined question posed in answerable form, and provided a comprehensive description of the competing alternatives. The effectiveness of the intervention was established based on RCT evidence for two studies,[21,22] and on an observational multicentre trial for one study.[20] The important and relevant costs and consequences for the alternatives included in each study were identified, and costs and consequences appeared to be measured accurately and credibly in appropriate physical units. Allowance was made for uncertainty in the estimates of costs and consequences for two studies.[21,22] None of the included studies adjusted costs and consequences for differential timing, and only one study[21] included an incremental analysis of costs and consequences of alternatives performed. Two studies[21,22] made allowance for uncertainty in the estimates of costs and consequences. For all three studies, the presentation and discussion of study results seemed to include all issues of concern to users.

### *Guidelines*

All six included guidelines,[23-28] and the SR of guidelines[29] used a systematic search methodology to generate their recommendations, and of these, only one [23] did not have a clear description of the guideline development groups. Competing interests of both the authors and the members of guideline development groups were easily identified in all included guidelines. All guidelines and the SR of guidelines had clearly stated objectives, defined health questions, and a specific and clear target population for whom the guidelines were intended for.

A limitation of most included guidelines was a lack of acknowledgment of any issues of applicability that the recommendations may have. Only one guideline[24] described potential barriers to the application of recommendations in detail, with two others[23,28] mentioning them briefly. Additionally, only one guideline[26] provided advice on how to put the recommendations into practice. None of the guidelines described auditing or monitoring criteria. Three guidelines[24,25,27] used patient input or sent drafts out to patients for public comment, but the majority of guidelines did not appear to consider patient preference in their report. Three guidelines[23,25,26] were not externally peer-reviewed prior to publication.

## Summary of Findings

The summary of findings is presented below and in Appendix 4, Table A7. A summary of guideline recommendations is presented below and in Appendix 4, Table A8.

*What is the clinical effectiveness of viscosupplementation for the treatment of adults with osteoarthritis of the knee?*

### *Pain, Function, and Stiffness*

**HA Versus CS**

Evidence from one MA that included 12 RCTs indicated that CS was significantly more effective for pain relief (as measured by the VAS and WOMAC scales) than HA in the short term (up to 1 month), while HA was significantly more effective in the longer term (up to six months).[10] Both therapies were of similar benefit for improvement in knee function improvement.[10]

Similarly, evidence from another MA that included seven RCTs showed that HA has a similar level of pain relief compared with CS in the short term (up to one month); however, HA is more effective than CS over a longer time period (up to six months).[15] The scales used to asses pain in the RCTs included VAS, WOMAC, the Knee Society Clinical Rating System (KSS) and the Lequesne index.

**HA Versus CS or Placebo**

One SR that included 14 RCTs reported that for OA pain, there was a beneficial effect for the use of HA over placebo, which peaks at around week 8 following the last injection, but very little evidence to support this effect at six months.[6] CS tends to be superior to HA up to four weeks, with HA becoming superior between four and eight weeks.[6] The instrument used to assess outcomes was not reported for all included studies. Reported outcome measures included VAS, WOMAC, KSS and the Lequesne index.[6]

**HA Versus Placebo**

One SR of 13 studies, including six RCTs, five SRs; and two MAs, that provided a limited synthesis of the included studies, reported that there was no evidence to recommend for or against the use of HA as compared with placebo.[14] Where it was reported, WOMAC was the scale used to evaluate outcomes in the included studies.

One SR that included five MAs and three RCTs reported conflicting outcomes in the included MAs, with two concluding that IA HA provided what the MA authors described as a clinically meaningful benefit compared with placebo, and three MAs providing contrary conclusions.[3] The three included RCTs published subsequently to the included MAs provided no evidence for clinically meaningful improvement over placebo.[3] Follow-up for the included studies ranged from six weeks to 40 months. Where it was reported, WOMAC and VAS were used to assess outcomes in the included studies.

Evidence from one SR with MA of two of the five included studies (both studies with six months follow-up utilizing VAS)reported that there was no significant difference in the improvement of weight-bearing pain utilizing a specific HA (Hylan G-F 20) as compared with IA placebo.[4]

One MA[12] including 19 RCTs conducted a meta-regression analysis to evaluate the effect of characteristics of the included trials on pain, function and stiffness. They reported that

double-blinded, sham-controlled trials of HA versus IA placebo had much smaller treatment effects than trials that were not sufficiently blinded. Included trials had a follow-up of between six weeks to 52 weeks and evaluated outcomes using ether VAS or WOMAC.

**HA Versus Other HAs or Placebo**

One SR[13] included 18 RCTs evaluating pain and function outcomes, 10 of which compared HA with placebo, and eight comparing HA against other HAs. A MA of the 10 placebo-controlled RCTs showed a statistically significant improvement in WOMAC-assessed function following HA treatment, compared to placebo. Seven of the 10 included trials reported outcomes at six months; follow-up was not reported for the other trials. The authors reported insufficient evidence for comparisons of efficacy across HA agents.[13]

**HA Versus PRP**

A MA of six RCTs with follow-up of up to one year showed that PRP was significantly more effective than HA as evidenced by WOMAC scores.[11]

**HA Versus Placebo, NSAIDs, PRP, and CS**

One SR of 14 MAs with follow-up ranging from three weeks to approximately 135 weeks reported conflicting evidence for the effectiveness of HA in knee pain and function .[19] Of the 10 studies comparing HA with placebo, five found that HA resulted in improvements in pain and four found that it resulted in improvements in function. However, three MAs reported no difference in terms of pain, and four studies found no difference in function. The two remaining studies showed no clinically relevant differences in either pain or function.[19] Three studies that evaluated HA versus NSAIDs demonstrated no differences that the authors considered clinically relevant.[19] Two studies evaluated HA compared with IA corticosteroids and reported that HA provided better pain relief during the first 4 weeks after injection, but were greatest at the 5- to 13-week post-injection time point, and this relief was evident for up to 26 weeks.[19] One study evaluated HA versus IA-PRP, and reported that both improved knee function at two and six months after injection, but the effects of PRP were more robust. The authors stated that no definitive conclusions could be drawn about the best HA product in the studies that compared different HA agents.

**HA Versus Placebo, CS, Acetaminophen, Celecoxib, Naproxen, Ibuprofen, or Diclofenac**

A NMA of 137 RCTs (68 with an HA arm) with follow-up of two months to six months (with preference for data at three months or data point closest to three-month mark), showed that for pain relief, all interventions (HA, CS, acetaminophen, celecoxib, naproxen, ibuprofen, and diclofenac) were statistically significantly superior than oral placebo, with HA being the most efficacious treatment.[17] Naproxen, ibuprofen, diclofenac, HA, and CS were all statistically significantly superior to acetaminophen for pain relief. For function, evidence demonstrated that HA was statistically significantly superior than both IA and oral placebo, and CS. HA was statistically significantly superior than IA placebo for stiffness.[17] Citing different outcome measures in the included studies, the NMA authors translated WOMAC, VAS, and Likert scale scores in each study into Hedges *g* effect sizes.

*Best Evidence*

Two SRs of MAs[18,19] employed the Jadad scale to identify the best-evidence MAs included in their analysis, and based on the three selected MAs, concluded that that viscosupplementation with HA is an effective intervention in treating knee OA in terms of

improvements in knee pain and function, without increased risk of adverse events. These two SRs compared HA with placebo,[18,19] and HA with CS or NSAIDs.[19]

### *Adverse Events*

#### HA Versus CS

A MA of 12 RCTs with unreported follow-up reported that both HA and CS were relatively safe, but HA was associated with significantly more topical adverse effects compared with CS.[10] One MA of seven RCTs with follow-up ranging from 12 weeks to six months, with three trials reporting adverse events, reported no statistically significant differences in adverse events between HA and CS.[15]

#### HAs Versus Other HAs or Placebo

A NMA of 74 RCTs with follow-up of up to six months investigated the safety profile of all available HA products and found that they are relatively well tolerated, and that the incidence of any particular adverse events is very low.[16] Three treatment-related serious adverse events (SAEs) were reported among 9214 participants, including one report of septic arthritis, a probable pseudoseptic reaction and an episode of anaphylactic shock shortly after injection. Comparisons between HA products, and against IA placebo, demonstrated a similar safety profile.[16]

One SR of 48 studies (RCTs, cohort studies, and case reports) that included adverse events as an outcome, with varying lengths of follow-up, indicated that there were very few serious adverse events reported, and no statistically significant differences in the rates of serious or non-serious adverse events between HA and placebo.[13]

#### HA Versus Placebo, CS, Acetaminophen, Celecoxib, Naproxen, Ibuprofen, or Diclofenac

One NMA of 137 RCTs (68 with an HA arm) with follow-up ranging from two months to six months reported that withdrawals due to AEs were more common among oral treatments (acetaminophen, nonselective NSAIDs, and celecoxib) than IA therapies including HA.[17] The most commonly reported adverse events among the IA therapies were transient local reactions, such as pain, swelling, and arthralgia. These events were reported to be similar between different IA therapies (CS vs HA).

### *Delay or Avoidance of TKR*

#### HAs Versus Other HAs or Placebo

One SR included three RCTs (one year follow-up) and 13 observational studies (follow-up six months to 12 years) evaluating delay or avoidance of TKR and reported that no conclusions could be drawn from the available literature on delay or avoidance of TKR through the use of HA.[13]

### *Quality of Life*

#### HAs Versus Other HAs or Placebo

One SR included three RCTs that evaluated QoL, one compared with placebo, and two that compared two HA agents. They reported no differences between HA and placebo for QoL at 6 months follow-up.[13] Conflicting QoL results were reported for the comparisons between HA agents.

*What is the cost-effectiveness of viscosupplementation for the treatment of adults with osteoarthritis of the knee?*

Three cost-utility analyses suggested that viscosupplementation with two different HA agents was cost-effective compared with other OA interventions including NSAIDS and other analgesics, as well as other forms of conservative care such as physiotherapy, weight loss, and ambulatory aids.[20-22]

One cost analysis [20] reported that the HA agent under study resulted in significant improvements in both WOMAC and EQ-5D scores as compared with NSAIDs. The EQ-5D score differences at 3 and 6 months, were converted into QALYs attributed to HA, leading to QALY gain equivalent to half of a month at six-month follow-up, with an improved benefit-risk ratio due to a decrease in NSAIDs consumption. Another study[21] reported an average utility gain of 0.163 QALYs over 52 weeks for the HA agent evaluated, as compared with conventional care, which included NSAIDs and other analgesics. The incremental cost-effectiveness ratio (ICER) of the HA agent evaluated was $US 38,741/QALY gained, and was sensitive to response rates in both the HA and control groups. The final study[22] reported an estimated prevalence of approximately 12 million people suffering from symptomatic knee OA in the US, and of these, approximately four million with Kellgren–Lawrence (K–L) OA severity grades 2 to 3 that are eligible for HA. The authors estimated that the HA agent evaluated could save an estimated 36,730 QALYs per year in this population, as compared with conservative care (which was defined as all non-IA-HA treatments (NSAIDS and other analgesics, physiotherapy, weight loss, and ambulatory aids).[22]

*What are the evidence-based guidelines associated with viscosupplementation for the treatment of adults with osteoarthritis of the knee?*

The majority of guidelines did not find sufficient evidence to make a recommendation for or against the use of HA for knee OA.[25-29] However, some guidelines recommended it in certain situations, such as after failure of other treatments,[28] or in certain age groups (60 years or older) with a certain OA grade.[23] The National Institute for Health and Care Excellence (NICE)[24] recommended against HA for knee OA, as did Osteoarthritis Research Society International (OARSI)[25] Only one guideline rated the strength of their recommendations, rating one recommendation against the use of HA for knee OA as "strong".[27]

## Limitations

### *Generalizability*

While the population in all of the included studies was patients with knee OA, most of the included SRs/MAs did not report the stage of OA for the patients in the included studies, or whether the patients had failed other therapies before HA therapy. Most SRs did not report the age of the included study population; one NMA[17] reporting an age range of 45 to 76 years, one NMA[16] reporting an age range of 45 to 71 years, and one SR including studies in patients with a mean age greater than or equal to 65 years. One SR reported that some of the included studies included young patients with mild OA, while others included elderly patients with severe OA.[14] This has implications for bias as well as generalizability. Finally, since none of the included studies were conducted in Canada, the results and recommendations may not be generalizable to the Canadian population.

*Risk of Bias*

At least two SRs reported that the majority of trials identified for their analysis did not meet their criteria for a low risk of bias, due to factors including inadequate reporting of details such as recruitment strategy, and method for allocation concealment.[3,13] In one SR, a number of studies had dropout rates higher than 20% and although most studies excluded individuals who had recently received CS or other courses of an HA, most allowed the use of other forms of pain relief, such as NSAIDS.[13] Few studies have attempted to identify whether response to HA was influenced by characteristics such as age, disease severity, or duration of treatment.[13] One study[12] conducted an MA of only the double-blinded, sham-controlled trials with at least sixty patients and reported no clinically important differences with HA compared with placebo. Stronger treatment effects were observed when non-blinded or improperly blinded trails were included.

A potential benefit from IA placebo, either due to a true placebo response, or the injection of fluid into the knee joint, is a concern that was noted in several SRs, and has itself been the subject of analysis.[4,17,30,31]. This could underestimate the effect of the HA intervention. Finally, fluid is often withdrawn from the affected knee prior to any IA therapy, which may also have benefits, thus overestimating the effect of the intervention.[4]

Several SRs reported that many HA studies could be vulnerable to financial conflict of interest, either through direct industry funding of the research or employment of the study authors by manufacturers of the agents being tested.[3,13,17,32]

Different HA agents were used across most of the included SRs, with differences in molecular weights, injection schedules (between one and five injections depending on the HA agent selected), dose injected per application, the number of cycles used, and the time between injections.[14]. It is clear that efficacy could vary with the HA agent used. One SR[18] noted that considerable between-product variability in the clinical response.

High heterogeneity of included studies was a factor reported in at least three studies.[3,12,18] In one study, significant factors impacting heterogeneity included study design variables such as improper blinding, follow-up duration, molecular make-up of the HA agent evaluated, and pain measurements reported at baseline. Follow-up times varied greatly across the included studies, and the timing and duration of follow-up could potentially impact the treatment effect. However, one study reported that follow-up duration was not significantly associated with HA treatment effect when unblinded trials were not included in the analysis.[12]

## Conclusions and Implications for Decision or Policy Making

There is a substantial amount of evidence investigating HA in adults with knee OA, but the evidence to support its efficacy is conflicting. Two SRs of MAs [18,19] that identified the best available MAs based on a standardized scale, reported that HA was superior to placebo, CS, and NSAIDs, in terms of improving knee pain and function, without increasing adverse events. Another study[12] reported that when only the best-evidence RCTs were meta-analyzed, differences in HA treatment over placebo were not observed. In general, the available evidence suggests that comparisons between various HA agents does not demonstrate significant differences in efficacy in outcomes, however, one study [18] noted considered between-product variability in clinical response.

Limitations to the body of evidence exist. Although most of the SRs included in this report were rated as high-quality using the AMSTAR tool, many of the individual studies included in the SRs were reported to be subject to one or more types of bias, including inadequate reporting, flawed study design, selection bias, potential conflicts of interest due to industry funding, a strong and documented IA placebo effect, use of rescue medications, and variation in molecular make-up, dosage, and treatment course for the various HA agents under study. Due to inadequate reporting of the included study populations, particularly in terms of severity of knee OA and treatment failure, is not possible to generalize study results to all patents with knee OA. Generalizability to Canadian populations is also not possible as none of the included studies were based in Canada.

Some authors have questioned whether statistical significance observed in some studies translates into a meaningful clinical significance.[3,12,13] Two SRs noted a lack of standardization for AE reporting and synthesis, which could lead to totally different conclusions about whether the risk of serious AEs outweighs its benefits.[13,33]

A limited amount of high-quality evidence suggests that HA is cost-effective in the treatment of knee OA compared with other interventions including NSAIDS and other analgesics, as well as other forms of conservative care such as physiotherapy, weight loss, and ambulatory aids, however only two types of HA agents were employed in the included studies.

The majority of guidelines did not find sufficient evidence to make a recommendation for or against the use of HA for knee OA .[25-29] However, some guidelines recommend HA in certain situations, such as after failure of other treatments,[28] or in certain age groups (60 years or older) with a certain OA grade.[23] Viscosupplementation is recommended against in one guideline published by NICE,[24] and recommended against for multiple joint OA (including the knee) in another guideline published by OARSI.[25]

## References


1. Davis A, Badley E, McGlasson R, Alleyne J. Reducing the impact of OA: A report on the prevention and effective management in Canada. Phase 1: stakeholder engagement. Phase 2: meeting [Internet]. [place unknown]: Bone and Joint Canada; 2014 Aug. [cited 2017 Jun 1]. Available from: http://boneandjointcanada.com/wp-content/uploads/2014/05/BJC-OA-Meeting-Report-Final.pdf
2. Table 1. Prevalence of osteoarthritis, by age group and site of joint pain, household population aged 20 or older diagnosed with arthritis, Canada excluding territories, 2009 [Internet]. Ottawa: Statistics Canada; 2015 Nov 27. [cited 2017 Jun 6]. (Health reports; vol. 25, no. 9). Available from: http://www.statcan.gc.ca/pub/82-003-x/2014009/article/14087/tbl/tbl1-eng.htm
3. Blue Cross Blue Shield Association. Intra-articular hyaluronic acid for osteoarthritis of the knee. Technol Eval Cent Assess Program Exec Summ. 2014 Oct;29(6):1-3.
4. Pai SK, Allgar V, Giannoudis PV. Are intra-articular injections of Hylan G-F 20 efficacious in painful osteoarthritis of the knee? A systematic review & meta-analysis. Int J Clin Pract. 2014 Aug;68(8):1041-7.
5. Vad VB. Viscosupplementation for knee osteoarthritis [Internet]. Deerfield (IL): Arthritis-health.com; 2013 Sep 20. [cited 2017 Jun 6]. Available from: https://www.arthritis-health.com/treatment/injections/viscosupplementation-knee-osteoarthritis
6. Trigkilidas D, Anand A. The effectiveness of hyaluronic acid intra-articular injections in managing osteoarthritic knee pain. Ann R Coll Surg Engl [Internet]. 2013 Nov [cited 2017 May 29];95(8):545-51. Available from: http://www.ncbi.nlm.nih.gov/pmc/articles/PMC4311527
7. Shea BJ, Grimshaw JM, Wells GA, Boers M, Andersson N, Hamel C, et al. Development of AMSTAR: a measurement tool to assess the methodological quality of systematic reviews. BMC Med Res Methodol [Internet]. 2007 [cited 2017 Jun 22];7:10. Available from: http://www.ncbi.nlm.nih.gov/pmc/articles/PMC1810543/pdf/1471-2288-7-10.pdf
8. Higgins JPT, Green S, editors. Cochrane handbook for systematic reviews of interventions [Internet]. Version 5.1.0. London (England): The Cochrane Collaboration; 2011 Mar. Figure 15.5.a: Drummond checklist (Drummond 1996). [cited 2017 Jun 22]. Available from: http://handbook.cochrane.org/chapter_15/figure_15_5_a_drummond_checklist_drummond_1996.htm
9. Brouwers M, Kho ME, Browman GP, Burgers JS, Cluzeau F, Feder G, et al. AGREE II: advancing guideline development, reporting and evaluation in healthcare. CMAJ [Internet]. 2010 Dec [cited 2017 Jun 22];182(18):E839-E842. Available from: http://www.ncbi.nlm.nih.gov/pmc/articles/PMC3001530/pdf/182e839.pdf
10. He WW, Kuang MJ, Zhao J, Sun L, Lu B, Wang Y, et al. Efficacy and safety of intraarticular hyaluronic acid and corticosteroid for knee osteoarthritis: A meta-analysis. Int J Surg. 2017 Mar;39:95-103.
11. Sadabad HN, Behzadifar M, Arasteh F, Behzadifar M, Dehghan HR. Efficacy of platelet-rich plasma versus hyaluronic acid for treatment of knee osteoarthritis: A systematic review and meta-analysis. Electron Physician [Internet]. 2016 Mar [cited 2017 May 29];8(3):2115-22. Available from: http://www.ncbi.nlm.nih.gov/pmc/articles/PMC4844477
12. Jevsevar D, Donnelly P, Brown GA, Cummins DS. Viscosupplementation for osteoarthritis of the knee: a systematic review of the evidence. J Bone Joint Surg Am. 2015 Dec 16;97(24):2047-60.
13. RAND Southern California Evidence-Based Practice Center, Newberry SJ, FitzGerald JD, Maglione MA, O'Hanlon CE, Booth M, et al. Systematic review for effectiveness of hyaluronic acid in the treatment of severe degenerative joint disease (DJD) of the knee [Internet]. Rockville (MD): Agency for Healthcare Research and Quality (AHRQ); 2015 Jul 23. (Technology assessment report). [cited 2017 Jun 1]. Available from: https://www.cms.gov/Medicare/Coverage/DeterminationProcess/Downloads/id101TA.pdf Project ID: DJDTO913.

14. Ammar TY, Pereira TA, Mistura SL, Kuhn A, Saggin JI, Lopes Junior OV. Viscosupplementation for treating knee osteoarthrosis: review of the literature. Rev Bras Ortop [Internet]. 2015 Sep [cited 2017 May 29];50(5):489-94. Available from: http://www.ncbi.nlm.nih.gov/pmc/articles/PMC4610977

15. Wang F, He X. Intra-articular hyaluronic acid and corticosteroids in the treatment of knee osteoarthritis: A meta-analysis. Exp Ther Med [Internet]. 2015 Feb [cited 2017 May 29];9(2):493-500. Available from: http://www.ncbi.nlm.nih.gov/pmc/articles/PMC4280939

16. Bannuru RR, Osani M, Vaysbrot EE, McAlindon TE. Comparative safety profile of hyaluronic acid products for knee osteoarthritis: a systematic review and network meta-analysis. Osteoarthritis Cartilage. 2016 Dec;24(12):2022-41.

17. Bannuru RR, Schmid CH, Kent DM, Vaysbrot EE, Wong JB, McAlindon TE. Comparative effectiveness of pharmacologic interventions for knee osteoarthritis: a systematic review and network meta-analysis. Ann Intern Med. 2015 Jan 6;162(1):46-54.

18. Xing D, Wang B, Liu Q, Ke Y, Xu Y, Li Z, et al. Intra-articular hyaluronic acid in treating knee osteoarthritis: a PRISMA-compliant systematic review of overlapping meta-analysis. Sci Rep [Internet]. 2016 Sep 12 [cited 2017 May 25];6:32790. Available from: http://www.ncbi.nlm.nih.gov/pmc/articles/PMC5018721

19. Campbell KA, Erickson BJ, Saltzman BM, Mascarenhas R, Bach BR, Jr., Cole BJ, et al. Is local viscosupplementation injection clinically superior to other therapies in the treatment of osteoarthritis of the knee: a systematic review of overlapping meta-analyses. Arthroscopy. 2015 Oct;31(10):2036-45.

20. Thomas T, Amouroux F, Vincent P. Intra articular hyaluronic acid in the management of knee osteoarthritis: Pharmaco-economic study from the perspective of the national health insurance system. PLoS ONE [Internet]. 2017 [cited 2017 May 29];12(3):e0173683. Available from: http://www.ncbi.nlm.nih.gov/pmc/articles/PMC5362080

21. Hatoum HT, Fierlinger AL, Lin SJ, Altman RD. Cost-effectiveness analysis of intra-articular injections of a high molecular weight bioengineered hyaluronic acid for the treatment of osteoarthritis knee pain. J Med Econ. 2014 May;17(5):326-37.

22. Rosen J, Sancheti P, Fierlinger A, Niazi F, Johal H, Bedi A. Potential impact of biologically derived hyaluronic acid on quality of life in patients with knee osteoarthritis in the United States. Adv Ther [Internet]. 2017 Jan [cited 2017 Jun 6];33(12):2200-10. Available from: http://www.ncbi.nlm.nih.gov/pmc/articles/PMC5126190

23. Trojian TH, Concoff AL, Joy SM, Hatzenbuehler JR, Saulsberry WJ, Coleman CI. AMSSM scientific statement concerning viscosupplementation injections for knee osteoarthritis: importance for individual patient outcomes. Br J Sports Med. 2016 Jan;50(2):84-92.

24. Osteoarthritis: care and management [Internet]. London (GB): National Institute for Health and Care Excellence; 2014 Feb. [cited 2017 Jun 6]. (NICE clinical guideline; no. 177). Available from: https://www.nice.org.uk/guidance/cg177/chapter/1-Recommendations

25. McAlindon TE, Bannuru RR, Sullivan MC, Arden NK, Berenbaum F, Bierma-Zeinstra SM, et al. OARSI guidelines for the non-surgical management of knee osteoarthritis. Osteoarthritis Cartilage [Internet]. 2014 Mar [cited 2017 May 29];22(3):363-88. Available from: https://www.oarsi.org/sites/default/files/docs/2014/non_surgical_treatment_of_knee_oa_march_2014.pdf

26. The Non-Surgical Management of Hip & Knee Osteoarthritis Working Group, The Office of Quality and Performance, Office of Evidence Based Practice, US Army Medical Command. VA/DoD clinical practice guidelines for the non-surgical management of hip & knee osteoarthritis [Internet]. Washington (DC): U.S. Department of Veterans Affairs; 2014. [cited 2017 Jun 6]. Available from: https://www.healthquality.va.gov/guidelines/cd/oa/index.asp

27. National Guideline Clearinghouse. American Academy of Orthopaedic Surgeons clinical practice guideline on the treatment of osteoarthritis of the knee, 2nd edition. In: National Guideline Clearinghouse [Internet]. Rockville (MD): Agency for Healthcare Research and Quality; 1996; revised 2013 May 18 [cited 2017 Jun 6]. Available from: https://www.guideline.gov/summaries/summary/46422/american-academy-of-orthopaedic-surgeons-clinical-practice-guideline-on-the-treatment-of-osteoarthritis-of-the-knee-2nd-edition?q=osteoarthritis

28. Hochberg MC, Altman RD, April KT, Benkhalti M, Guyatt G, McGowan J, et al. American College of Rheumatology 2012 recommendations for the use of nonpharmacologic and pharmacologic therapies in osteoarthritis of the hand, hip, and knee. Arthritis Care Res (Hoboken). 2012 Apr;64(4):465-74.

29. Nelson AE, Allen KD, Golightly YM, Goode AP, Jordan JM. A systematic review of recommendations and guidelines for the management of osteoarthritis: The chronic osteoarthritis management initiative of the U.S. bone and joint initiative. Semin Arthritis Rheum. 2014 Jun;43(6):701-12.

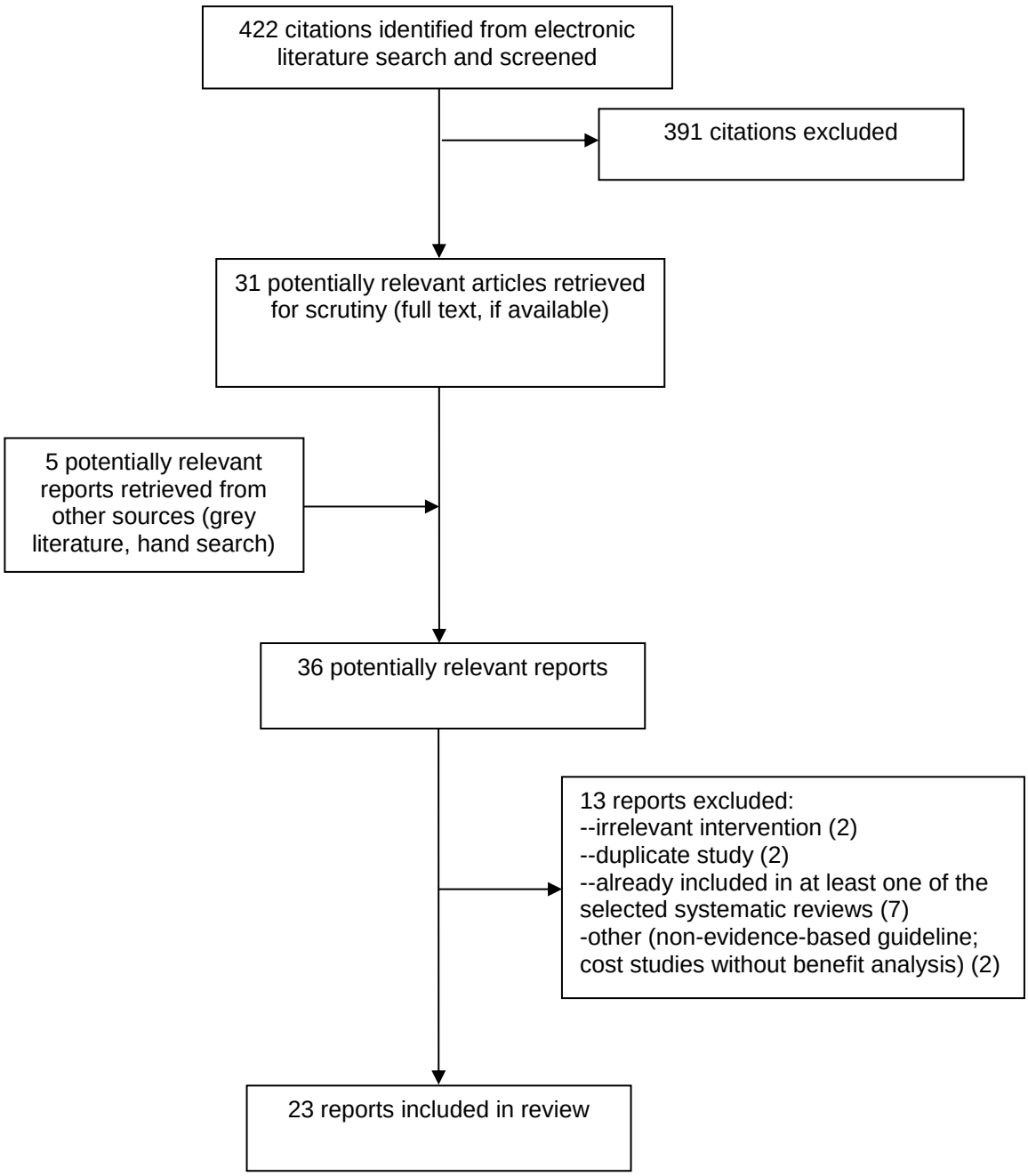
30. Altman RD, Devji T, Bhandari M, Fierlinger A, Niazi F, Christensen R. Clinical benefit of intra-articular saline as a comparator in clinical trials of knee osteoarthritis treatments: A systematic review and meta-analysis of randomized trials. Semin Arthritis Rheum. 2016 Oct;46(2):151-9.

31. Bannuru RR, McAlindon TE, Sullivan MC, Wong JB, Kent DM, Schmid CH. Effectiveness and Implications of Alternative Placebo Treatments: A Systematic Review and Network Meta-analysis of Osteoarthritis Trials. Ann Intern Med. 2015 Sep 1;163(5):365-72.

32. Printz JO, Lee JJ, Knesek M, Urquhart AG. Conflict of interest in the assessment of hyaluronic acid injections for osteoarthritis of the knee: an updated systematic review. J Arthroplasty. 2013 Sep;28(8 Suppl):30-3.

33. O'Hanlon CE, Newberry SJ, Booth M, Grant S, Motala A, Maglione MA, et al. Hyaluronic acid injection therapy for osteoarthritis of the knee: concordant efficacy and conflicting serious adverse events in two systematic reviews. Syst Rev [Internet]. 2016 Nov 4 [cited 2017 May 29];5(1):186. Available from: http://www.ncbi.nlm.nih.gov/pmc/articles/PMC5097414

# Appendix 1: Selection of Included Studies



# Appendix 2: Characteristics of Included Publications

## Table A1: Characteristics of Included SRs and MAs

| Study, Year, Country, Design Quality Assessment Tool | Electronic searches, and Search Range | Studies: Types, Numbers, Publication Year, Follow-up | Population: Number, condition | Intervention and Control Groups (No. of study) | Outcomes |
|---|---|---|---|---|---|
| He et al, 2017[10]<br><br>China<br><br>MA<br><br>Jadad scale | PubMed, Embase, Web of Science, Cochrane Library<br><br>Inception (presumed) to August 2016 | 12 RCTs<br><br>1995 to 2016<br><br>Follow-up: NR | N = 1794 patients with knee OA<br><br>n = 673 males,<br><br>n = 1121 females | **Intervention:**<br>HA; n = 971 patients;<br><br>Various HA agents<br><br>**Control**<br><br>IA-CS; n = 823 | VAS<br><br>WOMAC<br><br>Rescue medication use after initiation of treatment<br><br>Withdrawal for knee pain<br><br>Range of motion of the knee<br><br>Adverse events |
| Bannuru, et al; 2016[16]<br><br>USA<br><br>**SR and network MA**<br>**Cochrane risk of bias tool** | Medline, Web of Science, EMBASE, Google Scholar, Cochrane Central Register of Controlled Trials Inception to October 1, 2015 | 74 RCTs<br><br>1983 to 2015<br><br>Follow-up: Up to 6 months | N = 13,032 patients with knee OA<br><br>Average age: 45 to 71 years old; Proportion of women: 28% to 100% of participants | IA-placebo controlled (n = 56 trials) or comparisons between 2 or more HAs (n = 18) | AEs<br><br>Withdrawals due to AEs;<br><br>SAEs |
| Xing et al; 2016[18]<br><br>China<br><br>SR of MAs<br><br>AMSTAR and Jadad | MEDLINE, EMBASE and Cochrane library<br><br>Inception (presumed) to November 2015 | 12 MAs with between 5 to 89 RCTs or quasi RCTs<br><br>2003 to 2015<br><br>Follow-up: NR | Knee OA | Intervention: HA<br><br>Control: Placebo | Best evidence MA for clinical effects of HA in treating knee OA |
| Sadabad et al[11]; 2016<br><br>Iran<br><br>MA<br><br>Cochrane Risk of Bias; Jadad | Pubmed, Cochrane library, Scopus, Ovid databases<br><br>2005 to August 2015 | N = 6 RCTs<br><br>2008 to 2015<br><br>Follow-up: max. 1 year | N = 722 patients with knee OA<br><br>Average number of subjects for each study was 120. | Intervention: PRP, n = 364<br>Control: HA, n = 358 | WOMAC |

## Table A1: Characteristics of Included SRs and MAs

| Study, Year, Country, Design Quality Assessment Tool | Electronic searches, and Search Range | Studies: Types, Numbers, Publication Year, Follow-up | Population: Number, condition | Intervention and Control Groups (No. of study) | Outcomes |
|---|---|---|---|---|---|
| Jevsevar et al; 2015[12]<br><br>USA<br><br>SR<br><br>NR | PubMed, EMBASE, the Physiotherapy Evidence Database, Cochrane Central Register of Controlled Trials<br><br>Inception (presumed) to February 16, 2015 | N = 19 RCTs<br><br>Follow-up: 6 to 52 weeks, with the most common end-point at 26 weeks. | N = 4485 patients with knee OA | HA: Various<br><br>HA versus placebo: n = 14 RCTs;<br><br>HA versus usual care: n = 2 RCTs<br><br>HA with an additional active treatment compared with active treatment alone: n = 3 | Best Evidence<br>VAS<br>WOMAC |
| Campbell et al; 2015[19]<br><br>USA<br><br>SR of MAs<br><br>Jadad and QUOROM | PubMed database, CINAHL Complete, Cochrane DSR, Scopus, Embase<br><br>Inception (presumed) to August 2014 | 14 MAs<br><br>2003 to 2014<br><br>Mean follow-up: 3 weeks to 135.2 weeks | 20,049 patients: with knee OA<br><br>Between 606 to 12,667 patients in each study | Intervention: IA-HA, n = 13,698<br><br>Control:<br><br>NSAIDs, n = 355;<br><br>IA-CS, n = 294;<br><br>IA-Placebo, n = 5,702<br><br>(for studies that reported the number of patients in each group)<br><br>IA-PRP = NR | Pain<br><br>Function<br><br>Best evidence MA |
| Newbery et al; 2105[13]<br><br>USA<br><br>SR<br><br>Cochrane Risk of Bias Assessment Tool; Newcastle-Ottawa Scale; McHarms; AMSTAR; GRADE | Searches of Medline, Cochrane Library, Web of Science, Clinicaltrials.gov, FDA Premarket Approval database<br><br>1990 – December 2014 | N = 63 studies; (n = 25 RCTs, n = 20 case series and cohorts, n = 18 case reports reporting AEs.<br><br>1987 to 2012<br><br>Follow-up: At least 4 weeks and up to 12 years | Adults with OA, mean age >/= 65 | Intervention: Various IA – HA:<br><br>Control: IA placebo/sham; other HAs | Receipt of TKR;<br><br>Time elapsed between HA therapy and TKR;<br><br>Change in functional status (as measured using the WOMAC, Lequesne, or KOOS scales), |

## Table A1: Characteristics of Included SRs and MAs

| Study, Year, Country, Design Quality Assessment Tool | Electronic searches, and Search Range | Studies: Types, Numbers, Publication Year, Follow-up | Population: Number, condition | Intervention and Control Groups (No. of study) | Outcomes |
|---|---|---|---|---|---|
| | | | | | Range of motion;<br><br>ADLs/IADLs;<br><br>QoL/Health-related QoL,<br><br>AEs |
| Ammar, et al.[14]; 2015<br><br>Brazil<br><br>SR<br><br>NR | Medline, PubMed, Cochrane Controlled Trial Register; Cochrane Systematic Review (Cochrane Library) Databases<br><br>Search dates: NR | N = 13; n = 6 RCTs, n = 5 SRs; n = 2 MAs<br><br>1998 to 2013<br><br>Follow-up: Up to 40 months (NR for all but two trials) | OA | Intervention: HA (Hylan G-F 20, Sodium hyaluronate, Hylan); High Molecular weight HA<br><br>Control: Placebo<br><br>100 or more patients per arm. | WOMAC |
| Wang et al.[15]; 2015<br><br>China<br><br>MA<br><br>Jadad | PubMed, EMBASE and The Cochrane Central Register of Controlled Trials.<br><br>Inception (presumed) to July 2013 | N = 7 RCTs<br><br>1995 to 2010<br><br>Follow-up: 12 weeks to 6 months | N = 583 patients with knee OA (222 males and 361 females) | Intervention: HA, n = 298<br>Control: CS, n = 285 | VAS<br><br>Lequesne index<br><br>Gait Pattern<br><br>WOMAC<br><br>KSS<br><br>AEs |
| Bannuru et al; 2015[17]<br><br>USA<br><br>SR and Network MA<br><br>Cochrane Risk of Bias | MEDLINE, EMBASE, Web of Science, Google Scholar, Cochrane Central Register of Controlled Trials<br><br>Inception to August 15, 2014 | N = 137 RCTs (68 with an HA arm)<br><br>1980 to 2014<br><br>Follow-up: 2 to 6 months (preference for 3-month data or data point closest to 3-month mark) | N = 4806 patients with knee OA (in the studies with an HA arm)<br><br>Average age (all interventions): 45 to 76 years (median, 62; inter-quartile range, 60 to 64) | Diclofenac vs. IA HA: n = 2 studies<br><br>Ibuprofen vs. IA HA: n =1 study<br><br>Naproxen vs. IA HA: n = 1 study<br><br>IA HA vs. IA CS: n = 12 studies | Pain<br><br>Function<br><br>Stiffness |

## Table A1: Characteristics of Included SRs and MAs

| Study, Year, Country, Design Quality Assessment Tool | Electronic searches, and Search Range | Studies: Types, Numbers, Publication Year, Follow-up | Population: Number, condition | Intervention and Control Groups (No. of study) | Outcomes |
|---|---|---|---|---|---|
| | | | Proportion of women (all interventions) ranged from 3% to 100% (median, 67%; interquartile range, 62% to 72%) | IA HA vs. IA placebo: n = 52 studies<br><br>**Only studies with an HA arm are reported here* | |
| Blue Cross/Blue Shield, 2014[3]<br><br>USA<br><br>SR<br><br>AMSTAR; U.S. Preventive Services Task Force criteria | MEDLINE, EMBASE<br><br>January 1, 2011, to August 25, 2014, | N = 5 MAs and 3 RCTs<br><br>2011 to 2013<br><br>Follow-up 6 weeks to 40 months (for included RCTs) | Patients with knee OA<br><br>MAs: n = 14 to 89 studies<br><br>RCTS: n = 218 to 306 randomized participants | Intervention: HA (various);<br><br>Control: Placebo | Pain<br><br>Function<br><br>Safety<br><br>QoL |
| Pai, 2014[4]<br><br>MA<br><br>UK<br><br>Jadad | PubMed; EMBASE<br><br>Inception to July 2013 | N = 6 RCTs for qualitative synthesis, 2 RCTs for MA<br><br>1994 to 2010<br><br>Follow-up: 8 to 26 weeks for SR; 6 months for inclusion in MA (n = 2 studies) | 269 OA knees for MA | Intervention: Hylan G-F 20, n = 5, 3-injection regime; n = 1, single injection regime.<br><br>Control: IA Placebo | Pain (VAS) |
| Trigkilidas, 2013[6]<br><br>SR<br><br>UK<br><br>Critical Appraisal Skills Programme checklist | MEDLINE®, Embase and CINAHL<br><br>Inception (presumed) to November 30, 2011 | N = 14 RCTs<br><br>1993 to 2010<br><br>Follow-up: NR | N = 60 to 372 participants with knee OA per study | Intervention: HA<br><br>Control: IA Placebo, n = 12;<br>IA-CS, n = 2 | Pain<br><br>Function |

ADL = activities of daily living; AE = adverse event; CS = corticosteroids; HA = hyaluronic acid; IA = intra-articular; IADL = instrumental activities of daily living; KOOS = Knee Injury and Osteoarthritis Outcome Score (KOOS); KSS = Knee Society Clinical Rating System; MA = meta-analysis; NASHA = non-animal stabilized hyaluronic acid; NR = not reported; OA = osteoarthritis; QoL = quality of life; RCT = randomized controlled trial; SR = systematic review; TKR = total knee replacement; VAS = Visual Analog Scale; WOMAC = Western Ontario and McMaster Universities Osteoarthritis Index

## Table A2: Characteristics of Included Cost Studies

| First Author, Year, Country, | Study Objectives | Interventions/ Comparators | Patients | Outcomes |
|---|---|---|---|---|
| **Thomas, et al, 2017**[20]<br><br>France | *"The objectives of this study were a benefit-risk analysis (based on the assessment of NSAIDs consumption) and a cost-utility analysis (based on the assessment of treatment costs and health improvement) before and after administration of IA HA or alternatively continuing NSAIDs, under the conditions of every day practice.* " (p. 2) | NSAIDS: n= 199<br><br>IA-HA: n = 202 (HA agent: 3 injections at one-week intervals) | Radiological grade of knee OA: grade II or III, in same proportion for both HA and NSAIDS.<br><br>Mean scores of WOMAC and EQ-5D were nearly identical for both HA and NSAIDS.<br><br>HA Group<br>Mean age: 62.3 years; 55 % female<br><br>NSAIDS Group<br>Mean age 65.6 years; 59% female<br>(women 59%)<br><br>The radiological grade of knee OA was grade II or III, in same proportion for both groups.<br><br>Mean scores of WOMAC and EQ-5D at baseline were nearly identical (p = 0.75 to 0.95). | WOMAC sub-scores<br><br>EQ-5D QoL Index<br><br>Cost-Utility Analysis<br><br>Benefit-risk analysis<br><br>. |
| **Rosen, et al 2016**[22]<br><br>USA | *"The purpose of this study is to determine the current and potential impact that a biologically derived high molecular weight IA-HA (Euflexxa) may have on quality adjusted life years (QALY) if used more widely for patients suffering with knee OA." (p. 2200)* | For RCT:<br><br>Intervention: HA agent<br><br>Comparator: IA placebo<br><br>Comparators for economic model: All non-IA-HA treatments (NSAIDS and other analgesics, physiotherapy, weight loss, ambulatory aids.) | 433 subjects, 219 who received IA-HA and 214 who received IA-SA<br><br>433 subjects, 219 who received IA-HA and 214 who received IA-SA<br><br>Mild-to-moderate OA knee pain;<br>in adequate response to conventional therapies;<br>Kellgren-Lawrence grade 2 or 3 OA of the target knee | Estimated number of people in the US with symptomatic knee OA graded according to severity<br><br>Current and potential impact of HA agent on treatment for knee OA.<br><br>QALYs |
| **Hatoum, et al, 2014**[21] | *"To determine the cost-effectiveness of bioengineered hyaluronic acid (BioHA, 1%* | For RCT:<br><br>Intervention: HA | 433 subjects, 219 who received IA-HA and 214 who received IA-SA | Cost-utility analysis<br><br>ICER |

## Table A2: Characteristics of Included Cost Studies

| First Author, Year, Country, | Study Objectives | Interventions/ Comparators | Patients | Outcomes |
|---|---|---|---|---|
| | *sodium hyaluronate) intra-articular injections in treating osteoarthritis knee pain in poor responders to conventional care (CC) including non-steroidal anti-inflammatory drugs (NSAIDs) and analgesics."* | agent<br><br>Comparator: IA placebo<br><br>Comparators for economic model: NSAIDs, analgesics, CS, and surgical options. | Mild-to-moderate OA knee pain;<br>in adequate response to conventional therapies;<br>Kellgren-Lawrence grade 2 or 3 OA of the target knee | QALYs |

CS = corticosteroids; HA = hyaluronic acid; IA = intra-articular; ICER = incremental cost-effectiveness ratio;); NSAIDs = non-steroidal anti-inflammatory drugs; OA = osteoarthritis; QoL = quality of life; QALY = quality-adjusted life year; RCT = randomized controlled trial; WOMAC = Western Ontario and McMaster Universities Osteoarthritis Index.

## Table A3: Characteristics of Included Guidelines or SRs of Guidelines

| First Author/Guideline Society or Institute, Year, Country | Objective | Target Users | Methodology |
|---|---|---|---|
| **Guidelines** | | | |
| **AMSSM, 2016, USA**[23] | Provide a best-practice summary for non-operative treatment of OA | Physicians | Systematic literature search from 1960 to August 2014 in MEDLINE, Embase and Cochrane Central. Manual search of RCTs, prior meta-analyses and review articles.<br><br>Quality of RCTs assessed using Cochrane Risk of Bias |
| **NICE, 2014, UK**[24] | Recommendations for the care and management of adults with osteoarthritis | Healthcare professionals, adults with osteoarthritis, their families and carers | Systematic literature search up to May 2013 in MEDLINE (1946–), Embase, the Cochrane Library, and Allied and Complementary Medicine database.<br><br>Quality of evidence for each outcome assessed using GRADE. |
| **OARSI, 2014, USA**[25] | To be combined with individual patients needs and physician values to create an appropriate treatment plan for OA | Practitioners | Systematic literature search from 2010-2013 as an update to previous OARSI guidelines in Medline, EMBASE, Google Scholar, Web of Science, and the Cochrane Central Register of Controlled Trials. A manual search was also performed. Expert panel voted on recommendations and appropriateness of treatment modalities.<br><br>Quality of studies assessed using AMSTAR for systematic reviews and Cochrane Risk of Bias for RCTs. |
| **VA/Dod, 2014, USA**[26] | "…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" (p.9) | Primary care providers in an ambulatory care setting | Systematic literature search from 2002-2012 in 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<br><br>Quality of studies assessed using the USPSTF rating system |
| **AAOS, 2013, USA**[27] | "…help practitioners to integrate the current evidence and clinical practice, and it highlights gaps in the literature in need of future research." (p. 7) | Physicians and clinicians who manage the treatment of osteoarthritis of the knee | Systematic literature search up to May 2012 in PubMed, Embase, CINAHL, and The Cochrane Central Register of Controlled Trials. A manual search was also performed.<br><br>Quality of studies assessed using GRADE |
| **ACR, 2012, USA**[28] | Update of 2000 ACR recommendations for knee OA | Health care providers | Systematic literature search up to 2009 in MEDLINE (1950 –2009), Embase (1980 –2009), and The Cochrane Library (issue 3, 2009). Expert panel formed recommendations. |

## Table A3: Characteristics of Included Guidelines or SRs of Guidelines

| First Author/Guideline Society or Institute, Year, Country | Objective | Target Users | Methodology |
|---|---|---|---|
| | | | Quality of recommendations assessed using GRADE |
| **Systematic Reviews of Guidelines** | | | |
| **The Chronic Osteoarthritis Management Initiative of the U.S. Bone and Joint Initiative, 2014, USA[29]** | Determine commonalities between guidelines to translate to clinical practice | Not specified | Systematic literature search (for guidelines only) from 2000-2013 in MEDLINE, Agency for Healthcare Research & Quality Guidelines Clearinghouse.<br><br>Quality of guidelines assessed using AGREEII |

AAOS = American Academy of Orthopaedic Surgeons; ACR American College of Rheumatology; AMSSM = American Medical Society for Sports Medicine; AMSTAR = Assessment of Multiple Systematic Reviews Tool; CINAHL = Cumulative Index to Nursing and Allied Health Literature; NICE = The National Institute for Health and Care Excellence; OA = Osteoarthritis; OARSI = Osteoarthritis Research Society International; RCT = randomized controlled trials; USPSTF = U.S. Preventive Services Task Force; Va/DoD = Veterans Affairs/Department of Defense

# Appendix 3: Critical Appraisal of Included Publications

## Table A4: Quality Assessment of Systematic Reviews and Meta-Analyses using the AMSTAR checklist[7]

| AMSTAR Checklist[7] | He 2017[10] | Bannuru 2016[16] | Xing 2016[18] | Sadabad 2016[11] | Jevsevar 2015[12] | Campbell 2015[19] | Newberry 2015[13] | Ammar 2015[14] | Wang 2015[15] | Bannuru 2015[17] |
|---|---|---|---|---|---|---|---|---|---|---|
| 1. Was an a priori design provided | Yes | Yes | Yes | Yes | Yes | Yes | Yes | NR | Yes | Yes |
| 2. Was there duplicate study selection and data extraction | Yes | Yes | Yes | Yes | NR | Yes | Yes | NR | Yes | Yes |
| 3. Was a comprehensive literature search performed | Yes | Yes | Yes | Yes | Yes | Yes | Yes | Yes | Yes | Yes |
| 4. Was the status of publication used as an inclusion criteria? | Yes | Yes | Yes | Yes | Yes | Yes | Yes | No | Yes | Yes |
| 5. Was a list of studies (included and excluded) provided. | No | No | No | No | No | No | Yes | No | No | No |
| 6. Were the characteristics of the included studies provided | Yes | Yes | Yes | Yes | Yes | Yes | Yes | Yes | Yes | Yes |
| 7. Was the scientific quality of the included studies assessed and documented? | Yes | Yes | Yes | Yes | Yes | Yes | Yes | No | Yes | Yes |
| 8. Was the scientific quality of the included studies used appropriately in formulating conclusions? | Yes | Yes | Yes | Yes | Yes | Yes | Yes | No | Yes | Yes |
| 9. Were the methods used to combine the findings of studies appropriate? | Yes | Yes | Yes | Yes | Yes | Yes | Yes | No | Yes | Yes |
| 10. Was the likelihood of publication bias assessed? | No | No | No | Yes | Yes | No | Yes | No | Yes | No |
| 11. Was the conflict of interest included? | Yes | Yes | Yes | Yes | Yes | Yes | Yes | Yes | No | Yes |

## Quality Assessment of Systematic Reviews and Meta-Analyses, Cont'd

| AMSTAR Checklist | Blue Cross/Blue Shield 2014[3] | Pai 2014[4] | Trigkilidas 2013[6] |
|---|---|---|---|
| 1. Was an a priori design provided | Yes | Yes | Yes |
| 2. Was there duplicate study selection and data extraction | No | Yes | NR |
| 3. Was a comprehensive literature search performed | Yes | Yes | Yes |
| 4. Was the status of publication used as an inclusion criteria? | No | NR | No |
| 5. Was a list of studies (included and excluded) provided. | No | No | No |
| 6. Were the characteristics of the included studies provided | Yes | Yes | Yes |
| 7. Was the scientific quality of the included studies assessed and documented? | Yes | Yes | Yes |
| 8. Was the scientific quality of the included studies used appropriately in formulating conclusions? | Yes | Yes | Yes |
| 9. Were the methods used to combine the findings of studies appropriate? | Yes | Yes | Yes |
| 10. Was the likelihood of publication bias assessed? | Yes | No | No |
| 11. Was the conflict of interest included? | Yes | Yes | No |

## Table A5: Quality Assessment of Included Cost Studies using the Drummond checklist[8]

| Drummond checklist[8] | Thomas et al, 2017[20] | Rosen et al, 2016[22] | Hatoum et al, 2014[21] |
|---|---|---|---|
| 1. Was a well-defined question posed in answerable form | Yes | Yes | Yes |
| 2. Was a comprehensive description of the competing alternatives given (i.e. can you tell who did what to whom, where, and how often)? | Yes | Yes | Yes |
| 3. Was the effectiveness of the programme or services established? | Yes, observational data without randomization | Yes placebo-controlled RCT | Yes placebo-controlled RCT |
| 4. Were all the important and relevant costs and consequences for each alternative identified? | Only NSAIDs were considered | Yes | Yes |
| 5. Were costs and consequences measured accurately in appropriate physical units (e.g. hours of nursing time, number of physician visits, lost work-days, gained life years)? | Yes | Yes | Yes |
| 6. Were the cost and consequences valued credibly? | Yes | Yes | Yes |
| **7.** Were costs and consequences adjusted for differential timing? | No | No | No |
| **8.** Was an incremental analysis of costs and consequences of alternatives performed? | No | No | Yes |
| **9.** Was allowance made for uncertainty in the estimates of costs and consequences? | No | Yes | Yes |
| **10.** Did the presentation and discussion of study results include all issues of concern to users? | Yes | Yes | Yes |

## Table A6: Strengths and Limitations of Included Guidelines using AGREE II[9]

| Strengths | Limitations |
|---|---|
| **AMSSM: AMSSM Scientific statement concerning viscosupplementation injections for knee osteoarthritis: importance for individual patient outcomes[23]** | |
| • The overall objective of the guideline is specifically described.<br>• Systematic methods were used to search for evidence<br>• The health benefits, side effects, and risks have been considered in formulating the recommendations.<br>• The criteria for selecting the evidence are clearly described<br>• The recommendations are specific and unambiguous<br>• Key recommendations are easily identifiable.<br>• Competing interests of guideline development group members have been recorded and addressed | • The guideline was not externally reviewed by experts prior to its publication, only internally reviewed<br>• A procedure for updating the guideline is not provided.<br>• The funding body is not easily identifiable<br>• The guideline development group does not include individuals from all relevant professional groups, and is unclear<br>• The views and preferences of the target population have not been sought<br>• The guideline does not present monitoring or auditing criteria |
| **NICE: Osteoarthritis: Care and management[24]** | |
| • The overall objective of the guideline is specifically described.<br>• The health questions covered by the guidelines are specifically described<br>• The population to whom the guideline is meant to apply is specifically described, and the target users of the guideline are clearly defined.<br>• The guideline development group includes individuals from all relevant professional groups<br>• Systematic methods were used to search for evidence, with clearly described criteria for selecting evidence<br>• The strengths and limitations of the body of evidence are clearly described<br>• The methods for formulating the recommendations are clearly described<br>• The health benefits, side effects, and risks have been considered in formulating the recommendations<br>• There is an explicit link between the recommendations and the supporting evidence<br>• The guideline has been externally reviewed by experts prior to its publication<br>• A procedure for updating the guideline is provided<br>• Key recommendations are easily identifiable, specific and unambiguous<br>• Competing interests of guideline development group members have been recorded and addressed<br>• The funding body is easily identified | • The guideline does not provide advice or tools on how the recommendations can be put into practice<br>• The potential resource implications of applying the recommendations have not been considered<br>• The guideline does not present monitoring or auditing criteria |
| **OARSI: OARSI guidelines for the non-surgical management of knee osteoarthritis[25]** | |
| • The overall objectives of the guideline are specifically described.<br>• The health questions covered by the guideline are specifically described<br>• The population (patients, public, etc.) to whom the | • The criteria for selecting the evidence are not clearly described (i.e. no PICO table or criteria)<br>• Guideline was sent externally for public comment but not for external peer review<br>• A procedure for updating the guideline is not provided. |

## Table A6: Strengths and Limitations of Included Guidelines using AGREE II[9]

| Strengths | Limitations |
|---|---|
| guideline is meant to apply is specifically described<br>• The guideline development group includes individuals from all relevant professional groups<br>• The views and preferences of the target population (patients, public, etc.) have been sought through public comment<br>• The target users of the guideline are clearly defined<br>• Systematic methods were used to search for evidence<br>• The health benefits, side effects, and risks have been considered in formulating the recommendations<br>• The strengths and limitations of the body of evidence are clearly described<br>• The methods for formulating the recommendations are clearly described<br>• The different options for management of OA are clearly presented<br>• The views of the funding body have not influenced the content of the guideline<br>• Competing interests of guideline development group members have been recorded and addressed | • The recommendations are not specific and are slightly ambiguous<br>• The guideline does not describe facilitators and barriers to its application<br>• The guideline does not provide advice or tools on how the recommendations can be put into practice<br>• The potential resource implications of applying the recommendations have not been considered<br>• The guideline does not present monitoring or auditing criteria |
| **Va/DoD: VA/DoD clinical practice guideline for the non-surgical management of hip and knee osteoarthritis[26]** | |
| • The overall objectives of the guideline are specifically described<br>• The health questions covered by the guideline are specifically described<br>• The population (patients, public, etc.) to whom the guideline is meant to apply is specifically described<br>• The guideline development group includes individuals from all relevant professional groups<br>• The target users of the guideline are clearly defined<br>• Systematic methods were used to search for evidence<br>• The criteria for selecting the evidence are clearly described<br>• The strengths and limitations of the body of evidence are clearly described<br>• The methods for formulating the recommendations are clearly described<br>• The health benefits, side effects, and risks have been considered in formulating the recommendations<br>• There is an explicit link between the recommendations and the supporting evidence<br>• The recommendations are specific and unambiguous<br>• The different options for management of the condition or health issue are clearly presented<br>• Key recommendations are easily identifiable<br>• Competing interests of guideline development group members have been recorded and addressed | • The views and preferences of the target population (patients, public, etc.) have not been sought<br>• The guideline was not externally reviewed by experts prior to its publication, only internally reviewed<br>• A procedure for updating the guideline is not provided<br>• The guideline does not describe facilitators and barriers to its application<br>• The potential resource implications of applying the recommendations have not been considered<br>• The guideline does not present monitoring or auditing criteria<br>• The funding body is not easily identifiable |

## Table A6: Strengths and Limitations of Included Guidelines using AGREE II[9]

| Strengths | Limitations |
|---|---|
| **AAOS: American Academy of Orthopaedic Surgeons clinical practice guideline on the treatment of osteoarthritis of the knee, 2nd edition[27]** | |
| • The guideline development group includes individuals from all relevant professional groups<br>• The views and preferences of the target population (patients, public, etc.) have been sought.<br>• The target users of the guideline are clearly defined<br>• The guideline development group includes individuals from all relevant professional groups<br>• The views and preferences of the target population (patients, public, etc.) have been sought.<br>• The target users of the guideline are clearly defined.<br>• Systematic methods were used to search for evidence.<br>• The criteria for selecting the evidence are clearly described<br>• The strengths and limitations of the body of evidence are clearly described<br>• The methods for formulating the recommendations are clearly described.<br>• The health benefits, side effects, and risks have been considered in formulating the recommendations.<br>• There is an explicit link between the recommendations and the supporting evidence<br>• The guideline has been externally reviewed by experts prior to its publication.<br>• A procedure for updating the guideline is provided.<br>• The recommendations are specific and unambiguous<br>• The different options for management of the condition or health issue are clearly presented<br>• Key recommendations are easily identifiable.<br>• The views of the funding body have not influenced the content of the guideline<br>• Competing interests of guideline development group members have been recorded and addressed. | • The guideline does not describe facilitators and barriers to its application<br>• The guideline does not provide advice or tools on how the recommendations can be put into practice<br>• The potential resource implications of applying the recommendations have not been considered<br>• The guideline does not present monitoring or auditing criteria |
| **ACR: ACR 2012 recommendations for the use of nonpharmacologic and pharmacologic theories in osteoarthritis of the hand, hip and knee[28]** | |
| • The overall objectives of the guideline are specifically described<br>• The health questions covered by the guideline are specifically described<br>• The population (patients, public, etc.) to whom the guideline is meant to apply is specifically described<br>• The guideline development group includes individuals from all relevant professional groups<br>• The target users of the guideline are clearly defined<br>• Systematic methods were used to search for evidence<br>• The criteria for selecting the evidence are clearly described | • The views and preferences of the target population (patients, public, etc.) have not been sought<br>• The strengths and limitations of the body of evidence are not clearly described<br>• A procedure for updating the guideline is not provided<br>• The recommendations for HA injections are not specific or clear<br>• The guideline does not provide advice or tools on how the recommendations can be put into practice<br>• The potential resource implications of applying the recommendations have not been considered<br>• The guideline does not present monitoring or auditing |

## Table A6: Strengths and Limitations of Included Guidelines using AGREE II[9]

| Strengths | Limitations |
|---|---|
| • The methods for formulating the recommendations are clearly described<br>• The health benefits, side effects, and risks have been considered in formulating the recommendations<br>• There is an explicit link between the recommendations and the supporting evidence<br>• The guideline has been externally reviewed by experts prior to its publication<br>• The different options for management of the condition or health issue are clearly presented<br>• Key recommendations are easily identifiable<br>• The guideline describes facilitators and barriers to its application<br>• Competing interests of guideline development group members have been recorded and addressed | criteria<br>• The funding body is not clear |
| **Chronic OA<br>Management Initiative of the U.S. Bone and Joint Initiative: A systematic review of recommendations and guidelines for the management of osteoarthritis[29]** | |
| • The overall objectives of the guideline are specifically described.<br>• The health questions covered by the guideline are specifically described<br>• The population (patients, public, etc.) to whom the guideline is meant to apply is specifically described<br>• The guideline development group includes individuals from all relevant professional groups<br>• Systematic methods were used to search for evidence<br>• The criteria for selecting the evidence are clearly described<br>• The strengths and limitations of the included guidelines are clearly described<br>• The methods for formulating the recommendations are clearly described<br>• There is an explicit link between the recommendations and the supporting evidence<br>• The guideline has been externally reviewed by experts prior to its publication<br>• The recommendations are specific and unambiguous<br>• The different options for management of the condition or health issue are clearly presented<br>• Key recommendations are easily identifiable<br>• The views of the funding body have not influenced the content of the guideline<br>• Competing interests of guideline development group members have been recorded and addressed | • The views and preferences of the target population (patients, public, etc.) have not been sought<br>• The target users of the systematic review are not clearly defined<br>• The guideline does not describe facilitators and barriers to its application<br>• The guideline does not provide advice or tools on how the recommendations can be put into practice<br>• The potential resource implications of applying the recommendations have not been considered<br>• The guideline does not present monitoring or auditing criteria |

AAOS = American Academy of Orthopaedic Surgeons; ACR = American College of Rheumatology; AMSSM = American Medical Society for Sports Medicine; HA = hyaluronan; NICE = The National Institute for Health and Care Excellence; OA = Osteoarthritis; OARSI = Osteoarthritis Research Society International; Va/DoD = Veterans Affairs/Department of Defense

# Appendix 4: Main Study Findings and Author's Conclusions

## Table A7: Summary of Findings of Included Studies

| Main Study Findings | Author's Conclusion |
|---|---|
| **SRs and MAs** | |
| **He, 2017[10]** | |
| VAS scores at 1 month<br>n = 6 studies;<br>MD: 0.67,95%CI:0.07 to 1.27, p = 0.03<br><br>VAS score at 3 months<br>N = 8 studies<br>MD: 0.46, 95%CI: 1.31 to 0.39, p = 0.29;<br><br>VAS score at 6 months<br>N = 7 studies<br>MD: 0.73,95%CI: 1.25 to 0.21, p = 0.006; (favours HA)<br><br>WOMAC score at 3 months<br>n = 5 studies;<br>MD: 2.3,95%CI: 6.53 to 1.93, p = 0.29<br><br>WOMAC score at 6 months;<br>n = 4 studies<br>MD: 5.51,95%CI: 8.77 to 1.54, p = 0.005; (favours HA)<br><br>Proportion of rescue medication use<br>N = 3 studies<br>RR:1.04,95%CI:0.9 to 1.2, p = 0.58;<br><br>Proportion of withdrawal for knee pain<br>N = 5 studies<br>RR:1.29,95%CI:0.57 to 2.92, p = 0.54;<br><br>Active range of knee flexion at 3 months<br>n = 2 studies<br>MD:0.49,95%CI: 2.3 to 3.29, p = 0.73;<br><br>Active range of knee flexion at 6 months<br>N = 2 studies<br>MD:1.77,95%CI: 4.09 to 7.63, p = 0.55<br><br>**Treatment-related adverse effects**<br>N = 6 studies<br>RR:1.66,95%CI:1.34 to 2.06, p < 0.00001 (favours CS) | *"…Intraarticular CS is more effective on pain relief than intraarticular HA in short term (up to 1 month), while HA is more effective in long term (up to 6 months). Two therapies benefit similarly for knee function improvement. Both two methods are relatively safe, but intraarticular HA causes more topical adverse effects compared with intraarticular CS." (p. 102)* |
| **Bannaru, 2016[16]** | |
| **Any AEs**<br>N = Fifty-four studies (9,734 participants);<br>None of the 15 included HA products were statistically significantly different from IA placebo or each other. | *"This network meta-analysis investigated the safety profile of all available HA products and found that they are relatively well tolerated, and the incidence of any particular adverse events is very low. These products have a similar safety profile compared* |

## Table A7: Summary of Findings of Included Studies

| Main Study Findings | Author's Conclusion |
|---|---|
| **Local Reactions**<br>N = 57 trials (10,394 participants) involving 17 products and placebo contributed to the analysis of local reactions.<br><br>All the HA products had more reported local reactions than placebo, only 3 showed a statistically significant difference (BioHy, Durolane, and Synvisc)<br><br>BioHy performed statistically significantly worse than Euflexxa, Sinovial, Go-On, and Suvenyl.<br><br>**SAEs**<br>N = 47 trials including 9214 patients. For more widely studied products (received by 750 patients or more) percentages of patients reporting SAEs were similar and did not differ from the placebo event rate of 2.1%.<br><br>In studies of 13 other products that involved < 750 patients per product (n = 20 to 456) percentages of patients experiencing at least one SAE ranged from 0% to 9.4%. Most of the reported SAEs were unrelated to study treatment**.**<br><br>**Treatment-Related SAEs**<br>N = 41 trials including 8309 patients: 5661 receiving HA and 2648 receiving placebo. Among the 5661 patients who received an HA product, there were only 3 SAEs reported as potentially related to treatment; all of them were non-fatal. One event (septic arthritis), was reported among 709 patients receiving Orthovisc. Among the 1272 patients receiving Synvisc 2 events (a probable pseudoseptic reaction and an episode of anaphylactic shock shortly after injection) were reported. None of the patients receiving the other 15 HA products or placebo reported an SAE.<br><br>**Patient Withdrawals Due to Treatment-Related AEs**<br>N = 37 trials investigating 13 products and placebo, including 5550 patients. Among 900 patients receiving Hyalgan, 14 patients withdrew due to a treatment-related AE. 6 out of 135 patients receiving Hya-Ject and 5 of 281 patients receiving Durolane withdrew. 10 out of 1873 patients receiving placebo withdrew. 4 products (BioHy, N = 25, Go-On, N = 253, Supartz, N = 477, Synvisc, N = 636) had one withdrawal each. None of the other six products reported withdrawals<br><br>**Pseudoseptic Reaction**<br>N = 5 trials (1540 patients) of 5 products (Synvisc, Hyalgan, Orthovisc, Go-On, Structovial) as well as placebo. One pseudoseptic reaction was documented among 381 patients receiving Synvisc.<br><br>**Septic Joint**<br>Eighteen trials (2253 patients) assessed the outcome of septic | *with each other." (p. 230)* |

## Table A7: Summary of Findings of Included Studies

| Main Study Findings | Author's Conclusion |
|---|---|
| joint. One case of septic joint was documented among 783 patients receiving Orthovisc. No cases of septic joint were documented among patients receiving the eight other HA or placebo products. | |
| **Xing et al, 2016[18]** | |
| **Jadad Algorithm**<br>One 2006 Cochrane MA that was rated as the highest quality using the Jadad scale out of the included MAs was used to inform evidence on the efficacy of HA for knee OA.<br><br>HA has beneficial effects on pain, function and patient global assessment in the treatment of knee OA (effect size not reported).<br><br>HA was an effective treatment for knee OA at different post injection periods but especially at the 5 to 13-week post-injection period, and few adverse events were reported. However, there is considerable between-product, between-variable and time-dependent variability in the clinical response (effect size not reported). | *"Currently, the best evidence suggested that HA is an effective intervention in treating knee OA without increased risk of adverse events. Therefore, the evidence supports the use of the HA in the treating knee OA." (p. 10)* |
| **Jesevar, 2016[12]** | |
| **Treatment Effects**<br><br>Treatment effects were stratified by trial quality, follow-up duration, and molecular make-up of the HA under evaluation.<br><br>Double-blinded, sham-controlled trials had smaller treatment effects than trials that were not sufficiently blinded ($P < 0.05$).<br><br>For double-blinded trials, the overall treatment effect was less than half of the MID for pain, function, and stiffness.<br><br>Other significant associations were found for cross-linked HAs and follow-up duration.<br><br>The effect sizes among double-blinded trials of cross-linked HAs were still less than half of the MIDs for pain and stiffness.<br><br>The statistically significant effect of follow-up duration disappeared when the open-label trials were removed from the analysis. | *"Meta-analysis of only the double-blinded, sham-controlled trials with at least sixty patients did not show clinically important differences of HA treatment over placebo. When all literature was added to the analysis, the overall effect was greater but was biased toward stronger treatment effects because of the influence of nonblinded or improperly blinded trials."*<br><br>*"…this best-evidence systematic review assessing the clinical significance of outcomes involving pain relief and functional improvement does not support the routine use of intra-articular HA. In contrast to previous reviews, we found no significant evidence of publication bias in the studies that we selected for analysis. The patient benefit of intra-articular HA was not clinically important when compared with intra-articular saline solution injections used as a placebo. Subdividing HA preparations by molecular weight did not change the results of the analyses. Selecting the best evidence resulted in significantly reduced heterogeneity but did not change the outcome; no clinically important improvement in pain and other outcomes from a patient's perspective was found."(p. 2058)* |
| **Newberry, 2015[13]** | |
| **Delay or Avoidance of TKR**<br>N = 3 three RCTs: 2 did not specify TKR as a prespecified outcome of interest but as a treatment failure, whereas the third reported it as the primary outcome. One study reported higher rates of TKR among HA-treated patients, whereas the other two | *"Trials enrolling older participants show a small, statistically significant effect of HA on function. Whether this effect is clinically meaningful is less clear: The research literature varies on its definition of minimum clinically important improvement. Based on our analyses, HA demonstrated clinically important* |

## Table A7: Summary of Findings of Included Studies

| Main Study Findings | Author's Conclusion |
|---|---|
| reported higher rates among placebo-treated patients.<br><br>N = 6 case series and 7 cohort studies. Most studies reported delays in, or lower rates of, TKR with HA injections compared with the usual progression or the rate seen in an untreated cohort.<br><br>**Functional Outcomes**<br>N = 18 RCTs;<br>Pooled analysis of 10 sham-injection placebo-controlled, assessor-blinded trials showed a standardized mean difference of -0.23 (95% CI -0.34, -0.02) significantly favoring HA at 6 months' follow-up. Durability of effect could not be assessed because of the short duration of most studies. Too few head-to-head trials were available to assess superiority of one product over another.<br><br>Overall grade of evidence for HA versus placebo was low; for comparisons between HAs, insufficient.<br><br>**QoI**<br>N = 3 RCTs that compared changes in QoL and health-related QoL between HA and placebo-treated participants reported no differences between active treatment and placebo.<br><br>**AEs**<br>Studies of intra-articular HA reported few serious adverse events, with no statistically significant difference in the rates of serious or non-serious adverse events between HA and placebo. | *improvements using two out of three of these definitions for this assessment. HA shows relatively few serious adverse events; however no studies limited participation to those 65 years or older. No conclusions can be drawn from the available literature on delay or avoidance of TKR through the use of HA." (p. 73)* |
| **Sadabad, 2015[11]** | |
| WOMAC<br><br>SMD = -0.75 (95% CI: - 1.33 to -0.18, I2 = 92.6%; *P* = 0.000 (favouring PRP) | *"The results of this review showed that PRP was more effective than HA. PRP and HA are considered as non-surgical treatments for knee osteoarthritis. Using any of these methods has its own effects and complications. More studies should be conducted in the future to judge the efficacy of the two methods for more than a year." (p. 2120)* |
| **Campbell et al, 2015[19]** | |
| **IA-HA Versus IA-Placebo**<br>N = 10 studies; n = 5 found that IA-HA resulted in improvements in pain; n = 4 reported that IA-HA resulted in improvements in function; n = 3 found no difference between IA-HA and IA-placebo in terms of pain, and n = 4 found no difference in function. The remaining studies showed no clinically relevant differences in either pain or function.<br><br>**IA-HA Versus Oral NSAIDs**<br>N = 3 studies; No clinically relevant differences in the efficacy of IA-HA versus oral NSAIDs on knee pain and function were found; IA-HA was found to have a slightly more favorable | *"According to this systematic review of overlapping meta-analyses comparing IA-HA with other nonoperative treatment modalities for knee OA, the current highest level of evidence suggests that IA-HA is a viable option for patients with knee OA. Its use results in improvements in knee pain and function that can persist for up to 26 weeks in comparison with other treatment modalities. IA-HA has been shown to have a good safety profile, and its use should be considered in patients with early knee OA." (p. 9)* |

## Table A7: Summary of Findings of Included Studies

| Main Study Findings | Author's Conclusion |
|---|---|
| adverse reaction profile than NSAIDs.<br><br>**IA-HA Versus IA-PRP**<br>Both IA-HA and IA-PRP led to improvements in knee function at 2 and 6 months after injection, the positive effects of IA-HA were less robust than those of IA-PRP; there were no differences in adverse reactions.<br><br>**IA-HA Versus IA-Corticosteroids**<br>IA-corticosteroids provided better pain relief during the first 4 weeks after injection, but the positive effects of IA-HA were greatest at the 5- to 13-week post-injection time point, and this relief persisted for up to 26 weeks in 2 studies.<br><br>**IA-HA Product Comparisons**<br>No definitive conclusions could be drawn about the best HA product in the studies that compared the different formulations of HA products.<br><br>**JADAD Algorithm**<br>After application of the Jadad algorithm, 2 concordant high-quality meta-analyses were selected and both showed that IA-HA provided clinically relevant improvements in pain and function compared with IA-placebo. | |
| **Ammar, et al, 2015[14]** | |
| No synthesis provided. | *"In the light of the evidence that currently exists, there is still no solid basis for indicating or even for contraindicating the use of intra-articular viscosupplementation with hyaluronic acid or its derivatives for treating symptomatic knee osteoarthrosis." (p. 493)* |
| **Wang, et al, 2015[15]** | |
| **VAS at 1 Month**<br><br>MD 1.66: 95% CI; -0.90, 4.23), indicating equal efficacy for HA and CS.<br><br>**VAS at 3 Months**<br><br>MD: 12.58 (95% CI; -17.76, -7.40)<br><br>**VAS at 6 Months**<br><br>MD: -9.01 (95% CI; -12.62, -5.40), favoring HA.<br><br>**Other Outcomes**<br><br>For the additional indicators, including the Lequesne index, the KSS, maximum flexion and adverse events, no statistically significant differences were observed between the 2 treatment approaches. | *"HA has a similar level of pain relief compared with CS in the short term (up to one month); however, HA is more effective than CS over a longer time period (up to six months). The potential for adverse events are similar between the two interventions." (p. 500)* |

## Table A7: Summary of Findings of Included Studies

| Main Study Findings | Author's Conclusion |
|---|---|
| **Bannuru, 2015[17]** | |
| Effect Sizes for Pain Compared with HA (95% CrL)<br><br>Oral placebo: 0.63 (0.39 to 0.88)C<br>Acetaminophen: 0.45 (0.18 to 0.72)†<br>IA Placebo: 0.34 (0.26 to 0.42)†<br>Celecoxib: 0.30 (0.04 to 0.55)†<br>Naproxen: 0.25 (0.01 to 0.49)†<br>Ibuprofen: 0.19 (−0.09 to 0.47)<br>Diclofenac: 0.11 (−0.14 to 0.37)<br>IA corticosteroids: 0.02 (−0.12 to 0.17)<br><br>†Statistically significant<br><br>**Function**<br><br>All interventions except IA CS were statistically significantly superior to oral placebo, with effect sizes ranging from 0.15 to 0.45. Naproxen, ibuprofen, diclofenac, and celecoxib were statistically significantly better than acetaminophen. IA HA was statistically significantly better than IA placebo and IA corticosteroids (effect size not provided in article).<br><br>**Stiffness**<br><br>IA-HA was statistically significantly better than IA placebo (effect size not reported in article).<br><br>**AEs**<br><br>Withdrawals due to AEs were more common among oral treatments (acetaminophen, nonselective NSAIDs, and celecoxib) than IA therapies. The most commonly reported adverse events among the IA therapies were transient local reactions, such as pain, swelling, and arthralgia. These events were reported to be similar between different IA therapies (CS vs HA). Among the 29 trials reporting on septic arthritis, 1 patient who received IA placebo had a septic joint out of 3152 patients who had approximately 9500 IA injections | *"This network meta-analysis compared the most commonly used pharmacologic interventions for knee OA–related pain at 3 months and concluded that all treatments except acetaminophen showed clinically significant improvement in pain. Intra-articular treatments were more effective than NSAIDs for pain, which is possibly due to the contribution of the integrated IA placebo effect." (p. 53)* |
| **Blue Cross/Blue Shield, 2014[3]** | |
| **Pain and Function**<br>**2** MAs concluded IA HA provides a clinically meaningful benefit compared with placebo but 3 MAs offered contrary conclusions.<br><br>3 RCTs published subsequent to the search dates of the MAs provide no evidence that IA HA provides clinically meaningful improvement over placebo. | *"A large body of evidence comparing the effects of IAHA with placebo does not demonstrate IAHA improves the net health outcome in patients with knee OA." (p. 24)* |
| **Pai, 2014[4]** | |

## Table A7: Summary of Findings of Included Studies

| Main Study Findings | Author's Conclusion |
|---|---|
| VAS (MA of 2 studies) at 6-Month Follow-up<br><br>Mean Difference: –12.96 (95% CI: -35.48, 9.56), *P* = 0.26.<br><br>(No significant difference between Hylan G-F 20 and control in terms of reduction in VAS for weight bearing pain.) | *"On the basis of the available evidence, we conclude that there is no significant difference in the improvement of Visual Analogue Scores for weight-bearing pain in the osteoarthitic knees of patients treated with Hylan G-F 20 and control preparations." (p. 1046)* |
| **Trigkilidas, 2013[6]** | |
| **HA Versus Placebo**<br>(effect sizes not reported)<br>Of the 14 studies that were reviewed, 12 compared HA with a placebo<br><br>5 studies showed no statistically significant difference between the two groups.<br><br>1 study suggested an effect in favour of HA for up to a year following injection<br><br>1 study suggested an effect in favour of HA for up to six months following injection<br><br>3 studies suggested a statistically significant superiority of HA over placebo for a period of time not exceeding 18 weeks.<br><br>2 studies reported a modest effect in favour of HA over placebo for pain that was noticeable at 6 months, but not for function.<br><br>**HA Versus CS**<br>(no effect sizes reported)<br><br>2 studies compared HA with CS<br><br>1 showed no statistically significant difference between the two groups; the other had a very high dropout rate, and suggested that HA was better at six months than CS | *"There is weak evidence to support the efficacy of HA in managing knee osteoarthritic pain. The evidence that HA is more efficacious than steroid injections is even weaker. At very best, the effect of HA on knee OA can be described as modest. Overall, there appears to be a small effect with the use of HA over placebo, which peaks around week 8 following the last injection. There is very little evidence to support that the effect is still noticeable at six months. Compared with steroids, steroid injections tend to be superior to HA up to four weeks, with HA becoming superior after that timeframe and up to eight weeks." (p. 551)* |
| ***Cost Studies*** | |
| **Thomas, 2017[20]** | |
| WOMAC sub-scores and the EQ-5D QoL index were significantly improved in the IA HA group (*P* < 0.0001) at 3 and 6 months.<br><br>No evidence of additional cost from IA HA.<br><br>The cost-utility analysis was in favor of IA HA, with a gain of QALY equivalent to half a month at 6-month follow-up<br><br>NSAIDs consumption decreased in the IA HA group, resulting in an improved estimated benefit/risk ratio. | *"…treatment with intra articular hyaluronic acid (Arthrum H 2%), did not generate additional cost for the national health insurance and was associated with a functional improvement of knee OA and quality of life."(p. 14)*<br><br>*"…the cost-utility analysis had concluded in favor of hyaluronic acid, based on a better improvement of the pain, function and quality of life (+0.042 QALY), than with the conventional knee OA treatment. In parallel, NSAIDs consumption was significantly decreased (-46.7% in expense) in patients treated with hyaluronic acid, improving the estimated benefit-risk ratio." (p. 14)* |

## Table A7: Summary of Findings of Included Studies

| Main Study Findings | Author's Conclusion |
|---|---|
| ***Rosen, 2016***[22] | |
| **(US$)**<br>**Prevalence**<br>The target treatment group of OA with severity grades 2–3 is estimated at 4 million people eligible for HA in the USA.<br><br>**QALYs**<br>With current use, it is estimated that the HA agent can save 36,730 QALY/year among the US population, and has the potential to save an additional 369,181 QALY/year if used by all eligible patients. | *"This study demonstrates that more widely used, biologically derived, high molecular weight IA-HAs, such as Euflexxa, have the potential to save a substantial number of QALYs among the US population with symptomatic knee osteoarthritis."* (p. 2201) |
| ***Hatoum,2014***[21] | |
| **Utility Gain**<br><br>HA average utility gain was 0.163 QALYs (95% CI = −0.162 to 0.488) over 52 weeks.<br><br>**Treatment Costs**<br>Model 1 treatment costs were $US3469 and $US4562 for the BioHA and CC groups, respectively; sensitivity analyses showed BioHA to be the dominant treatment strategy, except when at the lower end of the 95% CI. Model 2 annual treatment costs per QALY gained were $US1446 and $US516 for the BioHA and CC groups, respectively.<br><br>**ICER**<br>Using care with NSADs and analgesics as a baseline strategy, the incremental cost-effectiveness ratio (ICER) of HA was $US38,741/QALY gained, and was sensitive to response rates in either the BioHA or CC groups. | *"BioHA is less costly and more effective than CC with NSAIDs and analgesics, and is the dominant treatment strategy. Compared with escalating CC, the $38,741/QALY ICER of BioHA remains within the $50,000 per QALY willingness-to-pay threshold to adopt a new technology."* |

AE = adverse event; CS = corticosteroids; CI = confidence interval; CrL: credible interval; EQ-5D = EuroQuol-5 Dimension; HA = hyaluronic acid; IA = intra-articular; ICER = incremental cost-effectiveness ratio; MD = mean difference; KSS = Knee Society Clinical Rating System; MID = minimal important difference; NSAIDs = non-steroidal anti-inflammatory drugs; OA = osteoarthritis; PRP = platelet-rich plasma; QALY = quality-adjusted life year; QoL = quality of life; RCT = randomized controlled trial; RR = relative risk; SAE = serious adverse event; SMD = standard mean difference; TKR = total knee replacement; VAS = Visual Analog Scale; WOMAC = Western Ontario and McMaster Universities Osteoarthritis Index.

## Table A8: Summary of Guideline Recommendations

| First Author/Guideline Society or Institute | Year | Recommendation | Strength of Recommendation | Quality of Evidence (Assessed by Guideline Authors) |
|---|---|---|---|---|
| **AMSSM**[23] | 2016 | • "We recommend viscosupplementation injections for Kellgren and Lawrence (KL) grade II-III knee OA in those patients above the age of 60 years of age based on high quality evidence demonstrating benefit using OMERACT-OARSI Responder Rating" (p. 91) | Not reported | High Quality |
| | | • "We suggest viscosupplementation injections for knee OA for those under the age of 60 years of age based on moderate quality evidence due to response of treatment in those over 60 years of age" (p. 91) | Not reported | Moderate Quality |
| **NICE**[24] | 2014 | • "Do not offer intra-articular hyaluronan injections for the management of osteoarthritis" (p. 401) | Not reported | Very low to moderate quality (licensed viscosupple-mentation)<br><br>Very low to high quality (unlicensed viscosupple-mentation) |
| **OARSI**[25] | 2014 | • "Uncertain: knee-only OA" (p. 374) | Not reported | Good quality |
| | | • "Not appropriate: multiple-joint OA" (p. 374) | Not reported | Good quality |
| **VA/Dod**[26] | 2014 | • "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" (p.16) | Not reported (Insufficient evidence) | Insufficient evidence |
| | | • "…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." (p. 42) | Not reported | Not reported |
| **AAOS**[27] | 2013 | • "We cannot recommend using hyaluronic acid for patients with symptomatic osteoarthritis of the knee." (p. 4) | Strong | Moderate to High Quality |
| **ACR**[28] | 2012 | • "We have no recommendations regarding the use of intraarticular hyaluronates, duloxetine, and opioid analgesics" (p. 470) | Not reported | Not reported |

## Table A8: Summary of Guideline Recommendations

| First Author/Guideline Society or Institute | Year | Recommendation | Strength of Recommendation | Quality of Evidence (Assessed by Guideline Authors) |
|---|---|---|---|---|
| | | • "If the patient does not have a satisfactory clinical response to full-dose acetaminophen…for persons age ≥75 years… the TEP conditionally recommends the use of tramadol, duloxetine, or intraarticular hyaluronan injections" (p. 470) | Not reported | Not reported |
| **The Chronic Osteoarthritis Management Initiative of the U.S. Bone and Joint Initiative**[29] | 2014 | • "Insufficient evidence currently exists to provide a general recommendation regarding intra-articular hyaluronans." (p. 708) | Not reported | Not reported |

AAOS = American Academy of Orthopaedic Surgeons; ACR = American College of Rheumatology; AMSSM = American Medical Society for Sports Medicine; HA = hyaluronan; NICE = The National Institute for Health and Care Excellence; OA = Osteoarthritis; OARSI = Osteoarthritis Research Society International; Va/DoD = Veterans Affairs/Department of Defense

# Appendix 5: Additional References of Potential Interest

PRP Intervention with HA as One of the Comparators

Shen L, Yuan T, Chen S, Xie X, Zhang C. The temporal effect of platelet-rich plasma on pain and physical function in the treatment of knee osteoarthritis: systematic review and meta-analysis of randomized controlled trials. J Orthop Surg Res. 2017 Jan 23;12(1):16. Available from:

Kanchanatawan W, Arirachakaran A, Chaijenkij K, Prasathaporn N, Boonard M, Piyapittayanun P, et al. Short-term outcomes of platelet-rich plasma injection for treatment of osteoarthritis of the knee. Knee Surg Sports Traumatol Arthrosc. 2016 May;24(5):1665-77.

Meheux CJ, McCulloch PC, Lintner DM, Varner KE, Harris JD. Efficacy of Intra-articular Platelet-Rich Plasma Injections in Knee Osteoarthritis: A Systematic Review. Arthroscopy. 2016 Mar;32(3):495-505.

Sadabad HN, Behzadifar M, Arasteh F, Behzadifar M, Dehghan HR. Efficacy of Platelet-Rich Plasma versus Hyaluronic Acid for treatment of Knee Osteoarthritis: A systematic review and meta-analysis. Electron Physician. 2016 Mar;8(3):2115-22.

Campbell KA, Saltzman BM, Mascarenhas R, Khair MM, Verma NN, Bach BR, Jr., et al. Does Intra-articular Platelet-Rich Plasma Injection Provide Clinically Superior Outcomes Compared With Other Therapies in the Treatment of Knee Osteoarthritis? A Systematic Review of Overlapping Meta-analyses. Arthroscopy. 2015 Nov;31(11):2213-21.

Lai LP, Stitik TP, Foye PM, Georgy JS, Patibanda V, Chen B. Use of Platelet-Rich Plasma in Intra-Articular Knee Injections for Osteoarthritis: A Systematic Review. Pm r. 2015 Jun;7(6):637-48.

Laudy AB, Bakker EW, Rekers M, Moen MH. Efficacy of platelet-rich plasma injections in osteoarthritis of the knee: a systematic review and meta-analysis. Br J Sports Med. 2015 May;49(10):657-72.

Chang KV, Hung CY, Aliwarga F, Wang TG, Han DS, Chen WS. Comparative effectiveness of platelet-rich plasma injections for treating knee joint cartilage degenerative pathology: a systematic review and meta-analysis. Arch Phys Med Rehabil. 2014 Mar;95(3):562-75.

Khoshbin A, Leroux T, Wasserstein D, Marks P, Theodoropoulos J, Ogilvie-Harris D, et al. The efficacy of platelet-rich plasma in the treatment of symptomatic knee osteoarthritis: a systematic review with quantitative synthesis. Arthroscopy. 2013 Dec;29(12):2037-48.

Dai WL, Zhou AG, Zhang H, Zhang J. Efficacy of Platelet-Rich Plasma in the Treatment of Knee Osteoarthritis: A Meta-analysis of Randomized Controlled Trials. Arthroscopy. 2017 Mar;33(3):659-70.