

Technology Assessment



**Technology
Assessment Program**

Systematic Review for Effectiveness of Hyaluronic Acid in the Treatment of Severe Degenerative Joint Disease (DJD) of the Knee

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Systematic Review for Effectiveness of Hyaluronic Acid in the Treatment of Severe Degenerative Joint Disease (DJD) of the Knee

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Systematic Review of Effectiveness of Hyaluronic Acid in the Treatment of Severe Degenerative Joint Disease (DJD) of the Knee

Structured Abstract

Purpose. AHRQ's Office of Technology Assessment and its partner, the Centers for Medicare and Medicaid Services (CMS), requested a review of the evidence that intra-articular injections of hyaluronic acid (HA) in individuals with degenerative joint disease of the knee improve function and quality of life (QoL) and that they delay or prevent the need for knee replacement (KR), specifically for individuals age 65 and over.

Data Sources. Searches of Medline, Cochrane Library, Web of Science, Clinicaltrials.gov, the FDA Premarket Approval database, and unpublished documents identified in grey literature searches or provided by manufacturers.

Review Methods. Randomized controlled trials (RCTs) or observational studies that reported on HA administration and delay or avoidance of KR; double-blind placebo controlled RCTs that reported on functional outcomes or QoL; RCTs, case reports, and large cohort studies and case series that assessed the safety of HA; and unpublished data identified through grey literature searches or provided by manufacturers for efficacy or safety outcomes, in human subjects of mean age 65 or older, were considered for inclusion, as were recent comprehensive systematic reviews that reported on the effects of HA injections on knee pain as an outcome. A standardized protocol with predefined criteria was used to extract details on study design, interventions, outcomes, and study quality.

Results. Only one RCT reported on delay or avoidance of KR as a pre-specified outcome of interest and found a non-statistically significantly longer delay of KR compared with placebo; two RCTs reported KR only as a secondary outcome; and 13 observational studies reported on KR as an outcome in HA-treated participants.

Eighteen RCTs that enrolled participants of average age 65 or older reported on functional outcomes of intra-articular HA injection: pooled analysis of ten 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 (but not meeting the prespecified minimum clinically important difference of -0.37). 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. Three RCTs that compared changes in QoL/HRQoL between HA- and placebo-treated participants reported no differences between active treatment and placebo. A large, good quality systematic review that assessed the effects of HA on pain and function (pooling 71 and 52 RCTs respectively) showed a significant and clinically important effect of HA on both outcomes among adults of all ages, but a subgroup analysis that included only the larger double-blind placebo-controlled studies reduced the average effect of HA to less than the prespecified minimum clinically important difference. Stratified analysis that compared the pooled effect size of 54 sham-controlled RCTs with that of 18 studies without sham controls found that the sham-controlled studies significantly reduced

pain with an average effect just short of clinical importance. 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-treated groups.

Conclusions. Trials enrolling older participants show a small, statistically significant effect of HA on function, but the average effects do not meet the minimum clinically important difference; 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 KR through the use of HA. Studies, preferably randomized controlled trials, that can compare large numbers of treated and untreated individuals are needed to answer this question.

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Executive Summary

Background

Osteoarthritis (degenerative joint disease [DJD]) of the knee is a condition characterized by the progressive destruction of the cartilage that lines the knee joint, and when severe, results in bone-on-bone friction and accompanying pain, immobility, and reduction in the ability to complete activities of daily living (ADL).

In 2005, the estimated prevalence of osteoarthritis among adults in the United States, the number of individuals who had ever been told by a doctor that they had the condition, was approximately 27 million cases.¹ Prevalence rates vary by the joint involved and the method of ascertainment (clinical vs. radiographic): symptomatically, the knee is the most frequently affected joint.² The prevalence of osteoarthritis of the knee is increasing rapidly because of shifting population demographics: The primary risk factors for osteoarthritis of the knee are aging, obesity, prior injury, repetitive use,³ and female gender. The prevalence of symptomatic knee osteoarthritis may reach 50 percent by the age of 75. From 2002 to 2012, the number of individuals in the US with a total knee replacement doubled from some 2 million to approximately 4 million.⁴ The increase in obesity has translated not only into an increase in incidence of osteoarthritis of the knee but also into a younger age of onset and need for treatment; as a result, by the time individuals with osteoarthritis of the knee reach the age of Medicare eligibility, the length of time they have had the condition has grown, their cases are more advanced,⁵ and the risk that surgery will be needed has increased. Thus, the aging of the baby boomer population, along with the increased incidence and prevalence of obesity have increased the risk for this condition, all representing an increasing strain on Medicare resources.

Condition and Therapeutic Strategies

Diagnosis. Osteoarthritis of the knee is usually diagnosed clinically based on pain. Radiographic evidence of osteoarthritis may precede symptomatic osteoarthritis and unfortunately correlates weakly with symptom severity. Radiologic severity can be estimated and expressed using the Kellgren and Lawrence criteria; however, a number of versions of the criteria exist: At low cutoff scores, correlation with symptoms is poor,⁶ whereas at higher cutoff scores, agreement tends to be higher. The primary impact of these different versions of the criteria may be the challenge that they create in trying to assess, compare, and pool the findings of research studies:⁶ Some longitudinal studies have even used different criteria at different time points within the same study. Because of the variation in scores for radiographic finding under various versions of the criteria (especially for individuals with less-advanced disease), stratification is important.

Some evidence suggests that among individuals with knee pain, MRI demonstrates physical signs of osteoarthritic changes in the knee before they are visible radiographically.⁷ However, the sensitivity and specificity of MRI in diagnosis and monitoring of progression have not yet been definitively demonstrated and is not used in routine clinical practice.

Treatment. The goals of treatment for osteoarthritis of the knee include relief of pain and inflammation, slowing of progression, and improvement in or maintenance of mobility and function (ADLs and health-related quality of life [HRQoL]). Treatment options for osteoarthritis

of the knee include oral or topical analgesics (non-steroidal anti-inflammatories, acetaminophen), injected corticosteroids, physical therapy and exercise (both to strengthen muscles that support the affected joints and to increase range of motion), weight loss, partial or total arthroplasty (an alternative term for knee replacement) for advanced cases, and more recent therapies such as viscosupplementation, which involves local injections of the natural joint lubricant, hyaluronic acid, among other treatments.⁸

Hyaluronic acid (hyaluronate or hyaluronan) is a high molecular weight glycosaminoglycan synthesized in plasma membranes of connective tissues and secreted into the synovial fluid surrounding joints, where it forms part of the extracellular matrix.⁹ Progressive osteoarthritis of the knee includes loss of the cells responsible for synthesizing the substance, resulting in lower-viscosity endogenous hyaluronate. A large number of trials have examined the efficacy and safety of supplemental hyaluronic acid injections (classified by the United States Food and Drug Administration as a medical device), with varying efficacy outcomes. Systematic reviews have attempted to resolve these conflicting findings. Some reviews have reported positive outcomes^{10, 11} whereas some have reported mixed effects^{12, 13} or no effect.¹⁴ A 2010 update of an earlier systematic review actually found a decrease in the effect size for hyaluronic acid on knee osteoarthritis from the previous review.¹⁵ The discrepancies in outcomes are likely due to study heterogeneity both within and among reviews with respect to population characteristics, intervention modalities, treatment and followup duration, and the actual outcomes measured (e.g., pain, functionality, HRQoL), as well as the measures employed. Heterogeneity may also be attributable to how efficacy is expressed, i.e., the proportion of each treatment group that responds positively to treatment, vs. the mean change in that efficacy measure from baseline in the active treatment group vs. the comparison group.

In the 2012 update to their 2000 guidelines for the treatment of osteoarthritis of the knee, hip, and hand, the American College of Rheumatology conditionally recommended hyaluronic acid injections for patients who had an inadequate response to initial therapy.⁸ The 2013 American Academy of Orthopedic Surgeons guidelines for the treatment of osteoarthritis of the knee recommend against the use of hyaluronic acid to treat patients with symptomatic conditions.¹⁶

Assessment of Outcomes of Treatment

A number of assessment tools are used to assess pain, quality of life, and physical functioning in patients with osteoarthritis of the knee. These tools can be divided into those specifically developed for knee osteoarthritis and those that are used for a variety of conditions.

Tools specifically developed and validated to assess pain and functioning associated with osteoarthritis of the knee as well as treatment outcomes include the Western Ontario-Macmaster (WOMAC¹⁷), the Lequesne Index¹⁸, the Knee Injury and Osteoarthritis Outcomes Score (KOOS¹⁹), and the Animated Activity Questionnaire.²⁰ In 2004, the Osteoarthritis Research Society International (OARSI) developed a consensus set of guidelines to assess the outcomes of research trials on products intended to treat osteoarthritis; and under the International League of Rheumatologists, OMERACT (Outcome Measures in Rheumatology) has developed guidelines on outcome measures.²¹

General tools that have been adapted for use in assessing osteoarthritis of the knee include the Short form (SF)-36, developed at RAND for the Medical Outcomes Study²² and the Activities of Daily Living (ADLs) and IADLs assessment.

The Kinemax Outcomes Group has used a combination of the WOMAC, the SF-36, and a series of questions addressing demographic characteristics to predict patient outcomes of total knee arthroplasty.²³

The Aims of the Current Report. The scope of work for this task order includes an assessment of the evidence that hyaluronic acid injections prevent or delay the need for arthroplasty among individuals 65 and over. CMS currently covers hyaluronic acid injections for elderly Medicare recipients under certain conditions.²⁴ If hyaluronic acid is effective, it is postulated that it might effectively prevent or delay the need for life-disrupting surgery and rehabilitation by relieving pain and improving function with minimal inconvenience or adverse effects; however, if the treatment delays arthroplasty but fails to halt progressive degeneration, patients could potentially experience worse outcomes, although thus far, evidence for such outcomes has been weak. In addition to assessing the evidence for a role of HA in delaying or preventing the need for KR, this report aims to assess the evidence to date on the efficacy of intra-articular injections of HA with respect to the outcomes of function, ADLs/IADS, quality of life, and pain and on the safety of HA when used as indicated.

Scope and Key Questions

The key questions were provided by the CMS Coverage Analysis Group. They are presented here along with a description of the participants, interventions, comparators, outcomes, and timeframes (PICOTs) of interest, which defined the inclusion and exclusion criteria of the review. An analytic framework that shows the interrelationships among the presenting problems, the interventions and the outcomes of interest appears below.

Key question 1. Does intra-articular injection of hyaluronic acid eliminate the need for knee replacement surgery? Is this outcome affected by the type of hyaluronic acid, the type of presentation, severity at study entry, or age at study entry?

Key Question 2. Does intra-articular injection of hyaluronic acid significantly postpone the need for knee replacement surgery?

Key Question 3. Does intra-articular injection of hyaluronic acid improve the ability to successfully perform activities of daily living (ADLs) or instrumental activities of daily living (IADLs)?

Key Question 4. Does intra-articular injection of hyaluronic acid improve quality of life? PICOTs for KQ1 through 4 are the same with the exception of outcomes.

Criteria for Inclusion/Exclusion of Studies in the Review We sought randomized placebo-controlled trials, head-to-head trials, or quasi-randomized trials that reported results for individuals whose average age was 65 or older and were powered to see a clinically important difference; that assessed the effects of intra-articular HA; and that reported on any of the following outcomes: function, quality of life, delay of total knee replacement, and prevention of the need for total knee replacement (as well as factors that might affect these outcomes, such as age, disease severity, or comorbidities). If no RCTs were identified that reported the outcomes of interest, we included observational studies that assessed the outcome in question. Studies were

included that enrolled individuals with other comorbidities and that enrolled community dwelling or institutionalized participants. Acceptable comparators included placebo (sham injection) or other HA devices. Followup times of 4 weeks or longer were accepted. Adverse effects were assessed in randomized placebo-controlled trials and large observational studies. Although it was outside the original scope, we also assessed the effects of HA on pain because it is the most frequently reported primary outcome in trials of intraarticular HA injection ; for this outcome, we identified a recent, comprehensive, good quality systematic review as well as randomized placebo-controlled trials published after the reviews.

Figure A. Analytic framework of the effects of hyaluronic acid (HA) (vs. placebo or active comparator) on function, pain, adverse events, and delay/avoidance of total knee replacement (arthroplasty)

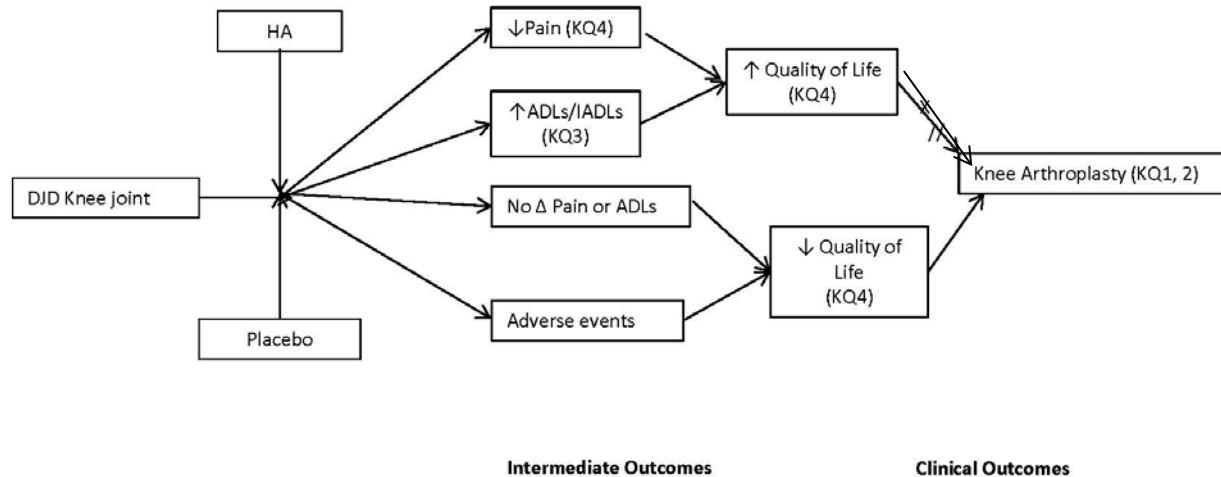


Table notes: ADL: Activities of Daily Living; DJD=Degenerative Joint Disease; HA=Hyaluronic Acid; IADLs=Instrumental Activities of Daily Living

Methods

Literature Search Strategy

The search strategy was based in part on a search conducted for a 2012 evidence review on HA,¹⁴ with the addition of search terms for the additional outcomes of interest: arthroplasty/total knee replacement, functional outcomes (e.g., WOMAC, Lequesne Index), ADLs, IADLs (including terms for the tools commonly used to assess ADLs and IADLs, e.g., Lawton IADL scale, Katz Index), and quality of life (Appendix A of the full report).

PubMed, CINAHL, EMBASE, Web of Science, SCOPUS, and Cochrane were searched from 1990 to the present to identify original studies of HA. The database Grey Matter was searched for grey literature, and clinicaltrials.gov was searched for not-yet-published findings and ongoing studies. The AHRQ Scientific Resource Center contacted the manufacturers of HA preparations approved for use in the US to obtain scientific information packets (SIPs). We searched the FDA Premarket Approval (PMA) database, any studies accepted for inclusion, and the SIPs for adverse events. Systematic reviews that reported on outcomes of interest were identified by searching the Cochrane Database, and original studies were obtained if not already identified among the results of the searches. Non-US studies were included if the intervention on which they reported was approved in the US for the indicated use, or if it was similar to a device

approved for use in the US. Non-English language studies were not included; however we surveyed a random sample of the abstracts of non-English language studies to assess whether these studies differed in any apparently systematic way from English-language studies (the results are presented in Appendix E of the full report).

The titles and abstracts obtained from the literature searches were dually screened after being input into the systematic review database, DistillerSR; all selected articles were obtained. A second round of screening was then conducted with full text to exclude articles that provided no usable data on the outcomes of interest; reported duplicate data; were observational in design and reported only on adverse events and enrolled fewer than 500 participants; or enrolled a population whose mean age was less than 65 years (unless the study outcomes were reported by age group and we could abstract outcomes for older individuals). When conference abstracts of interest were identified, we sought peer reviewed articles that reported the same data.

An update search will be conducted, dating back to 6 months prior to the initial searches, while the draft report undergoes peer review. Any new analogs that have entered testing or been approved for use will be added to the search strategy at that time and additional SIPs will be requested. Any new articles identified by the update search or suggested by peer reviewers will be screened using the methods applied initially.

Risk of Bias [Quality] Assessment of Individual Studies

Individual study quality/risk of bias (ROB) for randomized trials was assessed using a set of questions adapted from the Cochrane Risk of Bias Assessment Tool²⁵ and the EPC Methods Handbook (chapter 5).²⁶ The quality of observational studies included for assessment of efficacy was assessed using a modification of the Newcastle-Ottawa Scale.²⁷ The quality of systematic reviews was assessed using the AMSTAR tool.²⁸

Data Synthesis

Study-level details and outcome data were dually abstracted in DistillerSR. Disagreements were reconciled with the input of the principal investigator. Data that were collected fell into two categories: PICOTs (study-level data) and outcomes (study findings). Study-level data included the population demographics (age, sex, weight status), fitness level (if reported), comorbidities, disease stage, methods of ascertainment, intervention protocols, comparators, outcomes assessed in the study, and time course of interventions. Data were abstracted for the following outcomes, when reported: receipt of arthroplasty, time elapsed between HA therapy and surgery, change in functional status (including ADLs/IADLs), QoL/Health-related QoL, and adverse events.

If a sufficient number of studies was determined to be relatively homogeneous with respect to intervention, outcome, and follow-up times, we conducted a meta-analysis, estimating a pooled random-effects estimate of the overall effect size using the Hartung-Knapp-Sidik-Jonkman method for our random effects meta-analysis.²⁹ This method has been preferred when the number of pooled studies is small. It has been shown that the error rates are more acceptable than the previously used DerSimonian and Laird method.³⁰

To obtain an estimate of the clinical importance of the effect size, the minimum clinically important difference (MCID), we multiplied the pooled effect size by the standard deviation obtained from a large trial with a similar intervention for which functional outcome was assessed using the WOMAC. We then compared this change (based on a 100-point Visual Analog Scale

[VAS]), to the MCID employed by a number of studies of the effects of treatment on WOMAC-assessed function, including a recent large systematic review.¹⁴

Publication bias was assessed for all pooled outcomes using the Begg adjusted rank correlation test³¹ and Egger regression asymmetry test.³² Heterogeneity was assessed using the I² test.³³ An effect-size or odds ratio was calculated for trials that reported data but did not contribute to a pooled analysis, and these studies were described narratively. All efficacy analyses were conducted with Stata statistical software, version 12.0 (Stata Corp., College Station, Texas). Because we identified several large, recent, comprehensive systematic reviews on the outcome of pain, we selected the most recent (and comprehensive) and described the results of this review as well as those of newer original trials that were not included in a prior meta-analysis.

Strength of the Body of Evidence

The strength of evidence was assessed for each conclusion within each key question using the EPC modification of the GRADE system (Table A).³⁴ The domains are defined in Appendix G of the full report.³⁵

Applicability

The applicability of the findings was assessed based on age, study setting, and study design.

Results

We describe first the results of the literature searches, followed by the findings for effects of hyaluronic acid treatment on total knee replacement, function, quality of life, pain, and adverse events.

Results of Literature Searches

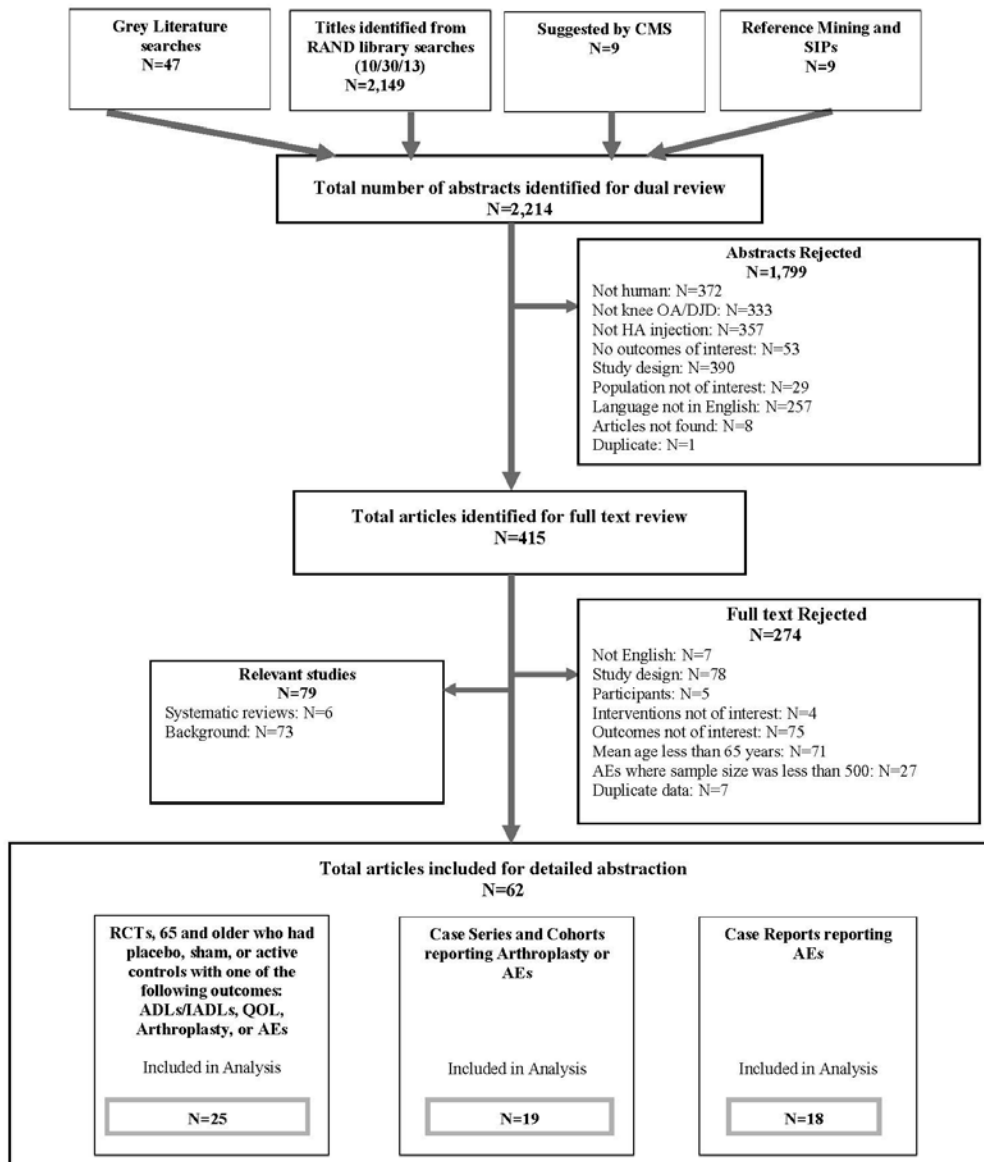
The searches of peer reviewed literature identified 2,149 unique titles. The partner, CMS, provided 84 titles, of which all but 9 were already included in the search results. Reference mining of those studies yielded an additional seven titles. The searches of grey literature yielded 47 titles. Information provided by manufacturers (Scientific Information Packets (SIPs)) included two titles, of which two unique titles were accepted. Altogether, 2,214 titles and abstracts went on to dual screening.

Of the 2,214 titles, 415 were initially identified for full-text review. The remaining 1,799 titles and abstracts were rejected for being animal or in vitro studies (372), not reporting on DJD of the knee (333), not using intra-articular HA injections (357), not reporting any outcomes of interest (53), having an inappropriate study design (e.g., obvious commentaries or non-systematic reviews) (390), not enrolling a population of interest (29), or being written in a non-English language (257). Eight articles could not be obtained.

A second level of screening was conducted on the 414 titles and abstracts initially identified for full-text review. Of the 414 titles, 274 were rejected: Studies were rejected at this stage for the following reasons: language not English (7), study design (78); participants excluded (5); interventions not of interest (4); outcomes not of interest (75); mean age less than 65 (71); adverse event (AE) reports with sample size less than 500 (27); or duplicate data (7). Of the

remaining 79 studies, 6 systematic reviews were accepted, 73 were background articles, and 62 were original studies that underwent detailed abstraction. These included RCTs that reported function, ADLs/IDLs, QoL, arthroplasty, and/or AEs (25); case series or prospective cohort studies reporting AEs or arthroplasty (total knee replacement) (19); or case reports reporting AEs (18). Of the case series and cohort studies that reported AEs, only those that enrolled populations of 500 or greater were included, to ensure detection of rare AEs.

Figure B. Literature Flow Diagram



Footnotes: ADLs=Activities of Daily Living; IADLs=Instrumental Activities of Daily Living AEs=Adverse events; CMS=Center for Medicaid Services; SIPs: Scientific Information Packets

Table A. Strength of Evidence

Outcome	Strength of evidence Grade	Study Design	No. Studies (N)	Study Limitations	Directness	Consistency	Precision	Reporting Bias	Other Issues	Finding
Arthroplasty	Insufficient	RCTs	3	High	Direct	Consistent	Imprecise	Suspected	KR not intended outcome in 2 trials	No pooled effect size
		Observational	13							
Function: HAs vs. placebo	Low	RCTs	10	Moderate	Direct	Inconsistent	Precise	None	2ndary outcome	-0.23 (-0.34, 0.02)
Function: HA vs. HA	Insufficient	RCTs	5	High	Direct	Inconsistent	Imprecise	unknown	2ndary outcome	No pooled effect size
Quality of Life	Insufficient	RCTs	2*	High	n/a	n/a	n/a	n/a	Different outcome measures	No pooled effect size
			1							
Adverse Events: total	Moderate	RCTs Observational cohort case reports	25 4 18	Moderate	Direct	Consistent	Precise	Unknown	Cohort studies included patients<65	Similar rates of AEs were reported in studies of HA and placebo
Adverse Events: serious (SAEs)	Moderate for the rarity of SAEs; Low for a difference between the intervention and placebo groups	RCTs	25	Moderate	Direct	Consistent	Imprecise	Unknown	Causal mechanism not proposed for some SAEs	Joint: 0.77(0.25, 2.31) Other: 0.62(0.23, 1.57)

*Two trials compared Synvisc® to Hyalgan®; one trial compared Hyalgan® to saline. Each used a different measure

Delay or avoidance of total knee replacement surgery

Three RCTs³⁶⁻³⁸ and 13 observational studies (reported in 15 articles)³⁹⁻⁵³ reported on total knee replacement (KR) after administration of intra-articular HA injections. Of the three RCTs, neither assessed KR as a prespecified outcome of interest: They reported it as a treatment failure.

Key Points

- Three RCTs enrolled small numbers of patients and reported on KR: Two did not specify KR 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 KR among HA-treated patients, whereas the other two reported higher rates among placebo-treated patients.
- Six case series and seven cohort studies reported on KR as an outcome following HA treatment. Most studies reported delays in KR with HA injections compared with the usual progression or lower rates of KR with HA injections than usually seen in the absence of treatment. Two studies that assessed risk factors for undergoing KR among those treated with HA found that only baseline severity and age were factors: those in the 60 to 69-year old age range in one study and in the 65 to 79-year range in the other were significantly more likely than those younger or older to undergo KR, and in the former study, the time from diagnosis to KR was faster for the 60–69 year old age group. No study reported the criteria for knee replacement surgery or the characteristics that distinguished those who underwent surgery.

Intra-articular injection of hyaluronic acid and measures of function

We identified 18 randomized trials that compared the effects of HA with another HA⁵⁴⁻⁵⁹ or sham placebo control^{36, 38, 56, 60-66} or both using a validated measure of function, including the WOMAC, Lequesne, ADLs, or IADLs, in individuals with OA of the knee whose average age was 65 or older. Two studies compared an HA to other active treatment.^{37, 67}

Key Points

- Our meta-analysis of 10 studies that compared the effect of an HA to that of a sham placebo control showed a statistically significant improvement in WOMAC-assessed function following HA treatment, compared to placebo (standardized effect size or standardized mean difference [SMD] -0.23, 95% CI -0.34, -0.02) that did not achieve the MCID of -0.37 at follow-up;^{36, 38, 56, 60-66} this effect size corresponds to 4.3 units on a 100mm VAS scale.
- The number of head-to-head trials is too small to be able to assess the relative superiority of one HA over another.
- Although no studies assessed the proportion of patients with improved function, seven studies assessed the proportion of patients with patient- or investigator reported global improvement; of the four that were placebo-controlled, three reported significant increases in the proportion of HA-treated patients who improved, compared with the proportion of placebo-treated patients who improved.
- No studies assessed the durability of effect.

Intra-articular injection of hyaluronic acid and quality of life

Three randomized trials were identified that assessed quality of life. A 2008 saline-controlled randomized trial assessed quality of life using the KOOS quality-of-life component.⁶⁴ Two head-to-head trials that compared Genzyme Synvisc® with FIDIA Hyalgan® also assessed quality of life/health-related quality of life (HRQoL), one using the SF-36 mental component summary,⁵⁷ and one using the EuroQol-5D index (for HRQoL).⁵⁹

Key Points

- Three trials that compared HA to saline or to another HA found no differences in quality of life between the two groups at 6 months follow-up.

Intra-articular injection of hyaluronic acid and pain

Pain is the most frequently assessed outcome for HA but was not within the scope of the present review. However, these studies have been assessed in numerous recent systematic reviews;^{13, 14, 68-71} thus, we summarized the results of the most recent and most comprehensive systematic review of the literature on HA and pain¹⁴ as well as the results of two recent randomized head-to-head trials not included in the previous reviews that assessed the effects of HA on pain in individuals of average age 65 and over.^{54, 57}

Key Points

- A large, comprehensive systematic review of RCTs that assessed the effects of HA on pain in 71 RCTs (with either sham or non-sham controls) reported that HA injections significantly reduce pain when assessed at 3 months (-0.37, 95% CI -0.46, -0.28) and the effect met the criterion for a MCID (-0.37, which corresponded to 9mm on a VAS scale of 0 to 100mm).
- When the reviewers performed a subgroup analysis that included only the 18 sham-controlled, assessor-blinded studies of sample size 100 or more per intervention group in the pooled analysis, the effect of HA was still statistically significant (-0.11, 95% CI -0.18, -0.04), but no longer met the criterion of clinical importance;
- When the reviewers conducted a stratified analysis to compare the effect size for the 54 studies with a sham control with that of 18 studies with a non-sham intervention, the pooled effect size for studies with a sham control was -0.34 (95% CI -0.44, -0.24), nearly equal to that for all studies and to the MCID.
- No new placebo-controlled trials were identified that were not already included in the comprehensive 2012 systematic review on the effects of HA, enrolled patients of average age 65 and older, and reported on pain outcomes.
- Two new head-to-head trials compared the effects of two different HAs on pain in individuals of average age 65 and over and were not included in prior SRs. One found that single injections of a high- and low-molecular weight were equally effective in reducing pain and improving function at 6 months (with no change in quality of life), whereas another found that three injections of an intermediate molecular weight HA

might be superior to low molecular weight HA over 6 months (with respect to reducing pain and improving function).

Intra-articular injection of hyaluronic acid and adverse events

Twenty four trials^{36-38, 54-67, 72-79} and 18 case reports⁸⁰⁻⁹⁷ were identified that reported on the incidence of adverse events among individuals 65 years of age and over.

Key Points

- In 24 placebo-controlled trials of HA, serious adverse events were small in number.
- Among three large cohort studies and case series, representing nearly 6,000 recipients of HA (some more than one series), one serious adverse event was reported: severe swelling and synovial fluid accumulation.
- Eighteen case reports provided reports of adverse events among 30 individuals 65 years of age or older, including five cases of sepsis (one case of staphylococcus scalded skin syndrome), and one case each of saphenous nerve injury, eosinophiluria, erythema, and herpes zoster (new onset).

Discussion

Key Findings and Strength of Evidence

Intra-articular HA and KR

Three randomized trials and 13 observational studies reported on total knee replacement (KR). Two of the trials did not regard receipt of TKR as a prespecified outcome of interest, one enrolled patients whose average was under 65, and those two trials were not powered to compare the rates of KR between HA and comparison groups. With only one trial powered to assess the effect of HA on KR and without larger retrospective case control or prospective cohort studies, it is not possible to draw conclusions at this time from the observational studies regarding the effect of HA treatment on delay or avoidance of KR.

The strength of evidence for this question is insufficient to draw any conclusions.

Intra-articular HA and Function

Pooling of ten placebo-controlled studies that reported outcomes for the WOMAC or Lequesne revealed a small but significant increase in function in favor of HA (-0.23, 95% CI - 0.34, -0.02); seven of the ten measured outcomes at 6 months. Two studies reported no difference between HA and placebo. Based on the pooled effect size, approximately 11 percent of patients would have exceeded the MCID in improvement.

One trial reported on the effects of HA on ADLs. This study found no change from baseline in the HA or placebo group.

Three of four placebo-controlled trials that assessed the effect of HA on global improvement reported statistically significant increases in the proportion of HA-treated patients who improved, compared with the proportion of placebo-treated patients who improved.

Too few head-to-head trials were identified to be able to draw any conclusions about the superiority of anyone product over another.

None of the identified studies stratified findings by age, sex, or any other outcome of interest.

The strength of evidence for the conclusion based on placebo-controlled trials is low. The strength of evidence for the conclusion based on head-to-head trials is insufficient.

Intra-articular HA and QoL

Three randomized trials reported on the effects of HA on QoL with mixed results. No conclusions can be drawn about the effects of HA on QoL. As only three trials reported both QoL and functional outcomes, no conclusions can be drawn about the relationship between these two parameters.

The strength of evidence for this conclusion is insufficient.

Intra-articular HA and Pain

One recent comprehensive systematic review and meta-analysis that assessed the literature on the effects of HA on reducing pain compared the effects of HA with all other interventions and with saline controls alone reported that HA injections significantly reduced pain, both statistically and clinically (that is, the effect reached the MCID) when measured at 3 months; however, this effect was no longer clinically significant when only double-blind placebo-controlled trials enrolling at least 100 participants per treatment group were included in the analysis. Based on the findings of the full sample analysis and the analysis stratified by the use of sham controls in the prior systematic review, we believe that the strength of evidence is low that HA reduces pain, on average, by an amount that achieves or just approaches the minimum clinically important difference.

Intra-articular HA and AEs

The findings of randomized trials, observational studies, and case reports suggest that the adverse events associated with intra-articular injections of HA are nearly all at the site of injection or within the joint, largely confined to pain or swelling, and as likely in the placebo-treated as in the actively treated individual. Serious adverse events are rare. In 24 placebo-controlled trials of HA, serious adverse events were small in number. Estimates are imprecise, and the magnitude of any increase in risk is very small, if present at all. The rate of non-serious AEs was higher but did not differ significantly between the HA-treated and placebo-control groups. The FDA PMA database revealed no post-marketing reports of unexpected adverse events. Information provided by manufacturers about five products was limited to already published data.

The strength of evidence for the conclusion that serious adverse events are rare is moderate. The strength of evidence for a statistically significant difference in SAEs and non-serious AEs between intervention and placebo groups is low.

Findings in Relation to What is Already Known

To our knowledge, this report represents the first systematic review to attempt to assess the effects of intra-articular HA injections on both delay or avoidance of KR, pain, function, quality of life, and adverse events.

No other systematic reviews have attempted to synthesize the effects of HA on KR, and the present review found insufficient evidence to draw a conclusion about the effects of HA on those outcomes.

Regarding its effect on function, we calculated that the effect size in our study corresponded to an improvement of 5.6 units (on a 0-100 VAS scale) which was smaller than the minimum clinically important difference of 9 units (which would be comparable to a 10 percent improvement in, e.g., the ability to walk downstairs or to rise from sitting).

One large 2012 systematic review assessed the effects of HA on pain, function, and AEs.¹⁴ That review identified a moderate effect of HA on function that was no longer considered clinically important when only large trials with assessor blinding were considered. The pooled effect size for the 52 trials was -0.33 (95% CI -0.43, -0.22); including only large trials with blinded outcome assessment resulted in a pooled effect size of -0.09 (95% CI -0.17, 0.00). Although we regard sham controls and blinded outcome assessment vital for assessing the effect of HA on function, we believe that limiting the pooled analysis to larger studies is not methodologically justified, given the small proportion of studies that fit the criteria and the fact that study size is not typically a criterion in assessing study quality/risk of bias.

The present review is also the first to consider only studies of individuals of average age 65 or older. Approximately half of the trials included in the pooled analysis of the effects of HA on pain by Rutjes enrolled populations of average age less than 65; and of the 52 trials they included in their analysis of the effects of HA on function, nearly all included participants of average age less than 65.¹⁴ No evidence exists that would suggest age would affect the ability to experience pain relief. Therefore, we believe the analyses in the prior review that included studies of patients whose average age was less than 65, given the much larger number of included studies, were more adequately powered to assess the effects of HA on pain than would be an analysis that includes a smaller number of studies limited to individuals of average age 65 and over.

The current review found only a small number of serious AEs. The 2012 review reported that 14 of 89 trials found an increased risk for serious AEs in the HA-treated groups:¹⁴ Fewer than half of the trials included in the 2012 review assessment of serious AEs reported on specific AEs, and those that did had methodological limitations. A 2013 review of 29 studies found no difference in AEs between HA- and placebo-treated groups.⁶⁸

Applicability

To increase potential applicability, we limited studies included in the current review with functional outcomes to those with an average age of 65 or older. Nevertheless, no studies excluded patients younger than 65. Given that the only study that assessed factors that might influence the likelihood of undergoing KR found that age was the only influential factor, age of study participants is likely to be an important consideration for this outcome.

The larger trials included in the assessment of functional outcomes were mostly conducted in academic settings; this typical characteristic of randomized trials tends to limit their applicability to community settings. However a number of the observational studies that addressed the outcome of KR were conducted in private medical practices.

Implications for Clinical and Policy Decision Making

The evidence identified for the current study is insufficient to support a decision either way about the efficacy of intra-articular HA injection based on the delay or avoidance of KR. In

addition, the strength of evidence is low regarding the efficacy of HA for improving quality of life or function in a population 65 years of age or older.

Limitations of the Comparative Effectiveness Review Process

Given the constraints of the project, we did not attempt to review studies of populations of average age less than 65 years to determine whether they found improvements in function or quality of life. However, removing the exclusion criterion of age we identified only one randomized trial that reported KR, and it was not considered a prespecified outcome of interest. We also did not contact authors of original research studies to request raw data by patient age and did not attempt to do new pooling of the studies included in the review by Rutjes and colleagues, to include only studies of older populations for reasons explained above.

Limitations of the Evidence Base

The majority of trials identified for the current report did not meet the criteria for a low risk of bias, primarily the result of inadequate reporting: Few trials described their recruitment strategy or method for allocation concealment. A number of studies had dropout rates higher than 20% (no studies addressed differences between dropouts and completers), and although most excluded individuals who had recently received corticosteroids or other courses of an HA, most also did not bar participants from using other modes of pain relief, such as NSAIDs. Further, few or no studies attempted to determine whether response to HA differed between groups of patients stratified by characteristics such as baseline age, disease severity (stage) or type; or duration of treatment, few studies followed patients long enough to measure duration of effect, and adverse events were not assessed using any type of standard methodology.

Specific to the outcome of function, only four placebo-controlled trials reported the actual percentage of participants who experienced global improvement, and only one trial measured knee replacement as a primary outcome.

Research Gaps

Clear research gaps exist regarding studies of the effectiveness of HA among individuals 65 years of age and older and the effect of HA, if any, on delay or avoidance of KR. Two searches for ongoing studies of HA and OA of the knee on Clinicaltrials.gov and review of entries provided by manufacturers revealed no completed, ongoing, or recruiting studies on older individuals with knee OA or with outcomes of KR. The observational studies identified for this review could not definitively answer the question of whether HA delays or prevents the need for KR. However, in the absence of a large, high quality RCT, we advocate analyzing data from any of the large administrative databases maintained by commercial payers, to answer the question as to whether beneficiaries who are treated with intra-articular HA proceed to KR at a slower rate than do those who do not receive HA. We realize that a number of factors might affect the decision to undergo KR, such as age, comorbidities, pain tolerance, activity level, aversion to surgical intervention, and expectations about one's life expectancy; at least some of these factors could be controlled for in a large, well-designed case control study, although an RCT would be needed to provide a definitive answer.

Conclusions

The literature identified for the current review cannot answer the question whether HA delays or prevents the need for KR in older individuals. The literature suggests a small role, of unclear importance, for HA in improving function among older individuals and an equally small role in reducing pain among adults, with few serious adverse events.

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Introduction

Background

Condition

Osteoarthritis (also known as degenerative joint disease [DJD]) of the knee is a condition characterized by the progressive destruction of the cartilage that lines the knee joint, resulting in bone-on-bone friction, excessive wear of the bone surfaces, potential bone spurs, and accompanying pain, immobility, and reduction in function and the ability to complete activities of daily living (ADL).

In 2005, the estimated prevalence of osteoarthritis among adults in the United States, the number of individuals who had ever been told by a doctor that they had the condition, was approximately 27 million cases.¹ Prevalence rates vary by the joint involved and the method of ascertainment (clinical vs. radiographic): symptomatically, the knee is the most frequently affected joint.² The prevalence of osteoarthritis of the knee is increasing rapidly because of shifting population demographics: The primary risk factors for osteoarthritis of the knee are aging, obesity, prior injury, repetitive use,³ and female gender. The prevalence of symptomatic knee osteoarthritis may reach 50 percent by the age of 75, a concern for Medicare resources. In the first decade of the 21st century, the number of individuals in the US with a total knee replacement doubled (from some 2 million to approximately 4 million).⁴ The increase in obesity has translated not only into an increase in incidence of osteoarthritis of the knee but also into a younger age of onset and need for treatment; as a result, by the time individuals with osteoarthritis of the knee reach the age of Medicare eligibility, the length of time they have had the condition has grown, their cases are more advanced,⁵ and the risk that surgery will be needed has increased. Thus, the aging of the baby boomer population, along with the increased incidence and prevalence of obesity have created a perfect storm for an increase in the number of cases and the proportion of the population at risk for this condition, all representing an increasing strain on Medicare resources.

Diagnosis Strategies

Osteoarthritis of the knee is usually diagnosed clinically based on pain. Radiographic evidence of osteoarthritis may precede symptomatic osteoarthritis and unfortunately correlates weakly with symptom severity. Radiologic severity can be estimated using the Kellgren and Lawrence criteria; however, a number of versions of the criteria exist: At low cutoff scores, correlation with symptoms is poor,⁶ whereas at higher cutoff scores, agreement tends to be higher. The primary impact of these different versions of the criteria may be the challenge that they create in trying to use the different versions to assess, compare, and pool the findings of research studies:⁶ Some longitudinal studies have even used different criteria at different time points within the same study. Because of the variation in scores for radiographic finding under various versions of the criteria (especially for individuals with less-advanced disease), stratification is important.

Some evidence suggests that among individuals with knee pain, MRI demonstrates physical signs of osteoarthritic changes in the knee before they are visible radiographically.⁷

Treatment Strategies

The goals of treatment for osteoarthritis of the knee include relief of pain and inflammation, slowing of progression, and improvement in or maintenance of mobility and function and quality of life. Measures used to assess the achievement of these outcomes are described below.

Treatment options for osteoarthritis of the knee include oral or topical analgesics (non-steroidal anti-inflammatories, acetaminophen), intra-articular injection of corticosteroids to reduce inflammation, physical therapy and exercise (both to strengthen muscles that support the affected joints and to increase range of motion), weight loss to reduce stress on the joints, bracing to reduce lateral motion and friction, partial or total arthroplasty (throughout this report, the terms arthroplasty and knee replacement are used interchangeably) for advanced cases, and more recent therapies such as viscosupplementation, involving local injections of the natural joint lubricant, hyaluronic acid, among other treatments.⁸

Hyaluronic acid (HA, hyaluronate or hyaluronan) is a high molecular weight glycosaminoglycan that is naturally synthesized in plasma membranes of connective tissues and secreted into the synovial fluid surrounding joints, where it forms part of the extracellular matrix.⁹ Progressive osteoarthritis of the knee includes loss of the cells responsible for synthesizing this substance, resulting in lower viscosity endogenous hyaluronate. A large number of trials have examined the efficacy and safety of supplemental intra-articular hyaluronic acid injections (classified by the United States Food and Drug Administration as a medical device) to relieve pain and improve function in patients with DJD of the knee, with varying efficacy results. A number of systematic reviews have attempted to resolve these conflicting findings. Some reviews have reported positive outcomes^{10, 11} whereas some have reported mixed effects^{12, 13} or no effect.¹⁴ A 2010 update of an earlier systematic review actually found a decrease in the effect size for HA on knee osteoarthritis from the previous review.¹⁵ The discrepancies in outcomes may be due to study heterogeneity both within and among reviews (and original studies, themselves) with respect to population characteristics (such as average age or body mass index), intervention modalities (the particular HA employed), treatment and followup duration (the number of treatments as well as how long after treatment initiation outcomes are measured), and the actual outcomes measured (e.g., pain, functionality, HRQoL), as well as the measures employed. Heterogeneity may also be attributable to how efficacy is expressed, i.e., the proportion of each treatment group that responds positively to treatment vs. the mean change in that efficacy measure from baseline in the active treatment group vs. the comparison group. Finally, whether or not a study reports a positive effect of HA has been shown to depend, at least in part, on study design: whether participants are credibly blinded to treatment allocation and the outcomes of active treatment are compared to that of a placebo control.¹⁴

Commercial preparations of HA differ in three respects: source, size, and dosing. Whereas the older HA were all purified from chicken comb (avian), some newer products are bioengineered in yeast cell cultures. The newer products also tend to be higher in molecular weight, the result of greater cross-linking. Products may be packed to be delivered as a single dose or in multiple doses. The products included in this report are shown in Table 1, along with their indications and recommended dosages (HA devices not approved for use in the United States are described in Appendix F).

Table 1. Hyaluronic Acid Devices Approved for Use in the United States

Device Source Approval Date Avian/Non-Avian Molecular Weight	Trade name(s)	Labeled indications	Dosing	Dose adjustments for special populations
1% sodium hyaluronate Ferring Pharmaceuticals, Inc. October 2011 Non-Avian 2400-3600 kD	Euflexxa® <i>Formerly Nuflexxa®, (Savient) approved December 2004</i>	Indicated for treatment of pain in osteoarthritis of the knee in patients who have failed to respond adequately to conservative non-pharmacologic therapy and to simple analgesics (e.g., acetaminophen)	Three weekly injections into knee joint (20mg/2 mL)	Safety/effectiveness not known in pregnant/lactating women or children
Sodium hyaluronate Seikagaku Corp. March 2011 Avian Unknown MW ("high")	Gel-One®	Indicated for the treatment of pain in osteoarthritis of the knee in patients who have failed to respond adequately to non-pharmacologic therapy, NSAIDs, or analgesics (e.g., acetaminophen).	Single injection into knee joint (30 mg/3 mL)	Safety/effectiveness not known in pregnant/lactating women or children
Sodium hyaluronate FIDIA Pharmaceutical Corp. May 1997 Avian 500-730 kD	Hyalgan®	Indicated for treatment of pain in osteoarthritis of the knee in patients who have failed to respond adequately to conservative non-pharmacologic therapy and simple analgesics, (e.g., acetaminophen)	Five* weekly injections into knee joint (20 mg/2 mL)	Safety/effectiveness not known in pregnant/lactating women or children
Hyaluronan Anika Therapeutics, Inc. February 2014 Non-Avian Unknown MW ("high")	Monovisc™	Indicated for treatment of pain in osteoarthritis of the knee in patients who have failed to respond adequately to conservative non-pharmacologic therapy (e.g., acetaminophen)	Single injection into knee joint (88 mg/4 mL)	Safety/effectiveness not known in pregnant/lactating women or children
Hyaluronan Anika Therapeutics, Inc. February 2004 Non-Avian 1000-2900 kD	Orthovisc®	Indicated for treatment of pain in osteoarthritis of the knee in patients who have failed to respond adequately to conservative non-	Three or four weekly injections into knee joint (30 mg/2 mL)	Safety/effectiveness not known in pregnant/lactating women or children

Device Source Approval Date Avian/Non-Avian Molecular Weight	Trade name(s)	Labeled indications	Dosing	Dose adjustments for special populations
		pharmacologic therapy and to simple analgesics (e.g., acetaminophen)		
Sodium Hyaluronate Seikagaku Corp. January 2001 Avian 620-1170 kD	Supartz® <i>Marketed as Artz® or Artzal® outside U.S.</i>	Indicated for the treatment of pain in osteoarthritis of the knee in patient show have failed to respond adequately to conservative non-pharmacologic therapy and simple analgesics (e.g., acetaminophen)	Five weekly injections into knee joint (25 mg/2.5 mL)	Safety/effectiveness not known in pregnant/lactating women or children
Hylan GF-20 Genzyme Corp. (Biomatrix, Inc.) August 1997 Avian 6,000 kD	Synvisc®	Indicated for treatment of pain in osteoarthritis of the knee in patients who have failed to respond adequately to conservative non-pharmacologic therapy and to simple analgesics (e.g., acetaminophen)	Three weekly injections into knee joint (16 mg/2 mL)	Safety/effectiveness not known in pregnant/lactating women or children
Hylan GF-20 Genzyme Corp. February 2009 Avian 6,000 kD	Synvisc-One®	Indicated for treatment of pain in osteoarthritis of the knee in patients who have failed to respond adequately to conservative non-pharmacologic therapy and to simple analgesics (e.g., acetaminophen)	Single injection into knee joint (48 mg/6 mL)	Safety/effectiveness not known in pregnant/lactating women or children

Treatment Guidelines

In the 2012 update to their 2000 guidelines for the treatment of osteoarthritis of the knee, hip, and hand, the American College of Rheumatology conditionally recommended hyaluronic acid injections for patients who had an inadequate response to initial (standard or more conservative) therapy.⁸ The 2013 American Academy of Orthopedic Surgeons guidelines for the treatment of osteoarthritis of the knee recommend against the use of hyaluronic acid to treat patients with symptomatic conditions.¹⁶

Assessment of Outcomes of Treatment

A number of assessment tools are used to assess pain, quality of life, and physical functioning in patients with osteoarthritis of the knee. These tools can be divided into those specifically developed for knee osteoarthritis and those that are used for a variety of conditions.

Tools specifically developed and validated to assess pain and functioning associated with osteoarthritis of the knee as well as treatment outcomes include the Western Ontario-Macmaster (WOMAC¹⁷), the Lequesne Index¹⁸, the Knee Injury and Osteoarthritis Outcomes Score (KOOS¹⁹), and the Animated Activity Questionnaire.²⁰ The Visual Analog Scale, which rates patient-reported responses on a scale from 0 to 100, is often used to quantify patient-reported outcomes for these scales as well as being used on its own. The WOMAC, probably the most widely used tool for assessing knee osteoarthritis, comprises three scales: pain, function, and stiffness; the function scale comprises 17 items that can be rated using a 5-item Likert scale (where 0=no difficulty and 4=extreme difficulty) or a 10 or 100-point Visual Analog Scale (VAS).¹⁷ In 2004, the Osteoarthritis Research Society International (OARSI) developed a consensus set of guidelines to assess the outcomes of research trials on products intended to treat osteoarthritis; and under the International League of Rheumatologists, OMERACT (Outcome Measures in Rheumatology) has developed guidelines on outcome measures.²¹

Several tools have been adapted for use in assessing osteoarthritis of the knee. One such tool, the Short form (SF)-36, developed at RAND for the Medical Outcomes Study,²² is generally used to measure quality of life. Assessment of health-related quality of life is an attempt to measure the impact of a health condition and its treatment on a patient's life; the Euroqol has been validated for use in patients with osteoarthritis of the knee.²³ The Activities of Daily Living scale (ADLs)²⁴ measures the ability to perform basic daily tasks such as dressing/bathing, eating, ambulating, toileting, and hygiene. The Instrumental Activities of Daily Living (IADLs) scale allows the assessment²⁵ of activities that are not needed for basic functioning but allow independent living.

The Kinemax Outcomes Group has used a combination of the WOMAC, the SF-36, and a series of questions addressing demographic characteristics to predict patient outcomes of total knee arthroplasty.²⁶

Appendix H provides the WOMAC, Lequesne, and SF-36 instruments.

Scope and Key Questions

Scope of the Review

The purpose of this review is to assess the evidence on the effects of intra-articular injections of HA on functional outcomes and quality of life/health-related quality of life as well as their ability to prevent or delay the need for arthroplasty among individuals 65 and over. The Centers for Medicaid and Medicare Services (CMS) currently covers HA injections for elderly Medicare recipients under certain conditions.²⁷ Arthroplasty and the postoperative rehabilitation it requires can be life-disrupting. If HA can relieve pain and improve function with minimal adverse effects, it may prevent or delay the need for this surgery. However, if the treatment delays arthroplasty but fails to halt progressive degeneration, patients could potentially experience worse outcomes, although thus far, evidence for such outcomes has been weak. In addition to assessing the evidence for a role of HA in delaying or preventing the need for KR, this report aims to assess the evidence to date on the efficacy of intra-articular injections of HA with respect to the outcomes of function, ADLs/IADS, quality of life, and pain and on the safety of HA when used

as indicated. The Coverage and Analysis Group at the Centers for Medicare and Medicaid Services (CMS) requested this report from The Technology Assessment Program (TAP) at the Agency for Healthcare Research and Quality (AHRQ). AHRQ assigned this report to the Southern CA Evidence-based Practice Center (HHS A290201200006I). A protocol for the review was provided to, and approved by, the AHRQ TAP.

Key Questions

The key questions were provided by the CMS Coverage Analysis Group. Their inter-relationship and association with the topic are described in the analytic framework below (Figure 1).

Key Question 1. Does intra-articular injection of hyaluronic acid eliminate the need for knee replacement surgery? Is this outcome affected by the type of hyaluronic acid, the type of presentation, severity at study entry, or age at study entry?

Key Question 2. Does intra-articular injection of hyaluronic acid significantly postpone the need for knee replacement surgery?

Key Question 3. Does intra-articular injection of hyaluronic acid improve the ability to successfully perform activities of daily living (ADLs) or instrumental activities of daily living (IADLs)?

Key Question 4. Does intra-articular injection of hyaluronic acid improve quality of life? PICOTs are the same as for KQ1-3 with the exception of outcomes.

The effects of hyaluronic acid injection on pain and adverse events associated with hyaluronic acid injection were not included in the key questions posed by CMS. However because pain is regarded as an important component of effectiveness for treatments for degenerative joint disease of the knee and because safety is also an important consideration, we volunteered to appraise this literature.

Figure 1. Analytic Framework

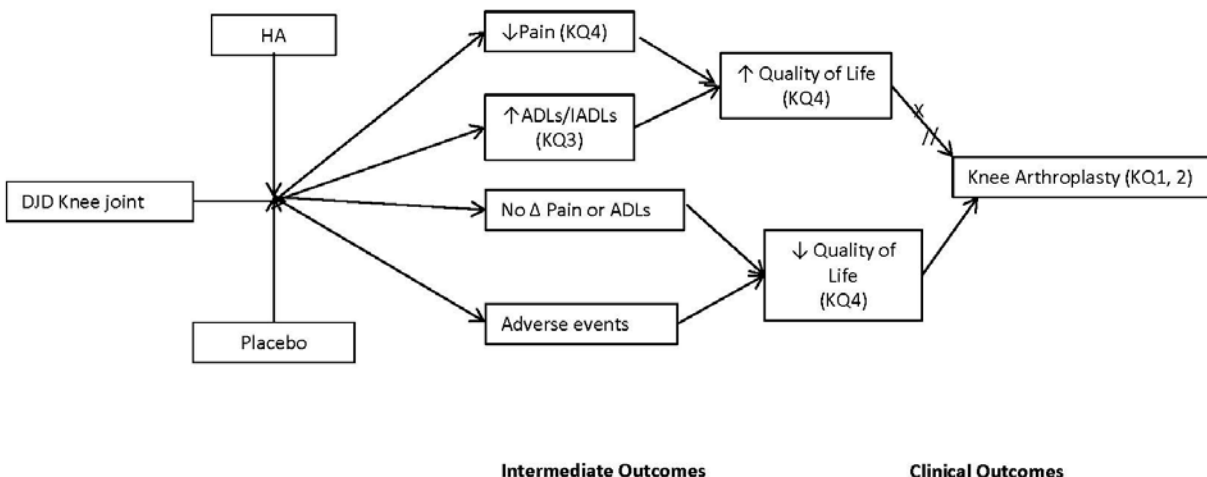


Table notes: ADL: Activities of Daily Living; DJD=Degenerative Joint Disease; HA=Hyaluronic Acid; IADLs=Instrumental Activities of Daily Living

Organization of this report

The remainder of this report presents the methods used to conduct the literature searches, data abstraction, and analysis for this review; the results of the literature searches; the conclusions; and a discussion of the limitations as well as suggestions for future research.

Methods

Criteria for Inclusion/Exclusion of Studies in the Review

This report is based on a systematic search for randomized placebo-controlled trials, head-to-head trials, or quasi-randomized trials that reported results for individuals whose average age was 65 or older, and were powered to see a clinically important difference; that assessed the effects of HA; and that reported on any of the following outcomes: function, quality of life, delay of total knee replacement, prevention of the need for total knee replacement, and adverse events (as well as factors that might affect these outcomes, such as age, disease severity, or comorbidities). If no studies were identified that included the outcomes of interest, we included observational studies that assessed the outcome in question. Studies were included that enrolled individuals with other comorbidities and that enrolled community dwelling or institutionalized participants. The populations, interventions, comparators, outcomes, timeframes, and settings (PICOTs) of included studies are outlined below.

The efficacy of HA for pain relief has been reviewed in a number of systematic reviews within the past two years, including one comprehensive, high-quality systematic review. Therefore, to address the outcome of pain, we include this review as well as any original studies published concurrently or subsequently and not included in that review.

To broaden our search for reports of rare adverse events, we included observational studies (prospective cohort studies and case series) that enrolled or followed more than 500 individuals and individual case reports. We also searched for reports in the Food and Drug Administration's Pre-Market Approval (PMA) database and requested information from the manufacturers of HA devices approved for use in the United States. Information obtained from the latter sources was checked against published data to ensure no duplicate data were included.

Only English-language studies were accepted for data abstraction. However, to ensure we were not systematically excluding studies that might report important outcomes, we screened the titles and English-language abstracts of a random selection of 30 non-English-language articles. Descriptions of these articles appear in Appendix E; none qualified for inclusion.

PICOTs

- **Population(s):**
 - Individuals with severe degenerative joint disease of the knee and no prior arthroplasty on the affected limb;
 - Comorbidities: studies that do not explicitly exclude individuals with any comorbidities that significantly and independently affect quality of life and activities of daily living (including involvement of the contralateral knee or of other joints) would be excluded or considered separately
 - Age 65 and over, male or female, community-dwelling or institutionalized (if studies enrolling only individuals 65 and over were not identified, we would broaden our inclusion criteria to include studies enrolling populations with mean age 65 and over)
- **Interventions:**
 - Hyaluronan
- **Comparators:**
 - Placebo (sham treatment)

- Non-steroidal anti-inflammatory drugs
- Corticosteroids
- Other forms/brands of hyaluronic acid

- **Outcome measures:**
 - Receipt of arthroplasty surgery within follow-up time, length of time before undergoing surgery
 - Range of motion
 - Pain
 - Activities of daily living/Instrumental activities of daily living
 - (Health-related) quality of life
 - Adverse effects of HA injection: physical effects, progression of disease (including flare ups)

- **Timing:**
 - Surgical postponement outcomes: 12 months or longer
 - Other efficacy outcomes: 3 months or longer

- **Settings:**
 - All settings

Literature Search Strategies for Identification of Relevant Studies to Answer the Key Questions

The search strategy was based on one used for a 2012 evidence review on HA,¹⁴ with the addition of search terms for the additional outcomes of interest: arthroplasty/total knee replacement, ADLs, IADLs (including terms for the tools commonly used to assess ADLs and IADLs, e.g., Lawton IADL scale, Katz Index), and quality of life (Appendix A). To test the search strategy, we checked for the inclusion of a set of 84 articles provided to us by the CMS.

PubMed, EMBASE, Web of Science, SCOPUS, and the Cochrane Collection were searched from January 1, 1990 to late November, 2013 to identify original studies of HA. An update search will be conducted while this draft report is under review. To capture unpublished or not-yet-published efficacy and adverse event findings, we searched the NY Academy of Sciences database of grey literature; Grey Matters, a grey literature tool from the Canadian Agency for Drugs and Technologies in Health; clinicaltrials.gov; and the FDA PMA database as described above. The AHRQ SRC contacted the manufacturers of HA devices approved for use in the US to obtain scientific information packets (SIPS) on their products.

Systematic reviews of potential relevance were identified by searching the Cochrane Database. For the outcomes of function, ADLs/IADLs, quality of life, and prevention or delay of total knee replacement, systematic reviews were assessed for any original studies not already identified among the results of the searches. For the outcome of pain, we identified several recent comprehensive systematic reviews.

The output of the literature searches was transferred to DistillerSR™ for screening. Article titles and abstracts were dually screened with all selected articles obtained. A second round of screening was then conducted with full text to exclude articles that provided no usable data, reported duplicate data, enrolled participants whose mean age was less than 65 years of age, or reported only pain as an outcome. We searched accepted studies for additional references and

screened any articles of apparent interest. For studies of apparent interest reported in meeting abstracts, we searched for peer-reviewed articles; abstracts were not included as a source of original data.

Data Abstraction and Data Management

Articles accepted for inclusion were dually abstracted in DistillerSR, and any disagreements reconciled with the input of the project manager, SCEPC director, or local subject matter expert.

Study-level data (PICOTs) included the population demographics (average age, age range, sex, body mass index), comorbidities, disease stage, methods of ascertainment, intervention protocols, comparators, outcomes assessed in the study, and time course of interventions and follow-up.

Outcomes data were abstracted from original research studies for the following outcomes if reported: receipt of arthroplasty, time elapsed between HA therapy and surgery, change or improvement in ADLs/IADLs and other measures of function, QoL/Health-related QoL, and harms (adverse effects).

Assessment of Methodological Quality of Individual Studies

The quality/risk of bias (ROB) of trials that reported on efficacy outcomes was assessed using the Cochrane Risk of Bias tool²⁸ with the addition of several questions to assess elements of importance to this review. ROB was assessed in duplicate, with reconciliation of differences. A copy of the questions appears in Appendix D.

The quality of observational studies that reported on delay or avoidance of total knee replacement surgery was assessed using a modification of the Newcastle-Ottawa scale.²⁹ A copy of the criteria is included in Appendix D.

To assess the quality of included systematic reviews and meta-analyses, we used AMSTAR, a measurement tool for the assessment of multiple systematic reviews.³⁰ This tool contains eleven yes/ no items, such as whether the literature search was comprehensive, dual abstraction was used, and individual study characteristics are displayed. The tool has strong face and content validity, inter-rater reliability, and construct validity.³¹ A copy is included in Appendix D.

We rated the quality of RCTs included in the assessment of adverse events (AEs) using the McHarms assessment tool.³²

Data Synthesis

Studies Reporting on Efficacy. For the assessment of functional outcomes, we considered randomized placebo-controlled or head-to-head trials with blinded outcome assessment that reported changes in the score on a functional assessment scale such as ADL/IADLS, WOMAC or Lequesne); or changes in a measure of quality of life. Trials might report more than one outcome.

For RCTs that compared the effects of interventions with HA with placebo for functional outcomes (WOMAC, Lequesne, or KOOS scales), most trials reported the WOMAC as the measure of function for followup times that ranged from 4 to 52 weeks (all but three studies reported outcomes at 6 months). A standardized effect size was calculated for trials that reported a mean change from baseline by treatment group for a continuous outcome. In some cases, a mean change from baseline was not reported, but the mean outcome at baseline and at follow-up

was reported. Using this information, we could estimate the mean change from baseline. Because various scales (or various ranges of the same scale) were reported, we calculated a standardized effect size. This provides a unit-less measure. For trials that did not report the standard deviation of the mean change, one was estimated using the standard deviations of the baseline and follow-up means. If a follow-up standard deviation was not reported, then we assumed that the standard deviation was one-fourth the theoretical range for the specific measure in the trial.

For each comparison of interest, an unbiased estimate of Hedges' g effect size³³ and its standard deviation were calculated. A negative effect size indicates that the treatment group is doing better than its comparator group (i.e. placebo group or other active comparator). For trials that reported the number of patients having arthroplasty, a Peto's odds-ratio (OR) was estimated. An OR less than 1 indicates that the treatment group has fewer arthroplasty patients than the comparison group.

Trials similar in outcome and treatment comparison were considered for meta-analytic pooling. Since some trials reported only the Lequesne score, we looked at trials that reported both the WOMAC and the Lequesne score to see if conclusions were the same. If so, then we felt justified in pooling the WOMAC and Lequesne score together. For trials that reported more than one follow-up time, the time closest to 26 weeks was used. Sensitivity analyses were conducted by excluding trials with follow-up times not close to 26 weeks. For comparisons that had at least three trials, we derived a pooled estimate of the overall effect size using the Hartung-Knapp-Sidik-Jonkman (HKSJ) method for our random effects meta-analysis.³⁴ This method has been preferred when the number of pooled studies is small. It has been shown that the error rates are more acceptable than the previously used DerSimonian and Laird method.³⁵ Publication bias was assessed for all pooled outcomes using the Begg adjusted rank correlation test³⁶ and Egger regression asymmetry test.³⁷ Heterogeneity was assessed using the I^2 test.³⁸ An effect-size or odds ratio was calculated for trials that reported data but did not contribute to a pooled analysis. All efficacy analyses were conducted with Stata statistical software, version 12.0 (Stata Corp., College Station, Texas).

To obtain an estimate of the clinical importance of the effect size, the minimum clinically important difference (MCID), we multiplied the pooled effect size by the standard deviation obtained from a large trial with a similar intervention for which functional outcome was assessed using the WOMAC. We then compared this change (based on a 100-point VAS scale), to the MCID employed by a number of studies of the effects of treatment on WOMAC-assessed function, including a recent large systematic review.¹⁴

In addition to obtaining the standardized effect size for each trial, we attempted to abstract the proportion of participants who reported improvement in function; a subset of studies reported on global improvement only.

The RCTs that compared active treatments head to head were not pooled, as the numbers of studies comparing the same interventions were insufficient. Similarly, the numbers of studies that reported on ADLs or quality of life were insufficient to allow pooling. The results are reported narratively. RCTs reporting on total knee replacement/arthroplasty were also small in number and are described narratively. Because only three RCTs reported on arthroplasty (and only one considered it as a treatment outcome), we included observational studies that assessed arthroplasty. The results of these studies are described narratively.

The effect of HA treatment on pain has been assessed in a number of recent systematic reviews, including one relatively high quality review published in 2012. This review pooled 71 RCTs that met their inclusion criteria of a minimum of 3 months follow up (without regard to

type of control or mean age of participants); in addition, they pooled only the 18 trials that had both placebo (sham) controls and enrolled more than 100 participants per study arm. They also conducted stratified analysis on a number of potential effect modifiers, including use of a sham control intervention. We describe the findings of this review and subsequent studies that reported on pain as an outcome narratively.

Studies Reporting on Adverse Events. Trials of any length were considered for the safety analysis. The AHRQ EPC Scientific Resource Center (SRC) contacted manufacturers of all HA devices approved for use in the US; citations for published studies received from manufacturers were deduplicated with published studies already identified in the literature searches. No unpublished data were provided. We also accessed the Food and Drug Administration (FDA) PostMarketing Assessment (PMA) database for information posted about HA products (code MOZ) this database includes information for six products approved for use in the US. Finally, we accessed the FDA Manufacturer and User Device Experience (MAUDE) database; however, we did not include MAUDE data in the report because the ages of the individuals about which the reports were filed could not be determined and because we did not include single case reports of adverse events.

Adverse event data extracted from RCTs included the name of each trial group, the description of the adverse event from the original article, the number of subjects in each group, and the number of subjects with each adverse event. Each event was counted as if it represented a unique individual. Because a single individual might have experienced more than one event, this assumption may have overestimated the number of people having an adverse event. Events described as adverse events or harms (and reported as part of a safety assessment) were extracted regardless of whether the study authors described them as being unrelated or related to the interventions.

Adverse events reported in RCTs were grouped using clinical expertise into three categories: local, joint, and other. Within those categories, events were further categorized as serious or not serious. For groups of events that occurred in three or more trials, we performed a meta-analysis to estimate the pooled odds ratio and its associated 95% confidence interval. Given that many of the events were rare, we used exact conditional inference to perform the pooling rather than applying the usual asymptotic methods that assume normality. We conducted the meta-analyses using the statistical software package StatXact Procs v9.0 (Cytel Software, Cambridge, MA).

Any significant pooled odds ratio greater than one indicates the odds of the adverse event associated with HA are larger than the odds associated with the comparison (placebo or active control) group.

Adverse events were also abstracted from prospective cohort studies and case series of 500 or more patients, and case reports of individuals age 65 or older.

Grading the Evidence for Each Key Question

The overall strength of evidence (SOE) was assessed for each conclusion within each key question using the EPC modification of the GRADE system.³⁹ Domains included were study limitations (risk of bias), directness, consistency, precision, and reporting bias (definitions and criteria for these domains are provided in Appendix G).⁴⁰ This method classifies the evidence according to the following criteria:

High = High confidence that the evidence reflects the true effect. Further research is very unlikely to change our confidence in the estimate of effect.

Moderate = Moderate confidence that the evidence reflects the true effect. Further research may change our confidence in the estimate of effect and may change the estimate.

Low = Low confidence that the evidence reflects the true effect. Further research is likely to change our confidence in the estimate of effect and is likely to change the estimate.

Insufficient = Evidence either is unavailable or does not permit a conclusion.

The applicability of the findings was assessed based on age, community residence, comorbidities, weight status, and study size.

Peer Review and Public Commentary

To Be Added for Final Version

Results

Introduction

This chapter first describes the results of the literature searches and then provides the results for the outcomes of interest in the following order: delay or avoidance of total knee replacement; measures of function, including ADLs/IADLs; quality of life; pain; and adverse events.

Results of Literature Searches

The searches of peer reviewed literature identified 2,149 unique titles (Figure 2). The partner, CMS, provided 84 titles, of which all but 9 were already included in the search results. Reference mining of those studies yielded an additional seven titles. The searches of grey literature yielded 47 titles. Information provided by manufacturers (Scientific Information Packets (SIPs)) included two titles, of which two unique titles were accepted. Altogether, 2,214 titles and abstracts went on to dual screening.

Of the 2,214 titles, 415 were initially identified for full-text review. The remaining 1,799 titles and abstracts were rejected for being animal or in vitro studies (372), not reporting on DJD of the knee (333), not using intra-articular HA injections (357), not reporting any outcomes of interest (53), having an inappropriate study design (e.g., obvious commentaries or non-systematic reviews) (390), not enrolling a population of interest (29), or being written in a non-English language (257). Eight articles could not be obtained.

A second level of screening was conducted on the 415 titles and abstracts initially identified for full-text review. Of the 415 titles, 275 were rejected: Studies were rejected at this stage for the following reasons: language not English (7), study design (78); participants excluded (5); interventions not of interest (4); outcomes not of interest (75); mean age less than 65 (71); AE reports with sample size less than 500 (27); or duplicate data (7). Of the remaining 79 studies, 6 systematic reviews were accepted, 73 were background articles, and 62 were original studies that underwent detailed abstraction. These included RCTs that reported function, ADLs/IDLs, QoL, arthroplasty, and/or AEs (25); case series or prospective cohort studies reporting AEs or arthroplasty (total knee replacement) (19); or case reports reporting AEs (18). Of the case series and cohort studies that reported AEs, only those that enrolled populations of 500 or greater were included, to ensure detection of rare AEs. Appendix B provides a list of excluded studies with the reasons for exclusion.

Figure 2. Literature Flow Diagram

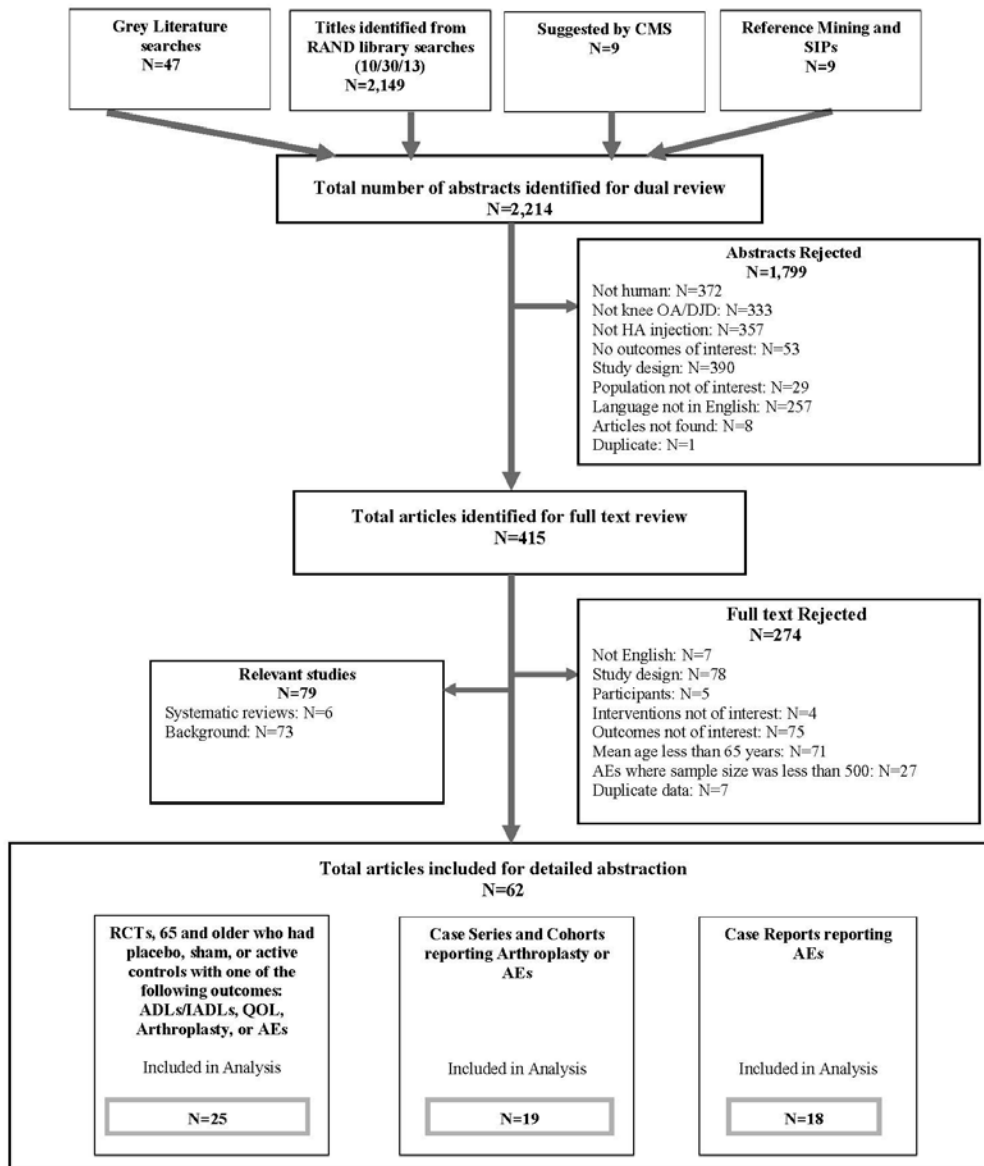


Figure Notes: ADLs=Activities of Daily Living; IADLs=Instrumental Activities of Daily Living; AEs=Adverse events; CMS=Center for Medicaid Services; SIPs: Scientific Information Packets

Table 2. Strength of Evidence

Outcome	Strength of evidence Grade	Study Design	No. Studies (N)	Study Limitations	Directness	Consistency	Precision	Reporting Bias	Other Issues	Finding
Arthroplasty	Insufficient	RCTs	2	High	Direct	Consistent	Imprecise	Suspected	KR not intended outcome	No pooled effect size
		Observational	13							
Function: HAs vs. placebo	Low	RCTs	10	Moderate	Direct	Inconsistent	Precise	None	2ndary outcome	-0.23 (-0.34, 0.02)
Function: HA vs. HA	Insufficient	RCTs	5	High	Direct	Inconsistent	Imprecise	unknown	2ndary outcome	No pooled effect size
Quality of Life	Insufficient	RCTs	2* 1	High	n/a	n/a	n/a	n/a	Different outcome measures	No pooled effect size
Adverse Events: total	Moderate	RCTs Observational cohort case reports	25 4 18	Moderate	Direct	Consistent	Precise	Unknown	Cohort studies included patients<65	Similar rates of AEs were reported in studies of HA and placebo
Adverse Events: serious (SAEs)	Moderate for the rarity of SAEs; Low for a difference between the intervention and placebo groups	RCTs	25	Moderate	Direct	Consistent	Imprecise	Unknown	Causal mechanism not proposed for some SAEs	Joint: 0.77(0.25, 2.31) Other: 0.62(0.23, 1.57)

Table Notes: *Two trials compared Synvisc® to Hyalgan®; one trial compared Hyalgan® to saline. Each used a different measure

Delay or avoidance of knee replacement surgery

Three RCTs and 14 observational studies reported on knee replacement (KR) after administration of intra-articular HA injections. Of the three RCTs, only one assessed KR as a prespecified outcome; the other two reported it as a treatment failure.

Key Points

- Three RCTs enrolled small numbers of patients and reported on KR, although it was not a prespecified outcome of interest in two of the studies: One reported higher rates of KR among HA-treated patients, whereas the other two reported higher rates among placebo-treated patients.
- Six case series and seven cohort studies reported on KR as an outcome following HA treatment. Most studies reported delays in KR in patients who received HA injections compared with the usual progression among patients who did not receive HA, or lower rates of KR in patients receiving HA than usually seen in the absence of such treatment. Two studies that assessed risk factors for undergoing KR among patients who received HA found that only baseline severity and age were factors: those in the 60 to 69 year old age range in one study and in the 65 to 79-year range in the other were significantly more likely than those younger or older to undergo TKR, and in the former study, the time from diagnosis to TKR was faster for this age group. No study reported the criteria for knee replacement surgery or the characteristics that distinguished those who underwent surgery.

Detailed Synthesis

No systematic reviews were identified that reported on studies assessing the rate of KR among patients who were treated with HA.

We identified three randomized trials^{41, 42, 43} that reported the number of people needing arthroplasty. However, KR was a pre-specified outcome of interest in only one of the studies, and the others showed indications of high risk of bias. Two of the three trials demonstrated non-significant trends, indicating that fewer people in the Hyalgan® group had arthroplasty than the placebo group.

The first study was a 1-year trial of Hyalectin, a higher molecular weight avian product (four weekly doses) vs. saline placebo conducted in 1993 (quality assessed as moderate risk for bias).⁴¹ A group of 110 patients (mean age 68, 71% women) were divided into two groups; the primary outcome was improvement in effusion and secondary outcomes were pain and function. Between week 7 and 52, two patients in the active intervention group and 5 in the placebo group underwent KR (OR 0.41, 95% CI 0.09, 1.89).

The second study was a 1-year trial of Hyalgan, a lower molecular weight avian product (5 weekly doses) vs. arthroscopic washout conducted in 2003 (quality assessed as moderate risk).⁴² A group of 38 patients (mean age 62, proportion of women not reported) were randomized into the two groups. At 1 year, two patients from the active intervention and one patient from the arthroscopy group had undergone KR; one patient from the active intervention and two patients from the arthroscopy group were on a waiting list for KR; and two additional patients from the active intervention group had undergone arthroscopy and were on a waiting list for KR (OR 0.54, 95% CI 0.08, 3.59). The third study was a 1-year trial of two cycles of Hyalgan (5 weekly doses each) vs. placebo control conducted in 2008 (quality assessed as low risk of bias).⁴³ A

group of 42 patients (mean age 67.9, 76% women) on the waiting list for KR were randomly assigned to the two treatment groups. The primary outcome was avoidance or delay of KR; secondary outcomes included WOMAC pain, function, and stiffness, and adverse events. At one year, survival analysis showed a non-statistically significant higher survival time until knee replacement in the HA group compared with the placebo group (368.8 days vs. 253.9 days, $p=0.249$). The proportion who discontinued treatment at 24 weeks due to lack of efficacy was also non-statistically significantly higher in the placebo group (87% vs. 64%, $p=0.06$). Knee surgery was avoided in 9 HA-treated patients and 3 placebo-treated patients (OR 0.30, 95% CI, 0.08, 1.10). The randomized trials are described in evidence tables included in Appendix C.

Six case series reported on KR as an outcome (Table 3).⁴⁴⁻⁴⁹ Numbers of enrolled patients ranged from 69 (73 knees) to 863 (1,187 knees). Three of the studies administered Hylan GF-20 (Synvisc®), a higher molecular weight avian product), one administered Hyalgan, one administered Suplasyn, a lower molecular weight synthetic, and one administered Supartz™, a medium-high molecular weight avian hyaluronic acid. Follow-up times ranged from 6 months to 5 years. Rates of KR in these studies of HA-treated patients varied from fewer than 1% for 310 patients treated with Suplasyn and followed for 6 months,⁴⁷ to 19% of 1,187 knees treated with Hylan GF-20 and followed over 5 years.⁴⁸ None of the studies specified the criteria for recommending patients to undergo surgery.

Two medium^{44,46} and one large⁴⁸ retrospective case series on patients treated with HA assessed the effect of various factors on the likelihood of these patients undergoing TKR and the time to TKR by age group. One medium-size study⁴⁴ reported that those who underwent TKR tended to be older than those who did not but that BMI did not differ between the groups. The other medium sized study reported that those with Grade IV (67%) and those 65-79 years of age (34%) were more likely than those with less severe disease or in older or younger age groups to get KR.⁴⁶ The larger study found that the likelihood of undergoing KR did not differ by sex, BMI, history of effusion, or baseline VAS for pain. Only age range was a factor. HA-treated patients 60 to 69 were significantly more likely to undergo KR than patients under 50, patients 70 to 79, and those over 80, and patients in the younger age groups (50-79) were 2-3 fold more likely to get a KR than those 80 and over. Median time to KR for HA recipients was 1.8 years (14-2,147 days). Median followup time was 2.2 years (7-2,222 days). Seventy-five percent of knees had not had KR by 3.8 years. Time to KR was associated only with age: 60-69 year olds had a significantly shorter time to KR than other age groups.⁴⁸

Several other case series also reported on the average or longest time to KR in treated patients. For example two case series reported mean lag times of more than 6 months in those who underwent the procedure,^{44,46} and a large multi-site study of Supartz™ reported that the mean time to KR was 1.99 years and time to KR was as long as 4 years.⁴⁹

Nine articles reported on seven cohort studies that assessed KR as an outcome (Table 4).⁵⁰⁻⁵⁸ Numbers of enrolled patients ranged from 76 (92 knees) to 1,047 (1,489 knees). All studies enrolled patients with mean ages over 65, except one.⁵⁷ Three studies administered Hylan GF-20 (Synvisc); two administered Hyalgan; one administered Durolane, a non-avian product of medium molecular weight administered as a single injection; and one administered Adant, a non-avian medium molecular weight product administered in three to five weekly doses. Follow up times ranged from 6 months to 4.5 years. Rates of KR varied among studies as did the methods of reporting. One study that administered Hyalgan reported that over two years, 12 of 15 patients originally scheduled for KR cancelled the procedure.⁵⁰ The study that reported its findings in

three articles reported that over a followup of 24 months, 20% of patients underwent KR,⁵³ over 54 months, 28.4% of patients had undergone TKR, with a mean time to surgery of 15.4 months.⁵² When they stratified patients by Ahlback Grade, 4% of patients in the lowest severity group (Ahlback Grades of 1 or 2) underwent KR, 32.9% of patients in the medium severity group underwent KR, and 13.4% of patients in the highest severity group underwent KR.⁵⁴ Hylan GF-20 was associated with lower rates of KR in two studies by the same group,^{55,56} but with a 22% rate of KR in another study.⁵⁷ As with the retrospective studies, no study specified the criteria used to recommend patients proceed to KR.

A modification of the Newcastle-Ottawa instrument was used to assess the risk of bias of the included observational studies (Table 5). Risk of bias varied, with most studies indicating scoring on the moderate to high risk of bias side. Few studies attempted to control for baseline differences in comorbidities, few reported financial conflicts of interest, and patients were aware of their treatment in every instance.

Table 3. Case Series Reporting on Knee Replacement as an Outcome

Author, Year Country	# patients/ mean age (SD)/age range/ % female/ mean BMI/ mediating factors	Inclusion criteria/ exclusion criteria	Intervention/ dosing schedule/ follow-up times	Outcomes reported	Efficacy results	AEs results	Conclusions and comments
Barrett, 2002 ⁴⁴	249 patients (363 knees) treated Mean age 72 years /range 30-97 years/ 51.2% female/ BMI 29 Non-participants (those unavailable to be assessed): 127 (176 knees)	Inclusion: ACR OA diagnosis and radiogram within prior 6 months, completion of 5-injection course Exclusion: receipt of 2 nd course within 12 months (to study effects of single treatment course); significant alteration in exercise routine within 6 months	Hyalgan 5 injections/ 1 per week 6 months	Lack of TKR or other significant intervention therapy; secondary outcomes assessed in patients who avoided KR: QOL, pain (reported as improvement , non-improvement)	60.1% of knees (61.8% of patients) were considered clinically improved at 6 mos. 39.9% were judged as failures (20.3% underwent TKR); Risk for KR depended somewhat on compartmental involvement	“Excellent safety profile”	Single-course Hyalgan delayed or avoided TKR for at least 6 months in the majority of knees. Successes tended to be younger but did not differ on BMI Comment: 1. Unclear whether comparison group received treatments or what their success rate was 2. one of the 2 authors is employed by the manufacturer
Campbell, 2004 ⁴⁵	69 (73 knees)/ 62.2 years /range 37-90/ 44% women	Inclusion: Confirmation with plain x-rays or arthroscopy; Exclusion: none	Hylan GF-20 (Synvisc) 3 injections immediately after arthrocentesis Mean FU 8 months	Subjective improvement, total knee replacement, other treatments	61 patients identified for followup (90%) 51% of respondents reported a range of improvement; 11 patients underwent surgery including 7 knee replacements	Swelling/redness (6 patients) Pain at injection site (12) Apparent sepsis (3)	Patients were allowed to continue other methods of management; HA provided short-term relief for about half of patients but authors had largely discontinued use
Evanich, 2001 ⁴⁶	84 patients	First 100 knees to	Hylan GF-20	Pain, function,	Loss to followup	12 knees	Higher and lower

Author, Year Country	# patients/ mean age (SD)/age range/ % female/ mean BMI/ mediating factors	Inclusion criteria/ exclusion criteria	Intervention/ dosing schedule/ follow-up times	Outcomes reported	Efficacy results	AEs results	Conclusions and comments
US	/66±14 years/age range NR/61% women/BMI NR	receive HA at authors' clinic	(Synvisc) 3 injections FU 12 months	KR, other procedures (CS injection, arthroscopy) over 12 months	14 patients; 80 knees in 70 patients followed over 12 months 20 of 80 (25%) knees underwent TKR (20 patients) at an average of 6.7 months Those with Grade IV (67%) and those 65-79 years of age (34%) were more likely than those with less severe disease or in other age groups to get KR. 2 more had arthroscopy.	experienced AEs: 1 case of staph septic arthritis (2 weeks post initial injection), 11 cases of pain and swelling	age (compared with 65-79 years) and lesser severity decreased likelihood of undergoing TKR. Outcomes assessed by clinic nurse, not patient's own provider
Mazieres, 2007 ⁴⁷ France MESSAGE Study	310 patients, 296 of whom were assessed for outcomes:/69± 10 years/age range 36-88; 65% women/BMI 28±5 (30% obese) 36.5% of patients had both knees affected	Inclusion:>18 years; knee OA meeting ACR criteria; inadequate self- or MD-reported response to level 1 or 2 analgesics or NSAIDS within last 3 months Exclusion: effusion; history of intra-articular CS therapy within past 3 months, history of HA therapy within last year;	Suplasyn 3 injections FU 3 months, 6 months	Kellgren Lawrence, Lequesne; WOMAC pain and function, QoL (SF-12); costs (including procedures)	Of the 310, 14 were withdrawn early; 296 patients were assessed for outcomes: 1 partial KR and 1 KR were performed; significant improvements in WOMAC, Lequesne, SF-12	NR	<1% TKR after at least 2 injections Suplasyn

Author, Year Country	# patients/ mean age (SD)/age range/ % female/ mean BMI/ mediating factors	Inclusion criteria/ exclusion criteria	Intervention/ dosing schedule/ follow-up times	Outcomes reported	Efficacy results	AEs results	Conclusions and comments
		scheduled surgery on target knee; contraindications to intra-articular injections; known hypersensitivity to HA; pregnancy					
Waddell, 2007 ⁴⁸ US	1,187 knees (863 patients)/mean age of patients who underwent KR: 66.8±10.02(36-89), patients without TKR: 67.5±13.3 (28-98); 60% Female for both groups	Inclusion criteria: Any grade OA; unsuccessful treatment with NSAIDs and analgesics (WOMAC or pain VAS score of 50 or more) Exclusion criteria: mechanical problems, deformities due to OA, contraindications to HA (hypersensitivity, target knee joint infections, skin diseases, infections in area of injection site) (inclusion criteria for KR: K-L Grade IV and VAS pain score ≥60)	Hylan GF-20 (Synvisc) 3 injections (1997-2003) administered using a fluoroscopic technique to ensure accurate needle placement; repeat courses for some patients; prescription pain killers allowed for post injection pain and swelling FU 5 years	Primary outcome time to TKR	19% of knees treated with HA underwent KR. Undergoing TKR did not differ by sex, mean age, BMI, history of effusion, or baseline VAS for pain. Only age range was a factor. Patients 60-69 were significantly more likely than patients under 50, patients 70-79, and those over 80 to undergo KR, and patients in the younger age groups (50-79) were 2-3 fold more likely to get a TKR than those 80 and over. Median time to KR for HA recipients was	NR	Retrospective case series review; KR candidates who are not candidates for HA in this clinic typically undergo surgery within 3 months of first visit; in comparison, median time to KR in HA recipients was 638 days (median followup 810 days). Authors acknowledge lack of information on patients who did not receive KR within the followup time and other limitations.

Author, Year Country	# patients/ mean age (SD)/age range/ % female/ mean BMI/ mediating factors	Inclusion criteria/ exclusion criteria	Intervention/ dosing schedule/ follow-up times	Outcomes reported	Efficacy results	AEs results	Conclusions and comments
					1.8 years (14-2,147 days). Median followup time was 2.2 years (7-2,222 days). 75% of knees had not had KR by 3.8 years. Time to KR was associated only with age: 60-69 year olds had a significantly shorter time to KR than other age groups.		
Whitman, 2010 ⁴⁹ US	220 patients (303 knees); average age 70.9; range 35-99; 74.5% female	Inclusion: age≥18 years, confirmed diagnosis of OA, at least one repeat treatment with Supartz™ Exclusion: NR	5 weekly injections, follow-up 5 years	Pain, KR, AEs	Overall rate of KR: 23/303 (7.6%) Local site rates (5 sites) ranged from 1.8% to 24.0%. Mean time to KR 1.99 years (0.5 to 4 years)	26 total AEs none severe	Supartz was thought to delay or prevent need for KR. 92 percent of patients reported improvement in pain

Table Notes: CS corticosteroids; FU follow-up; HA hyaluronic acid; OA osteoarthritis; KR total knee replacement

Table 4. Cohort Studies Reporting on Total Knee Replacement as an Outcome

Author, Year Country	# patients/ mean age (SD)/age range/ % female/ mean BMI/ mediating factors	Inclusion criteria/ exclusion criteria	Intervention/ dosing schedule	Outcomes reported/Follow- up times	Efficacy results	AEs results	Conclusions and comments
Anand, 2010 ⁵⁷ US	167 patients/ mean age 59.4 (range 15- 92)/57% female Ahlbeck classification used: 1 Grade 1, 20 Grade 2, 104 Grade 3, 5 Grade 4	Inclusion criteria (for analysis): 1 completed course of HA, failure at previous protocol (NSAIDS, strength training, weight reduction, shoe modification, bracing, topical anesthetics, intra- articular CS) 119 patients had undergone prior arthroscopy.	Patients offered HA or KR; all opted to try HA: Synvisc (1999-2003)	Self-reported satisfaction, KR, AEs/6 months—5 years FU	130 patients underwent chart evaluation. Average number of courses HA: 1.6, 6-36 months between intervals. 45 patients were advised to proceed to surgery (including 17 who responded poorly at 6 months). 29/45 underwent surgery, including 24 KR and 5 partial (22%). All KR patients were Grade 3-4 at baseline. Of 109 patients seen at 5-year followup, 58.7% had not had surgery and were doing well.	3 patients developed toxic synovitis	Authors conclude HA can delay need for KR
Jurado, 2013 ⁵¹ Spain	224 patients/65.7 years/age range 34-89/67.9% female/	Inclusion criteria: diagnosis of OA according to Spanish Society of Rheumatology criteria; no other mechanical joint problems; no contraindications to HA; consistent use of same HA product; minimum 1-year followup Criteria for referral	Durolane (NASHA HA) 22 patients (9.2%) did not receive HA	Referral and time to referral for KR/mean follow up 374 days (95% CI, 323, 425) (range 0- 1547 days) Effects of gender, age, comorbidity, number of joints affected, severity at last follow-up, progression, pain, HA on time	40 patients (17.9%) were referred for KR. Mean follow-up was 328 days (95% CI, 232, 424). 20 of the 40 referred received KR. 9.1% of these patients were referred for surgery (these patients had lower average Kellgren- Lawrence classifications than those treated with	NR	Age over 65, involvement of both knees, severity of OA, lower pain intensity, and HA were each associated with longer time to KR; HA was associated with 1093 days to KR (95% CI. 980, 1206) vs.

Author, Year Country	# patients/ mean age (SD)/age range/ % female/ mean BMI/ mediating factors	Inclusion criteria/ exclusion criteria	Intervention/ dosing schedule	Outcomes reported/Follow-up times	Efficacy results	AEs results	Conclusions and comments
		for KR were grade IV OA and age<75 or Grade III and age >60		to KR	HA) Viscosupplementation increased the time between referral until surgery but not significantly.		694 (95%CI, 548, 839) (p=.064)
Korkmaz, 2013 ⁵⁸ Turkey	705 patients/ mean ages and sex ratios reported by diagnostic group and treatment group; only Grade 4 patients in the HA group had mean age>65 (68±13.3)	Inclusion criteria: ACR diagnosis Exclusion criteria: intra-articular injection within prior 3 months; arthroscopic intervention within prior year; history of pain with intra-articular injection	218 patients received Adant once weekly for 3 weeks; 487 patients received only NSAIDs and exercise prescriptions (2007-2009)	Surgical intervention at 1-year follow-up	197 patients received all HA treatments. Of those patients, 20 surgical procedures were done, including 7 KR (3 were done in patients with grade 3 OA and 4 in patients with grade 4 OA). Of 487 patients who received NSAIDs, 62 had surgery, including 26 KR	NR	Rates of total surgical procedures did not differ between groups but there was a non-significant decrease in procedures among those with the most advanced OA treated with HA (compared with NSAIDs) and in KR among the HA-treated groups
Neustadt, 2003 ⁵⁰ US	76 patients (92 knees)/64±7.4 years/40-80 years/60% > 65 years/21% female	No inclusion/exclusion criteria; all patients had moderate-severe OA, Kellgren-Lawrence II-IV, pain unresponsive to conventional treatments	Hyalgan 5 weekly injections	Physical exam, radiographs, AEs, ADLs/QoL, KR/ weekly and then at 6, 12, and 24 months	72% of patients achieved >50% improvement in in pain for ≥1 year 12 of 15 patients scheduled for KR no longer considered procedure necessary at 1 year; 15 of 19 avoided or delayed KR at 2 years.	No systemic AEs Minor AEs were infrequent and included injection site bruising and pain, rare headache, nausea; no pseudoseptic reactions	HA seemed to be associated with reduced need for KR. Improvement decreased with increasing Kellgren-Lawrence score, but this was not determined for

Author, Year Country	# patients/ mean age (SD)/age range/ % female/ mean BMI/ mediating factors	Inclusion criteria/ exclusion criteria	Intervention/ dosing schedule	Outcomes reported/Follow- up times	Efficacy results	AEs results	Conclusions and comments
							KR
Turajane, 2009 ⁵² Thailand	183 patients (220 knees) /68.74 years/ range 50-84 years/75% female/BMI 25.21 (same as Turajane, 2007a)	Same as Turajane, 2007	Hyalgan: 3 weekly injections, at least 1 course Patients who responded well were recommended to receive additional courses at 6- 12-month intervals	Time to KR over 54-month follow- up	Incidence of KR was 28.4%, mean time to KR: 15.4 months (0.7- 51.7 months) Mean follow-up time for patients who did not undergo KR was 45.6 months (19.0- 53.1 months)	NRKR	Repeated courses of HA were efficacious in delaying KR in patients who responded to tx
Turajane, 2007a ⁵³ Thailand	195 patients (220 knees) /68.74 years/ range 50-84 years/75% female/BMI 25.21 (same as Turajane 2007b)	Same as Turajane, 2007a	Hyalgan: 3 weekly injections, at least 1 course Patients who responded well received additional courses at 12- month intervals	Cost analysis of HA after ≥2 years follow-up	183 patients completed treatment; 146 patients (164 knees) responded to HA; 37 patients required surgery by 24 months (20%). Of the responders, 83 patients received a second course of tx and 14 received a third course.	NR	Retrospective cohort study enrolled 2001- 2004 HA is cost effective
Turajane, 2007b ⁵⁴ Thailand	195 patients (220 knees) /68.74 years/ range 50-84 years/75% female/BMI 25.21 Patients divided into three groups by	Inclusion criteria: Primary knee OA by ACR criteria, failure of conservative treatment more than 6 months (anti- inflammatories), no contraindication for surgery Exclusion criteria:	Hyalgan: 3 weekly injections, at least 1 course Patients who responded well received additional courses at 12- month	WOMAC, delay or cancellation of surgery, AEs Follow-up >24 months (24-48 months)	183 patients (206 knees) completed study. WOMAC improved in all groups. Group 1 (Ahlback grades 1,2):89.1% of patients delayed or cancelled knee surgery; 10.9%	None reported	Retrospective cohort study enrolled 2001- 2004

Author, Year Country	# patients/ mean age (SD)/age range/ % female/ mean BMI/ mediating factors	Inclusion criteria/ exclusion criteria	Intervention/ dosing schedule	Outcomes reported/Follow- up times	Efficacy results	AEs results	Conclusions and comments
	radiographic evaluation (Ahlback grades)	other degenerative arthritis or other joint disease, previous surgery, allergy to avian protein or sodium hyaluronate, any intra-articular treatment within prior 6 months	intervals		underwent surgery: 2 underwent KR, 3 arthroscopy Group 2: 67.1% delayed/cancelled surgery; 23 patients (32.9%) underwent KR Group 3: 86.5% delayed surgery; 13.4% underwent KR		
Waddell, 2006 ⁵⁵ US	1,047 patients (1,489 knees)/mean age 65.3/60% female 71% grade IV Kellgren- Lawrence	Inclusion criteria: OA diagnosis, lack of response to NSAIDs and analgesics Exclusion criteria: mechanical symptoms or deformities due to OA, contraindications to HA	Hylan GF-20: 3 weekly injections	Pain, mobility, medication, AEs, KR, 26 weeks follow-up	21 patients (2%) underwent KR before the end of the 26- week followup period	49 patients experienced 54 local AEs (pain and swelling) 12 patients experienced severe local pain and swelling. All resolved spontaneously or with aspiration and corticosteroids. AEs did not affect efficacy.	Proportion of patients who underwent KR was low
Waddell, 2005 ⁵⁶ US	85 patients (66 completed 26 weeks, 24 completed 104 weeks;)65.5±11.1 years/64.8% female	Inclusion criteria: healthy, ambulatory men or women aged <u>40</u> years; diagnosed with OA (at least 3 months earlier, ACR criteria); WOMAC score ≥2 on pain while	Hylan GF-20: 3 weekly injections	Pain, mobility, medication, AEs, KR (counted as reason for loss to followup), 104 weeks follow-up	At 52 weeks, of 59 remaining patients, 1 patient had undergone KR. No more KR's were reported through 104 weeks.	AEs were reported only as possibly, probably, or definitely treatment- related. 1 patient experienced severe arthrosis. No AE- related discontinuations	Repeated course of HA provided continued pain relief

Author, Year Country	# patients/ mean age (SD)/age range/ % female/ mean BMI/ mediating factors	Inclusion criteria/ exclusion criteria	Intervention/ dosing schedule	Outcomes reported/Follow- up times	Efficacy results	AEs results	Conclusions and comments
		<p>walking on a flat surface; a score of 50-90 mm VAS; failure to obtain OA knee pain relief with previous therapy of analgesics or NSAIDs; having received a clinical benefit from an initial course given at least 3 months prior.</p> <p>Exclusion: any serious systemic disease or significant psychiatric or neurological disorder; pregnant or nursing women, or women of childbearing age not using reliable birth control; known allergy to avian products, any components of hyaluronan-based injection devices, or corticosteroid injections; acetaminophen hypersensitivity; or use of an investigational drug</p>					

Author, Year Country	# patients/ mean age (SD)/age range/ % female/ mean BMI/ mediating factors	Inclusion criteria/ exclusion criteria	Intervention/ dosing schedule	Outcomes reported/Follow- up times	Efficacy results	AEs results	Conclusions and comments
		<p>or device within 90 days prior to the study; other joint diseases or conditions; patella femoral knee pain; acute synovitis; palpable effusion at screening or baseline; local AE with first course of hylan G-F 20; history of any joint sepsis; major surgery or arthroscopy in either knee within 6 months before screening or planned during the study; arthroplasty at the target joint; oral or intra-articular corticosteroid or any other intra-articular injection at the target joint within 3 months, or at a non-target joint within 4 weeks of screening; or use of glucosamine or chondroitin sulfate within 30 days prior to study entry</p>					

Table 5. Risk of Bias Assessment for Observational Studies Included in Assessment of total Knee Replacement*

Author, Year	Representativeness	Control for differences	Loss to follow-up	Masking exposures	Ascertainment**	Other treatment modalities	Valid outcomes**	AE collection	Financial COI	Author COI
Anand, 2010 ⁵⁷	N	N	Y	N	Y	Y	Y	NA	Y	Y
Barrett, 2002 ⁴⁴	N	NR	Y	Y	Y	Y	Y	NA	N	N
Campbell, 2004 ⁴⁵	N	NR	N	Y	Y	N	Y	N	Y	Y
Evanich, 2001 ⁴⁶	Y	Y	N	Y	Y	N	Y	N	N	NR
Jurado, 2013 ⁵¹	N	Y	Y	N	Y	Y	Y	NA	Y	Y
Korkmaz, 2013 ⁵⁸	NR	N	Y	N	Y	N	Y	NA	NR	NR
Mazieres, 2007 ⁴⁷	Y	N	Y	Y	Y	Y	Y	NA	NR	NR
Neustadt, 2003 ⁵⁰	Y	Y	Y	N	Y	N	Y	Y	N	Y
Turajane, 2007 ⁵³	N	Y	Y	N	Y	N	Y	NA	NR	NR
Waddell, 2005 ⁴⁸	Y	Y	Y	N	Y	Y	Y	N	N	N
Waddell, 2006 ⁵⁵	Y	Y	Y	N	N	Y	Y	Y	N	Y
Waddell, 2005 ⁵⁶	N	Y	Y	N	Y	Y	Y	Y	N	NR
Whitman, 2010 ⁴⁹	Y	N	Y	N	Y	N	Y	N	N	N

Table Notes: *See Appendix D for assessment tool. Y=yes (low risk); N=no (high risk); NR=not reported; NA=not applicable; COI conflict of interest; #also includes Turajan, 2007⁵⁴ and 2009,⁵² ;**Ascertainment: Yes indicates the diagnosis and/or treatment outcome were validated by medical report; Validity of outcomes: Yes indicates the outcome measure(s) have been validated for the condition and treatment of interest.

Intra-articular injection of hyaluronic acid and measures of function

We identified 18 randomized trials that compared the effects of HA with placebo or another HA using a validated assessment of function that included the WOMAC, Lequesne Index, ADLs, or IADLs, in individuals with OA of the knee whose average age was 65 or older.

Description of included studies

Of the 18 trials that reported on function as an outcome, sample sizes ranged from 32 to 495.^{41, 42, 59-72, 73, 43} Only a small proportion were US studies; the rest were conducted in Canada, the UK, Germany, France, Denmark, Sweden, Thailand, and Taiwan, and one was a multinational European trial. Of the trials, 11 were compared to a placebo,^{41, 60, 62-65, 67, 70, 72, 73, 43} six compared two HA devices head to head (one study had both a head-to-head comparison and a placebo group),^{59, 61, 67-69, 71} and two studies compared an HA to another active treatment.^{42, 66} Two studies conducted followup at 52 weeks^{41, 73}, one conducted followup at 4 weeks,⁷⁰ one ran for 12 weeks,⁶⁹ and the remainder conducted follow-up at 6 months (26 weeks).^{42, 59-68, 71, 72, 43} Most studies included Hyalgan, five included Synvisc, and one each included Adant, NRD101 (a medium molecular weight non-avian HA), Orthovisc, Supartz, Suplasyn, and GO-ON.

Nearly all studies reported functional outcomes using either the WOMAC functional domain or Lequesne functional index; one study measured KOOS activities, and one measured ADLs. In order to decide if the Lequesne index was similar enough to the WOMAC for pooling, we looked at 4 trials^{61, 66, 67, 69} that reported both outcomes to see if they reached the same conclusions (within trial). Conclusions for three of the four trials were the same for WOMAC and Lequesne. The one that differed⁶⁹ had different follow-up times for the WOMAC and Lequesne Index. Thus, we believed that the results of trials that only reported the Lequesne Index could be pooled with those of WOMAC trials. The one trial⁵⁹ that reported on ADL/IADLs was deemed different enough from the other functioning outcomes and was not pooled. These studies are described in Table 6 and in the evidence table in Appendix C.

The risk of bias for these RCTs varied widely from 0 to 12 (of 12) indicators of unclear or high risk of bias (Figure 4). The characteristics most often not reported or clearly not considered were allocation concealment and blinding of providers. In addition, although not considered in assessment for risk of bias, almost no studies reported the proportion of participants who responded (reporting only the mean difference in response from baseline).

Key Points

- Our meta-analysis of ten studies that compared the effects of anHA to those of a placebo control showed a significant improvement in WOMAC-assessed function following HA treatment compared to placebo (standardized effect size or standardized mean difference [SMD] -0.23, 95% CI -0.34, -0.02) that did not achieve the MCID (0.37); this effect size corresponds to 4.3 units on a 100mm VAS scale.
- The number of head-to-head trials is too small to be able to assess the relative superiority of one HA over another.
- Although most studies reported findings at 6 months' follow-up, one study with 4 weeks follow-up and two studies with 52 weeks' follow-up also reported a positive effect of the device on functional outcomes.

- Although no studies assessed the proportion of patients with improved function, seven studies assessed the proportion of patients with patient- or investigator reported global improvement; of the four that were placebo-controlled, three reported significant increases in the proportion of HA-treated patients who improved, compared with the proportion of placebo-treated patients who improved.
- No studies assessed the durability of effect.

Detailed Synthesis

Eleven trials^{41, 60, 62-65, 67, 70, 72, 73, 43} presented data comparing the effect of HA on function to that of a sham-injected placebo group with blinded assessment. All but one⁶⁰ reported a mean change from baseline or a baseline and follow-up mean by treatment group. Four trials^{62, 65, 70, 72} did not report the standard deviation of the mean change, so we estimated it using the standard deviations of the baseline and follow-up mean change. One of these trials⁶² also did not report a follow-up standard deviation so it was imputed. We included the WOMAC function scale from 4 trials^{62-64, 70}, Lequesne index from 3 trials^{41, 65, 67} and KOOS activities from one trial⁷². One trial⁶⁷ reported both the WOMAC and the Lequesne Index. In this case, we used the Lequesne Index, as it provided more data.

Pooled analysis of ten placebo-controlled trials showed a small increase in function for the HA-treated group (standardized effect size or standardized mean difference [SMD] -0.23, 95% CI -0.41, -0.05) at follow-up when using the Dersimonian and Laird random effects method.^{41, 62-65, 67, 70, 72, 73, 43} This finding indicates that those in the HA group had better functioning than those in the placebo group. A repeat of the original meta-analysis using the HKSJ method showed that the effect of HA on function was statistically significant compared with placebo (-0.23, 95%CI -0.45, -0.01). We calculated that the effect size corresponded to an improvement of 8.28 units (on a 0-100 VAS scale) which was smaller than the minimum clinically important difference of 9 units used in a prior systematic review of the effects of HA.¹⁴

The I^2 is 54.0%, indicating low to moderate heterogeneity. Both the Begg's and Egger's test showed no evidence of publication bias ($p=0.245$ and $p=0.418$, respectively). One of the included studies reported a stronger effect for placebo than for the active treatment,⁶⁷ and one study showed no effect for either.⁷² All but three of the studies reported follow-up at 6 months; sensitivity analyses that excluded all of the studies that reported follow-up sooner (4 weeks)⁷⁰ or later (52 weeks)⁴¹ individually did not result in a large difference from our main result (SMD=-0.23 and SMD=-0.25, respectively) (Figure 3). Among the comparisons not included in the meta-analysis, one study compared the effect of Hyalgan to that of placebo using a standard assessment for ADLs.⁵⁹ This study found no significant improvement in ADLs at 6 months among the Hyalgan-treated group (SMD -0.08 95% CI -0.57, 0.42)

A study that compared Hyalgan (5 weekly treatments) to placebo as well as to NSAIDs found that Hyalgan significantly improved WOMAC function at 6 months over placebo but no differences were seen between Hyalgan and NSAIDs.⁶⁰ This study had a large sample size but a high dropout rate.

Five trials reported function data and compared HA to an active comparator^{61, 67, 68, 69, 71} at 26 weeks. Three of these trials had standard deviations imputed.^{68, 69, 71} Since the comparator groups were quite heterogeneous, we did not do a meta-analytic pooling.

A multi-site study that compared Hyalgan to a medium-molecular weight device, GO-ON, reported greater improvement in WOMAC-assessed function at 6 months for the GO-ON treated group than for the Hyalgan group (SMD -0.326, 95% CI -0.52, -0.13).⁶¹

Two studies compared Hyalgan to the high-molecular-weight HA, Synvisc.^{68, 71} One very small Thai study reported a significant improvement in WOMAC function for single injections of both devices at 6 months, with no difference between the two (SMD 0.053, 95% CI -0.66, 0.77).⁶⁸ A much larger UK study that compared five weekly treatments with Hyalgan (the standard dosing schedule) to three weekly treatments with Synvisc reported a significant and much larger effect for Synvisc than for Hyalgan (SMD -0.882, 95%CI -1.09,-0.68) at 6 months.⁷¹

One study compared Synvisc to Sinovial, a medium-molecular weight (800-1200kD) HA of non-avian origin.⁶⁹ At 12 weeks follow-up, both groups of patients showed the same degree of improvement on the Lequesne index (SMD 0.100, 95%CI -0.11, 0.30). At 6 months' follow-up, both groups showed a larger improvement in function, this time assessed by the WOMAC function scale, and again, no difference was seen between groups (SMD -0.009 95% CI -0.21, 0.19).

Two studies compared the effects of a HA to that of another active treatment. One small UK study that compared Hyalgan to arthroscopic washout of the affected knee found comparable improvement in function (as assessed by the Lequesne index) for both groups at 6 and 12 months (SMD -0.028 95% CI -0.66, 0.61).⁴²

One large trial in France compared the effects of a standard dosing schedule of Synvisc with that of conventional treatment (which was not defined by this study, but often indicates a series of treatments of increasing intensity, e.g., NSAIDs and exercise, physical therapy, orthotics, and bracing).⁶⁶ At 6 months' follow-up, Synvisc improved function significantly compared with conventional treatment, as assessed with both the WOMAC (SMD -0.567, 95% CI -0.75, -0.39) and the Lequesne index (SMD -0.494, 95% CI -0.67, -0.32).

None of the studies that met inclusion criteria reported the percentage of participants who met prespecified criteria for improvement in function. However, seven studies assessed the proportion of patients with patient- or investigator reported global improvement (according to prespecified criteria).^{61, 64, 66, 67, 69, 72, 73} Four were placebo-controlled (two others were head-to-head comparisons only, and the remaining study compared HA to conventional treatment);^{64, 67, 72, 73} Of the four placebo-controlled trials (26-52 weeks in duration), three reported increases in the proportion of HA-treated patients who improved (according to themselves or the investigator), compared with the proportion of placebo-treated patients who improved.^{64, 67, 72}

Effect duration could not be derived from the identified studies. As described above, the longest followup point for most of the included studies was 6 months; three studies assessed function at 52 weeks. One study that compared the effects of a course of Hyalgan with that of arthroscopic washout through 52 weeks on Lequesne Index score reported that function at 52 weeks was improved over function at baseline in both groups, that function appeared to be continuing to improve at 52 weeks in both groups, and that improvement was not significantly different in the HA-treated group than in the group that underwent washout.⁴² A study that compared the effect of Hyalectin to that of a saline placebo at 7 weeks and 52 weeks after initiation of treatment, showed that Lequesne Index scores continued to improve through 12 months in both groups but that improvement was significantly greater in the Hyalectin group ($p=0.03$).⁴¹ Finally, a third study compared the effects of Hylan G-F 20 (Synvisc) with that of a lower molecular weight preparation of HA on WOMAC function scores over 52 weeks: Hylan-G-F 20 recipients showed comparable improvement in WOMAC scores from 3 months through 12 months, whereas HA showed a significant improvement only at 3 months.⁷¹

Table 6. Summary of studies reporting functional outcomes

Author, Year Location	# Patients (Knees)/ Mean Age (SD)/ Age Range/% Female	Comorbidities	Study Arms	Relevant Outcomes Reported/ Follow Up Times
Altman et al., 1998 ⁶⁰ US	495(NR) Mean age: 64 (10 (whole group)) % Female: 57	NR	<p>Arm 1: N = 115 Mean age: 65 (10) Placebo/sham Acetaminophen up to 4000mg /day permitted as rescue</p> <p>Arm 2: N = 105 Mean age: 62(10) Hyalgan 20mg/2ml Molecular weight: 500-730kD Oral placebo for naproxen twice daily and Acetaminophen up to 4000mg /day permitted as rescue</p> <p>Arm 3: N = 113 Mean age: 63(9) NSAID</p> <p>Total treatments: 5 Time between treatment: 1 week</p>	<p><u>WOMAC physical function</u> (Follow up time: 26 weeks) Arm 1: Placebo, N=115</p> <p>Arm 2: Hyalgan 20mg/2ml 500-730kD, N=105</p> <p>Arm 3: NSAIDs, N=113</p> <p><u>Study-level:</u> WOMAC physical function HA group improvement more than placebo group p=0.047</p>

Author, Year Location	# Patients (Knees)/ Mean Age (SD)/ Age Range/% Female	Comorbidities	Study Arms	Relevant Outcomes Reported/ Follow Up Times
Berenbaum et al., 2012 ⁶¹ France, Germany	426(NR) Mean age: 67 (NR) % Female: 63		<p>Arm 1: N = 209 Mean age: 66.1 (8.1) Hyalgan Molecular weight: 500 kD-730 kD NSAID or paracetamol up to 4g/d as permitted as rescue medication</p> <p>Arm 2: N = 217 Mean age: 67.2 (7.8) GO-ON (2.5 ml, 10mg/ml) Molecular weight: 800 kD-1500 kD NSAID or paracetamol up to 4g/d as permitted as rescue medication</p> <p>Total treatments: 3 Time between treatment: 3 weeks</p>	<p><u>Lequesne index</u> (Follow up time: 26 weeks) Arm 1: Hyalgan 500 kD-730 kD, N=209 Mean change from baseline: -3 (3.7)</p> <p>Arm 2: GO-ON (2.5 ml, 10mg/ml) 800 kD-1500 kD, N=217 Mean change from baseline: -4.2 (3.8)</p> <p><u>WOMAC function</u> (Follow up time: 26 weeks) Arm 1: Hyalgan 500 kD-730 kD, N=209 Mean change from baseline: -15.4 (19.9)</p> <p>Arm 2: GO-ON (2.5 ml, 10mg/ml) 800 kD-1500 kD, N=217 Mean change from baseline: -22.2 (21.8)</p> <p><u>Study-level:</u> WOMAC function Standard mean difference: -0.326 (-0.52, -0.13)</p> <p>Lequesne index Standard mean difference: -0.320 (-0.51, -0.13)</p>

Author, Year Location	# Patients (Knees)/ Mean Age (SD)/ Age Range/% Female	Comorbidities	Study Arms	Relevant Outcomes Reported/ Follow Up Times
Blanco et al., 2008 ⁴³ Spain	42 Mean age: 68.3 ((9.1)) % Female: 76	NR	<p>Arm 1: N = 20 Mean age: 68.3(9.1) Placebo/sham Paracetamol and/or dicofenac as rescue analgesics</p> <p>Arm 2: N = 22 Mean age: 67.5(8.1) Adant Molecular weight: 900 kDa</p> <p>Total treatments: 10 (2 cycles of 5 weekly injections, separated by 24 weeks) Time between treatment: 1 week</p>	<p><u>Number of patients with knee surgery</u> (Follow up time: 24 weeks) Arm 1: Placebo, N=23 Count = 20 (87%) Arm 2: Adant 900 kDa, N=25 Count = 16 (64%)</p> <p><u>Physical function WOMAC</u> (Follow up time: 24 weeks) Arm 1: Placebo, N=20 Mean change from baseline: -4.4 (18.8) Arm 2: Adant 900 kDa, N=22 Mean change from baseline: -24.7 (18)</p> <p><u>Study-level:</u> Physical function WOMAC Standard mean difference: -1.080 (-1.74, -0.43)</p> <p>Number of patients with knee surgery OR: 0.300 (0.08, 1.10)</p>
Brandt et al., 2001 ⁶² US	226(NR) Mean age: NR (NR) % Female: 63	Involvement of both knees: HA: 78% Saline: 88%	<p>Arm 1: N = 112 Mean age: 67(8.4) Placebo/sham</p> <p>Arm 2: N = 114 Mean age: 65(8.4) Orthovisc (2 mL, 15mg/mL) Molecular weight: 1000-2900 kD (considered high MW)</p> <p>Total treatments: 3 Time between treatment: 1 week</p>	<p><u>WOMAC function</u> (Follow up time: 27 weeks) Arm 1: Placebo, N=69 Mean change from baseline: -9.8 (15.1) *</p> <p>Arm 2: Orthovisc (2 mL, 15mg/mL) 1000-2900 kD (considered high MW), N=66 Mean change from baseline: -14.7 (15.1) *</p> <p><u>Study-level:</u> WOMAC function Standard mean difference: -0.323 (-0.66, 0.02)</p>

Author, Year Location	# Patients (Knees)/ Mean Age (SD)/ Age Range/% Female	Comorbidities	Study Arms	Relevant Outcomes Reported/ Follow Up Times
DeCaria et al., 2012 ⁶³ Ontario Canada	30(na) Mean age: NR (NR) % Female: 47	NR	<p>Arm 1: N = 15 Mean age: 72.93 (5.48) 500 mg acetaminophen to be taken up to 4g/day as rescue medication Placebo/sham 1.2 ml 0.001 mg/ml inert HA</p> <p>Arm 2: N=15 Hyaluronic acid (2 ml, 20 mg/ml) Molecular weight: 730 kD 500 mg acetaminophen to be taken up to 4g/day as rescue medication</p> <p>Total treatments: 3 Time between treatment: 1 week</p>	<p><u>WOMAC function</u> (Follow up time: 26 weeks) Arm 1: Placebo, N=15 Mean change from baseline: -3.53 (10.15)</p> <p>Arm 2: Hyaluronic Acid 730 kD, N=15 Mean change from baseline: -9.07 (8.14)</p> <p><u>Study-level:</u> WOMAC function Standard mean difference: -0.586 (-1.32, 0.15)</p>
Dixon et al., 1988 ⁵⁹ UK	63(NR) Mean age: 68.5 (NR) % Female: 54	NR	<p>Arm 1: N = 33 Mean age: nr Hyalgan 0.2mg/2 ml Molecular weight: NR Placebo/sham</p> <p>Arm 2: N = 30 Mean age: nr Hyalgan 20mg/2 ml Molecular weight: NR Paracetamol was permitted but NSAIDS, corticosteroids, and strong analgesics were not</p> <p>Total treatments: Varied 1 for first 3 weeks and then 2</p>	<p><u>ADL/IDLS</u> (Follow up time: 25 weeks) Arm 1: Hyalgan 0.2mg/2 ml, N=33 Mean change from baseline: -1 (10.5) *</p> <p>Arm 2: Hyalgan 20mg/2 ml, N=30 Mean change from baseline: -1.8 (10.5) *</p> <p><u>Study-level:</u> ADL/IDLS Standard mean difference: -0.076 (-0.57, 0.42)</p>

Author, Year Location	# Patients (Knees)/ Mean Age (SD)/ Age Range/% Female	Comorbidities	Study Arms	Relevant Outcomes Reported/ Follow Up Times
Dougados et al., 1993 ⁴¹ France	110 Mean age: 69.0 (10.6) % Female: 71.0	NR	Arm 1: N=55 Placebo/sham Arm 2: N=55 Hyalectin (Hyalgan) Molecular weight: 500-730 kDa Total treatments: 4 Time between treatment: 1 week	<u>Lequesne index</u> (Follow up time: 52 weeks) Arm 1: Placebo, N=48 Mean change from baseline: -2.7 (4.1) Arm 2: Hyalgan 500-730 kDa, N=47 Mean change from baseline: -4.4 (5.1) <u>Number of patients with arthroscopy</u> (Follow up time: 52 weeks) Arm 1: Placebo, N=48 Count = 5 (10.4%) Arm 2: Hyalgan 500-730 kDa, N=47 Count = 2 (4.3%) <u>Study-level:</u> <u>Lequesne index</u> Standard mean difference: -0.360 (-0.77, 0.04) <u>Number of patients with arthroscopy</u> OR: 0.409 (0.09, 1.89)

Author, Year Location	# Patients (Knees)/ Mean Age (SD)/ Age Range/% Female	Comorbidities	Study Arms	Relevant Outcomes Reported/ Follow Up Times
Forster et al., 2003 ⁴² UK	38 Mean age: 61.5 (NR) % Female: NR	NR	Arm 1: N = 19 Mean age: 63 Arthroscopic washout Arm 2: N = 19 Mean age: 60 Hyalgan Molecular weight: 500-730 kD Total treatments: 5 Time between treatment: 1 week	<u>Lequesne index</u> (Follow up time: 26 weeks) Arm 1: Arthroscopic washout, N=19 Mean change from baseline: -1 (25) * Arm 2: Hyalgan 500-730 kD, N=19 Mean change from baseline: -1.5 (6) * <u>Number of patients with arthroscopy</u> (Follow up time: 52 weeks) Arm 1: Arthroscopic washout, N=15 Count = 3 (20%) Arm 2: Hyalgan 500-730 kD, N=17 Count = 2 (11.8%) <u>Study-level:</u> Lequesne index Standard mean difference: -0.028 (-0.66, 0.61) Number of patients with arthroscopy OR: 0.546 (0.08, 3.59)
Grecomoro et al., 1987 ⁷⁴ Italy	34(40) Mean age: 64.88 (10.94) % Female: 19/34	Involvement of both knees: 6/34	Arm 1: N = 20 knees Mean age: NR Placebo/sham Arm 2: N = 20 knees Mean age: NR Hyalgan Molecular weight: 500K-750K Total treatments: 3 Time between treatment: 1 week	

Author, Year Location	# Patients (Knees)/ Mean Age (SD)/ Age Range/% Female	Comorbidities	Study Arms	Relevant Outcomes Reported/ Follow Up Times
Henderson et al., 1994 ⁷⁵ UK	91(NR) Mean age: NR (NR) % Female: 69	Involvement of both knees: >99%	Arm 1: N = 20 (Severity group 1) Mean age: 60.0(1.9) Placebo/sham Arm 2: N = 26 Severity Group 2 Second placebo group Arm 3: N = 18 Severity Group 1 Mean age: 63.9(1.9) Hyalgan (20mg/2mL) Molecular weight: NR Arm 4: N = 26 Severity Group 2 Mean age: 67.0(1.7) Hyalgan Total treatments: 5 Time between treatment: 1 week	
Huang et al., 2011 ⁶⁴ Taiwan	200(NR) Mean age: 65.0 (8.3) % Female: 76	NR	Arm 1: N = 100 Mean age: 64.2(8.4) Placebo/sham Arm 2: N = 100 Mean age: 65.9(8.1) Hyalgan (20mg/2ml) Total treatments: 5 Time between treatment: 1 week	<u>WOMAC function</u> (Follow up time: 25 weeks) Arm 1: Placebo, N=98 Mean change from baseline: -18.2 (16.7) Arm 2: Hyalgan (20mg/2ml), N=100 Mean change from baseline: -25.16 (16.7) <u>Study-level:</u> WOMAC function Standard mean difference: -0.415 (-0.70, -0.13)

Author, Year Location	# Patients (Knees)/ Mean Age (SD)/ Age Range/% Female	Comorbidities	Study Arms	Relevant Outcomes Reported/ Follow Up Times
Huskisson et al., 1999 ⁶⁵ United Kingdom	100(NR) Mean age: nr (nr) % Female: 67		Arm 1: N = 50 Mean age: 64.8 (9.3) Placebo/sham Arm 2: N = 50 Mean age: 65.8 (8.8) Hyalgan Molecular weight: 500-730 kDa Total treatments: 5 Time between treatment: 1 week	<u>Lequesne functional index</u> (Follow up time: 26 weeks) Arm 1: Placebo, N=41 Mean change from baseline: -1.4 (7.8) Arm 2: Hyalgan 500-730 kDa, N=40 Mean change from baseline: -2.2 (7.9) <u>Study-level:</u> Lequesne functional index Standard mean difference: -0.101 (-0.54, 0.34)
Kahan et al., 2003 ⁶⁶ France	506 Mean age: 66 (10) % Female: 67.5	Involvement of both knees: 74	Arm 1: N = 253 Mean age: 66 (10) Conventional treatment Arm 2: N = 253 Mean age: 66 (10) Synvisc Molecular weight: NR Total treatments: 3 Time between treatment: 1 week	<u>Lequesne index</u> (Follow up time: 26 weeks) Arm 1: Conventional treatment, N=253 Mean change from baseline: -1.6 (4) Arm 2: Synvisc, N=253 Mean change from baseline: -3.6 (4.1) <u>WOMAC function</u> (Follow up time: 26 weeks) Arm 1: Conventional treatment, N=247 Mean change from baseline: -7 (20.6) Arm 2: Synvisc, N=251 Mean change from baseline: -18.4 (19.6) <u>Study-level:</u> Lequesne index Standard mean difference: -0.494 (-0.67, -0.32) WOMAC function Standard mean difference: -0.567 (-0.75, -0.39)

Author, Year Location	# Patients (Knees)/ Mean Age (SD)/ Age Range/% Female	Comorbidities	Study Arms	Relevant Outcomes Reported/ Follow Up Times
Karlsson et al., 2002 ⁶⁷ Sweden	246(NR) Mean age: reported by arm below (reported by arm below) % Female: 61	NR	<p>Arm 1: N = 66 (57 PP) Mean age: 71(6) Placebo/sham</p> <p>Arm 2: N = 92 (76 PP) Mean age: 72(7) Artzal (2.5 ml 1% hyaluronan) Molecular weight: 1,000 kDa</p> <p>Arm 3: N = 88 (77 PP) Mean age: 70(7) Synvisc (2 ml 0.8%) Molecular weight: 7,000 kDa</p> <p>Total treatments: 3 Time between treatment: 1 day</p>	<p><u>Lequesne algofunctional index</u> (Follow up time: 26 weeks) Arm 1: Placebo, N=57 Mean change from baseline: -4.7 (4.4)</p> <p>Arm 2: Artzal (2.5 ml 1% hyaluronan) 1,000 kDa, N=76 Mean change from baseline: -3.9 (4.6)</p> <p>Arm 3: Synvisc (2 ml 0.8%) 7,000 kDa, N=77 Mean change from baseline: -4.4 (4.1)</p> <p><u>WOMAC physical function</u> (Follow up time: 26 weeks) Arm 1: Placebo, N=57 Mean change from baseline: -11.1 (14.8) *</p> <p>Arm 2: Artzal (2.5 ml 1% hyaluronan) 1,000 kDa, N=76 Mean change from baseline: -7.3 (14.9) *</p> <p>Arm 3: Synvisc (2 ml 0.8%) 7,000 kDa, N=77 Mean change from baseline: -11.7 (14.7) *</p> <p><u>Study-level:</u> WOMAC physical function Standard mean difference: 0.260 (-0.09, 0.60) Arms 2 vs 1</p> <p>WOMAC physical function Standard mean difference: -0.297 (-0.62, 0.02) Arms 3 vs 2</p> <p>Lequesne algofunctional index Standard mean difference: 0.176 (-0.17, 0.52) Arms 2 vs 1</p> <p>Lequesne algofunctional index Standard mean difference: -0.115 (-0.43, 0.20) Arms 3 vs 2</p>

Author, Year Location	# Patients (Knees)/ Mean Age (SD)/ Age Range/% Female	Comorbidities	Study Arms	Relevant Outcomes Reported/ Follow Up Times
Khanasuk et al., 2012 ⁶⁸ Thailand	32(NR) Mean age: NR (NR) % Female: 80	NR	<p>Arm 1: N = 15 Mean age: 65.1(9.6) Hylan GF-20 (Synvisc)(single 6 ml injection) Molecular weight: Reported as High</p> <p>Arm 2: N = 15 Mean age: 67.0(9.5) Hyalgan (single injection) Molecular weight: Reported as Low</p> <p>Total treatments: 1</p>	<p><u>SF-36 PCS</u> (Follow up time: 26 weeks) Arm 1: Synvisc (single 6 ml injection), N=15 Mean change from baseline: -6 (25) *</p> <p>Arm 2: Hyalgan (single injection, N=15) Mean change from baseline: -4 (25) *</p> <p><u>WOMAC function</u> (Follow up time: 26 weeks) Arm 1: Synvisc (single 6 ml injection) Reported as High, N=15 Mean change from baseline: -20 (37.5) *</p> <p>Arm 2: Hyalgan (single injection Reported as Low, N=15) Mean change from baseline: -22 (37.5) *</p> <p><u>Study-level:</u> WOMAC function Standard mean difference: 0.053 (-0.66, 0.77)</p> <p>SF-36 PCS Standard mean difference: -0.080 (-0.80, 0.64)</p>
Leopold et al., 2003 ⁷⁶ US	100(NR) Mean age: NR (NR) % Female: CS: 56 HA: 52	NR	<p>Arm 1: N = 42 Mean age: 64</p> <p>Arm 2: N = 38 Mean age: 66 Hylan G-F 20 (16mg/2ml)</p> <p>Total treatments: 3 HA 1CS Time between treatment: 1 week</p>	

Author, Year Location	# Patients (Knees)/ Mean Age (SD)/ Age Range/% Female	Comorbidities	Study Arms	Relevant Outcomes Reported/ Follow Up Times
Lundsgaard et al., 2008 ⁷² Denmark	251 Mean age: 69.6 (7.27) % Female: 52.4	NR	<p>Arm 1: N=84 Saline 2ml</p> <p>Arm 2: N=83 Saline 20 mL, no hyaluronate</p> <p>Arm 3: N=84 Hyalgan Molecular weight: NR</p> <p>Total treatments: 4 Time between treatment: 1 week</p>	<p><u>KOOS activities</u> (Follow up time: 26 weeks) Arm 1: Saline 2ml, N=84 Mean change from baseline: -5 (16.3)</p> <p>Arm 2: Saline 20 mL, no hyaluronate, N=83 Mean change from baseline: -5.2 (15.1)</p> <p>Arm 3: Hyalgan 500 - 730 kD, N=84 Mean change from baseline: -4.4 (15.7)</p> <p><u>KOOS quality of life</u> (Follow up time: 26 weeks) Arm 1: Saline 2ml, N=84 Mean change from baseline: -6.4 (15.7)</p> <p>Arm 2: Saline 20 mL, no hyaluronate, N=83 Mean change from baseline: -7.1 (12.1)</p> <p>Arm 3: Hyalgan 500 - 730 kD, N=84 Mean change from baseline: -3.4 (15.4)</p> <p><u>Study-level:</u> <u>KOOS activities</u> Standard mean difference: 0.037 (-0.27, 0.34)</p> <p><u>KOOS quality of life</u> Standard mean difference: -0.193 (-0.50, 0.11)</p>

Author, Year Location	# Patients (Knees)/ Mean Age (SD)/ Age Range/% Female	Comorbidities	Study Arms	Relevant Outcomes Reported/ Follow Up Times
Pavelka et al., 2011 ⁶⁹ Czech Republic, France, Italy, Switzerland, the Slovak Republic and Germany	381 Mean age: 65 (9) % Female: 72.9	Involvement of both knees: 66%	Arm 1: N = 192 Mean age: 65.1 (9.1) Synovial Molecular weight: 800 - 1,200 kD Arm 2: N = 188 Mean age: 64.9 Synvisc Molecular weight: 6,000 kD Total treatments: 3 Time between treatment: 1 week	<u>Lequesne algofunctional index</u> (Follow up time: 12 weeks) Arm 1: Synovial 800 - 1,200 kD, N=192 Mean change from baseline: -3.9 (5.2) Arm 2: Synvisc 6,000 kD, N=188 Mean change from baseline: -3.4 (5.2) <u>WOMAC function</u> (Follow up time: 26 weeks) Arm 1: Sinovial 800 - 1,200 kD, N=192 Mean change from baseline: -28 (21.8) * Arm 2: Synvisc 6,000 kD, N=188 Mean change from baseline: -28.2 (21.7) * <u>Study-level:</u> WOMAC function Standard mean difference: -0.009 (-0.21, 0.19) Lequesne algofunctional index Standard mean difference: 0.100 (-0.11, 0.30)

Author, Year Location	# Patients (Knees)/ Mean Age (SD)/ Age Range/% Female	Comorbidities	Study Arms	Relevant Outcomes Reported/ Follow Up Times
Petrella et al., 2002 ⁷⁰ Canada	120 Mean age: 65.5 (9.5) % Female: 45.8	Involvement of both knees: 0%	<p>Arm 1: N = 28 Mean age: 62.6 (9.5) Placebo/sham</p> <p>Arm 2: N = 25 Mean age: 67.3 (8.9) Suplasyn Molecular weight: NR Placebo pill</p> <p>Arm 3: N = 29 Mean age: 65.0 (9.7) Suplasyn Molecular weight: NR NSAID</p> <p>Arm 4: N = 26 Mean age: 66.3 (8.8) NSAID</p> <p>Total treatments: 3 Time between treatment: 1 week</p>	<p><u>WOMAC disability</u> (Follow up time: 4 weeks) Arm 1: Placebo, N=28 Mean change from baseline: -0.99 (3)</p> <p>Arm 2: Suplasyn NR, N=25 Mean change from baseline: -1.65 (2.5)</p> <p>Arm 3: Suplasyn+NSAIDs NR, N=29 Mean change from baseline: -1.17 (2.7)</p> <p>Arm 4: NSAIDs, N=26 Mean change from baseline: -1.56 (2.8)</p> <p><u>Study-level:</u> WOMAC disability Standard mean difference: -0.234 (-0.77, 0.31)</p>

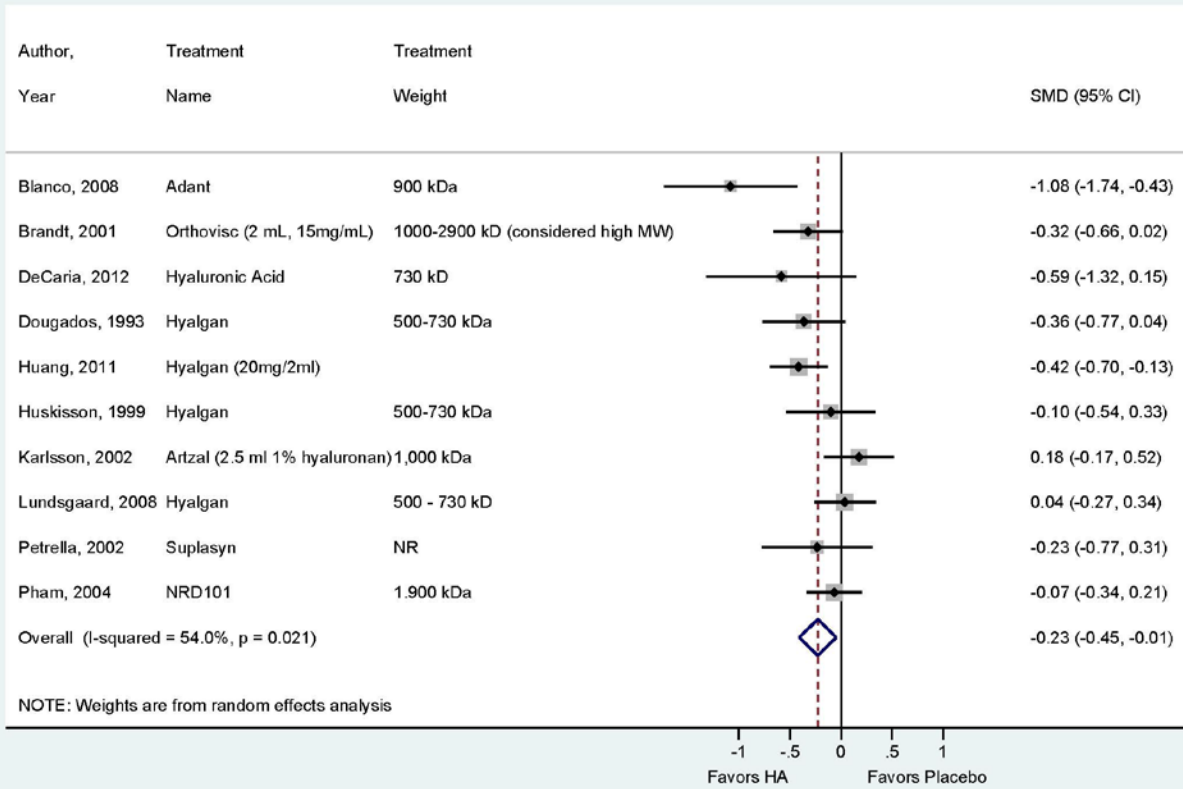
Author, Year Location	# Patients (Knees)/ Mean Age (SD)/ Age Range/% Female	Comorbidities	Study Arms	Relevant Outcomes Reported/ Follow Up Times
Petrella et al., 2008 ⁷⁷ Canada	200 Mean age: 71 (8) % Female: 30	NR	<p>Arm 1: N = 50 Mean age: 71+/-8 Placebo/sham</p> <p>Arm 2: N = 50 Mean age: 68+/-6 HA dual molecular weight Molecular weight: 580–780 kDa+1.2 to 2.0 million kDa</p> <p>Arm 3: N = 50 Mean age: 69+/-5 HA low molecular weight Molecular weight: 500–730 kDa</p> <p>Arm 4: N = 50 Mean age: 71+/-9 HA high molecular weight Molecular weight: 6 million kDa</p> <p>Total treatments: 3 Time between treatment: 1 week</p>	

Author, Year Location	# Patients (Knees)/ Mean Age (SD)/ Age Range/% Female	Comorbidities	Study Arms	Relevant Outcomes Reported/ Follow Up Times
Petrella et al., 2011 ⁷⁸ Canada	200 Mean age: 70 (8) % Female: 57	NR	<p>Arm 1: N = 50 Mean age: 71 (8) Placebo/sham</p> <p>Arm 2: N = 50 Mean age: 68 (6) sodium hyaluronate Molecular weight: Combined high & low weight</p> <p>Arm 3: N = 50 Mean age: 69 (5) sodium hyaluronate - low weight Molecular weight: 500-730 KDa</p> <p>Arm 4: N = 50 Mean age: 71 (9) sodium hyaluronate - high weight Molecular weight: 6000 KDa</p> <p>Total treatments: 3 Time between treatment: 1 week</p>	

Author, Year Location	# Patients (Knees)/ Mean Age (SD)/ Age Range/% Female	Comorbidities	Study Arms	Relevant Outcomes Reported/ Follow Up Times
Pham et al., 2004 ⁷³ France	301 Mean age: 64.9 (7.7) % Female: 65 average	NR	<p>Arm 1: N = 85 Mean age: 64.9 (7.7) Placebo/sham</p> <p>Arm 2: N = 131 Mean age: 71.0 NRD101 Molecular weight: 1.900 kDa</p> <p>Arm 3: N = 85 Mean age: 64.5 Diacerein</p> <p>Total treatments: 12? (3 course every 3 months for a year) Time between treatment: 1 week</p>	<p><u>Lequesne's algofunctional index</u> (Follow up time: 52 weeks) Arm 1: Oral placebo+saline, N=85 Mean change from baseline: 10.5 (3.1)</p> <p>Arm 3: NRD101 1.900 kDa, N=131 Mean change from baseline: 11.1 (2.8)</p> <p><u>Study-level:</u> Lequesne's algofunctional index Standard mean difference: -0.070 (-0.34, 0.21)</p>
Raman et al., 2008 ⁷¹ UK	392 Mean age: 67.2 (NR) % Female: 68	NR	<p>Arm 1: N = 199 Mean age: NR Synvisc (Hylan GF 20) Molecular weight: 6000 kD</p> <p>Arm 2: N = 193 Mean age: NR Hyalgan Molecular weight: 500 - 730 kD</p> <p>Total treatments: 3 for Synvisc, 5 for Hyalgan Time between treatment: 1 week</p>	<p><u>EQ-5D</u> (Follow up time: 26 weeks) Arm 1: Synvisc (Hylan GF 20) 6000 kD, N=199 Mean change from baseline: -12 (25) *</p> <p>Arm 2: Hyalgan 500 - 730 kD, N=193 Mean change from baseline: 1 (25) *</p> <p><u>WOMAC physical activity</u> (Follow up time: 26 weeks) Arm 1: Synvisc (Hylan GF 20) 6000 kD, N=199 Mean change from baseline: -21.8 (17) *</p> <p>Arm 2: Hyalgan 500 - 730 kD, N=193 Mean change from baseline: -6.8 (17) *</p> <p><u>Study-level:</u> WOMAC physical activity Standard mean difference: -0.882 (-1.09, -0.68)</p> <p>EQ-5D Standard mean difference: -0.520 (-0.72, -0.32)</p>

Author, Year Location	# Patients (Knees)/ Mean Age (SD)/ Age Range/% Female	Comorbidities	Study Arms	Relevant Outcomes Reported/ Follow Up Times
Roman et al., 2000 ⁷⁹ Spain	49 Mean age: 65.14 (9.77) % Female: 83.7	NR	Arm 1: N = 30 Mean age: NR Adant Molecular weight: 900 kD Arm 2: N = 19 Mean age: NR Hyalgan Molecular weight: 800 kD Total treatments: 5 Time between treatment: 1 week	
Tamir et al., 2001 ⁸⁰ Israel	49 Mean age: 71 (NR) % Female: 73.5	NR	Arm 1: N = 24 Mean age: 70 Placebo/sham Arm 2: N = 25 Mean age: 71 Bio-Hy Molecular weight: 3000 kDa Total treatments: 5 Time between treatment: 1 week	

Figure 3. Forest Plot for Comparisons of the Effect of Hyaluronic Acid Treatment with Placebo on function (WOMAC, Lequesne, or KOOS) at 26 Weeks Follow-up*



*Follow-up time for Petrella is 4 weeks and for Dougados and Pham it is 52 weeks

Figure 4. Risk of Bias Assessment on Randomized Controlled Trials

<i>Author, Year</i>	<i>Random sequence generation (selection bias)</i>	<i>Allocation concealment (selection bias)</i>	<i>Blinding of participants</i>	<i>Blinding of personnel/providers</i>	<i>Blinding of outcome assessors</i>	<i>Incomplete outcome data addressed (less than 20%)</i>	<i>Incomplete outcome data addressed (attrition bias) (Loss to follow-up missing or explained)</i>	<i>Selective reporting (reporting bias)</i>	<i>Other sources of bias (standardized measurement tool used)</i>	<i>Other sources of bias (washout period of at least 3 months for steroid injections or 6 months for Hyaluronic acid)</i>	<i>Other sources of bias (co-interventions either avoided in the trial design or did the authors ensure that they were similar between the index and control groups)</i>	<i>Complete outcome data</i>
Altman et al., 1998	+	+	+	+	+	+	+	+	+	+	+	+
Berenbaum et al., 2012	+	+	+	+	+	+	+	+	+	+	+	+
Blanco et al., 2008	+	?	+	+	+	+	+	+	+	+	+	+
Brandt et al., 2001	+	?	+	+	+	+	+	+	+	+	+	+
DeCaria et al., 2012	+	+	+	+	+	+	+	+	+	+	+	+
Dixon et al., 1988	+	?	+	+	+	+	+	+	+	+	+	+
Dougados et al., 1993	+	?	?	+	?	+	+	+	+	+	+	+
Forster et al., 2003	?	+	+	+	+	+	+	+	+	+	+	+
Henderson et al., 1994	+	?	+	+	+	+	+	+	+	+	+	+
Huang et al., 2011	+	?	+	?	+	+	+	+	+	+	+	+
Huskisson et al., 1999	+	?	+	+	+	+	+	+	+	+	+	+
Kahan et al., 2003	+	?	+	+	?	+	+	+	+	+	+	+
Karlsson et al., 2002	+	?	+	+	+	+	+	+	+	+	+	+
Khanasuk et al., 2012	+	+	+	+	+	+	+	+	+	+	+	+
Leopold et al., 2003	+	+	+	+	+	+	+	+	+	+	+	+
Lundsgaard et al., 2008	+	+	+	+	+	+	?	?	+	+	+	+
Pavelka et al., 2011	+	+	+	+	+	+	+	+	+	+	+	+
Pham et al., 2004	+	+	+	+	+	+	+	+	+	+	+	+
Petrella et al., 2002	+	?	+	+	+	+	+	+	+	+	+	+
Petrella et al., 2011	+	+	+	+	+	+	+	+	+	+	+	+
Raman et al., 2008	+	+	+	+	+	+	+	+	+	+	+	+
Roman et al., 2000	?	?	?	?	?	+	+	+	+	+	+	+
Tamir et al., 2001	+	+	?	?	?	+	+	+	+	+	+	?

Legend:

- Unclear= ?
- Low risk of bias= +
- High risk of bias= -

Intra-articular injection of hyaluronic acid and quality of life

Three randomized trials were identified that assessed quality of life.

Description of included studies

A 2008 randomized trial that compared treatment with Hyalgan to treatment with two different volumes of saline assessed quality of life using the KOOS quality-of-life component.⁷² A head-to-head trial that compared Synvisc with Hyalgan assessed quality of life using the SF-36 mental component summary,⁶⁸ and a second head-to-head trial that compared Synvisc with Hyalgan assessed health-related quality of life using the EuroQol-5D index⁷¹

Key Points

- Three trials that compared HA to saline or to another HA found no differences in quality of life or health-related quality of life between the two groups at 6 months follow-up.
- In one head to head trial of Synvisc and Hyalgan, health-related quality of life was improved in the Synvisc group from 3 weeks through the final follow-up at 12 months post-treatment.

Detailed Synthesis

Two trials^{68,71} that compared Hyalgan to Synvisc and one trial⁷² that compared Hyalgan to saline reported on quality of life or health-related quality of life.⁶⁹ All three needed to have standard deviations imputed. A meta-analytic pooling was not done since we did not have three trials with similar comparisons.

A 2008 randomized placebo-controlled trial of Hyalgan in 251 Danish adults (mean age 69, minimum age 59) assessed quality of life with the KOOS measure.⁷² No significant improvement was seen at 6 months compared with baseline, and there was no difference among the groups (-0.193 95% CI -0.496, 0.110), as was seen for the assessment of KOOS function.

A 2008 UK head-to-head trial comparing Hyalgan with Hylan GF-20 (Synvisc) in 393 OA patients found a significant increase in health-related quality of life at 3 months, as measured by the EuroQol EQ-5D, which was greater for the Hylan GF-20 group (-0.52 95% CI -0.72, -0.32), paralleling the WOMAC physical activity subscores, as reported above; the effect on EQ-5D score was sustained until 12 months in the Synvisc group but not the HA group.⁷¹ However a small 2012 trial in Thailand that compared the same devices among 32 patients found no improvement in quality of life in either group, as measured by the SF-36, (-0.08 95% CI -0.80, 0.64) (compared with WOMAC physical function scores, which improved equally in both groups).⁶⁸

None of the three studies conducted subgroup analysis to assess possible contributing factors (such as age, disease severity, or comorbidities) to the response of quality of life to treatment with HA.

Intra-articular injection of hyaluronic acid and pain

Description of included studies

We identified six articles published in 2012 and 2013 described as systematic reviews that summarized trials of the effects of HA on pain.^{13, 14, 81-84} One good quality 2012 review summarized the entire body of trials that compared the effects of HA with those of a sham or nonintervention control on pain; this review also included separate analysis for double-blind placebo control trials and stratified analyses for a number of potential effect modifiers. We summarize the results of this review below. We identified no double-blind placebo controlled randomized trials that reported the effects of HA on pain in individuals of average age 65 and over that were published subsequent to this systematic review; however we did identify two randomized head-to-head trials that compared the effects of two different HA products on pain in individuals of average 65 or over. These two studies are summarized below.

Key Points

- A large, comprehensive systematic review of RCTs that assessed the effects of HA on pain in 71 RCTs (with either sham or non-sham controls) reported that HA injections significantly reduce pain when assessed at 3 months (-0.37, 95% CI -0.46, -0.28) and the effect met the criterion for a minimum clinically important difference (MCID, -0.37, which corresponds to 9 mm on a VAS scale of 0 to 100mm);
- When the reviewers performed a subgroup analysis that included only the 18 sham-controlled, assessor-blinded studies of sample size 100 or more per intervention group, the effect of HA was still statistically significant (-0.11, 95%CI -0.18, -0.04) but no longer met the criterion for a MCID. When the reviewers conducted a stratified analysis to compare the effect size for the 54 studies with a sham control with that of 18 studies with a non-sham intervention, the pooled effect size for studies with a sham control was -0.34 (95% CI -0.44, -0.24), nearly equal to that for the 71 studies and to the MCID.
- No new placebo-controlled trials were identified that were not already included in the systematic review by Rutjes and colleagues, enrolled patients of average age 65 and older, and reported on pain outcomes.
- Two new head-to-head trials compared the effects of two different HAs on pain in individuals of average age 65 or over and were not included in prior SRs. One found that single injections of a high- and low-molecular weight were equally effective in reducing pain and improving function at 6 months (with no change in quality of life), whereas another found that three injections of an intermediate molecular weight might be superior to low molecular weight HA over 6 months (with respect to reducing pain and improving function).

Detailed Synthesis

Systematic review

Six systematic reviews of moderate to good quality, published in 2012-2013, were identified that compared the effects of intra-articular HA with some other intervention on pain; the quality of

the reviews was assessed with AMSTAR (Table 7).^{13, 14, 81-84} We describe only the largest and highest quality of the reviews. This 2012 systematic review and meta-analysis, which identified 89 published and unpublished randomized trials of HA with any control, assessed the effects on pain intensity.¹⁴ Of the 89 trials, the authors were able to pool 71 sham or non-intervention controlled trials (9,617 patients), obtaining an effect size of -0.37 (95%CI -0.46, -0.28), which just met their prespecified minimal clinically important difference. Pooling 18 of the larger (sample size greater than 100 per intervention group) assessor-blinded trials showed a statistically significant but clinically irrelevant effect size of -0.11(95%CI -0.18, -0.04). A stratified analysis that compared the pooled effect size for the 54 studies with a sham control with that of 18 studies with a non-sham intervention found a pooled effect size for studies with a sham control of -0.34 (95% CI -0.44, -0.24).

Table 7. AMSTAR Assessment for Systematic Reviews of HA and Pain*

Study	A priori design	Duplicate screening and extraction	Comprehensive search	Grey literature inclusions	Included/excluded studies listed	Study characteristics	Quality assessment	Quality considered	Pooling appropriate	Publication bias	COI assessment
Bannuru, 2013 ⁸⁴	N	Y	Y	Y	Y	Y	Y	Y	Y	N	Y
Colen, 2012 ¹³	C	Y	Y	N	N	N	N	C	Y	N	N
Miller, 2013 ⁸¹	C	Y	Y	Y	N	N	Y	N	Y	Y	Y
Printz, 2013 ⁸²	N	Y	Y	Y	N	N	N	NA	NA	Y	Y
Rutjes, 2012 ¹⁴	C#	Y	Y	Y	Y	N	Y	C	Y	Y	C
Trigkilidas, 2013 ⁸³	C	C	Y	N	N	Y	Y	Y	NA	N	N

*See Appendix D for assessment tool. Y=yes (low risk); N=no (high risk);C=can't respond; NA=not applicable; COI conflict of interest; #need to access supplemental files

Original studies

No new placebo-controlled trials were identified that were not already included in the systematic review by Rutjes and colleagues, enrolled patients of average age 65 and older, and reported on pain outcomes. Two randomized trials were identified that were not included in the systematic review, enrolled populations of OA patients of average age 65 or over, and assessed the effects of two different HA products head-to-head on pain. A multi-center trial in France and Germany compared the effects of three weekly injections of GO-ON, a non-avian medium-molecular weight HA (1800-1500kD) with those of Hyalgan, a low molecular weight product on pain in 426 patients.⁶¹ Mean differences in WOMAC pain change were 5.2(95% CI 0.9, 9.6) per protocol and 4.5 (95% CI 0.5, 8.5) (intention to treat) at 6 months, favoring GO-ON. Also, a higher proportion of patients responded to GO-ON than to Hyalgan. These differences paralleled the effects of the two devices on function as assessed by both the WOMAC (difference in effect size: -6.8, 95% CI -10.7, -2.8) and Lequesne indices (-1.2, 95% CI -2.0, -0.6), as described earlier in this report.

A Thai study compared the effects of a single injection of Hylan G-F 20 (Synvisc) and a single injection of Hyalgan on pain at 6 months in 30 patients. The WOMAC pain and function subscales showed significant improvement with no differences between the treatments at 6 months. QoL, as assessed by the SF-36, did not change over the same 6-month period.⁶⁸

Intra-articular injection of hyaluronic acid and adverse events

Description of included studies

Twenty four trials, three large cohort and case series studies, and 18 case reports were identified that reported on the incidence of adverse events among individuals 65 years of age and over.

Key Points

- In 24 placebo-controlled trials of HA, serious adverse events were small in number. Estimates are imprecise, and the magnitude of any increase in risk is very small, if present at all. The rate of non-serious AEs was higher but did not differ significantly between the HA-treated and placebo-control groups.
- Among three large cohort studies and case series, representing nearly 6,000 recipients of HA (some more than one series), one serious adverse event was reported: severe swelling and synovial fluid accumulation.
- Eighteen case reports provided reports of adverse events among 30 individuals 65 years of age or older, including five cases of sepsis (one case of staphylococcus scalded skin syndrome), and one case each of saphenous nerve injury, eosinophiluria, erythema, and herpes zoster (new onset).

Detailed Synthesis

Adverse events reported in trials. Twenty four trials reported data on adverse events (AEs).^{41, 43, 59-80} Thirteen trials^{41, 43, 62-65, 71-75, 77, 80} compared Hyalgan to placebo, and seven^{59, 61, 66, 68, 69, 76,}

⁷⁹ compared Hyalgan to an active comparator. Four trials^{60, 67, 70, 78} reported data on both comparison types.

Only the placebo comparisons had enough trials within adverse event categories to pool. The results are presented in Table 6. With the assistance of a rheumatologist, we grouped the adverse events into three groups based on their site (injection site, joint [intra-articular], or other [including systemic]) and within each of the three groups, we further divided events according to whether they were serious or not serious. Examples of each type of event are also provided in Table 8.

The RCTs included in the AE analyses were assessed using items from the McHarm scale (Table 10).³² Out of 24 RCTs, four described a protocol for collecting AEs or a predefined set of AEs; the remaining 20 were unclear or indicated no predefined list of AEs. To elaborate, these 20 studies did not describe whether assessors asked patients about specific AEs on a list. Four of 24 studies described an active form of AE collection; the remainder used a passive form of AE assessment (e.g., they asked patients something more generic such as “have you experienced any adverse reactions?”) or did not describe how AEs were assessed. Fourteen of the 24 RCTs did describe assessing AEs at prespecified intervals (e.g., at follow-up appointments). In addition, eight studies reported that no serious adverse events occurred, without defining the term “serious adverse events.” However, as these weaknesses apply to both the active and placebo arms (assessors were blinded to study arm), any systematic undercounting of AEs would apply to both arms and have little effect on the relative difference.

Table 8. Pooled adverse events reported in trials, according to category

AE Group	# studies	# event HA	sample size HA	# events placebo	sample size placebo	OR	95% CI
local, not serious (e.g., erythema)	6	79	493	98	492	0.70	(0.48, 1.03)
joint, serious (e.g., synovitis)	5	8	447	10	442	0.77	(0.25, 2.31)
joint, not serious (e.g., pain)	7	97	518	121	559	0.83	(0.60, 1.15)
other, serious (e.g., Herpes zoster)	6	8	570	17	614	0.62	(0.23, 1.57)
other, not serious (e.g., headache)	6	199	553	196	594	1.26	(0.94, 1.68)

Adverse Events reported in observational studies. In order to further investigate rare adverse events that may not have occurred during clinical trials, we searched for cohort studies that reported AEs and cases reported post-licensure.

We identified four observational studies with at least 500 subjects each that reported adverse events in patients receiving hyaluronic acid for knee osteoarthritis. Due to heterogeneity, the results are described narratively.

Petrella⁸⁵ published on a cohort of 537 hyaluronic acid-naïve patients who received at least one series of three injections of Suplasyn (500 – 730 kD) in a primary care center in Ontario, Canada. All had unilateral osteoarthritis of the knee with Kellgren-Lawrence grade 1 to 3; mean age was 68 years. All but 21 patients returned for a second series of three injections. Patients were followed for a mean of 6.7 years. The study was supported by the Canadian Institutes of Health; Suplaysn was purchased by the patients and was not subsidized by the manufacturer. The primary outcome studied was pain in walking, as measured using the VAS. No serious AEs were

reported, and there were no systemic (not local or intra-articular) AEs. Local AEs were observed following 1.48% and 1.32% of injections with the first and second series respectively. The authors provided no information on whether AEs were assessed passively or actively.

Kemper and colleagues⁸⁶ reported on 4,253 patients of 840 orthopedic surgeons in Germany. Patients received injection of Synvisc (6000 kD) at three visits; Kellgren-Lawrence grades were not reported; 8.1% of patients had previously received hyaluronic acid injections. Mean age of the patients was 63.9 years, 60.8% were female, and 23.7% had bilateral osteoarthritis. AEs were actively elicited, serious AEs were clearly defined, and MEDRA coding was used. Adverse events were reported in 5.3% of patients and 2.9% of injections. Only one serious AE was reported; this event involved severe swelling and synovial fluid accumulation. The most commonly reported AEs were joint effusion (2.4% of patients), joint swelling (1.3%), arthralgia (1.2%), joint warmth (0.6%) and injection site erythema (0.3%). Secondary analyses were performed; surprisingly, patients younger than 70 years old were more likely to experience an AE than were older patients. Those with a longer time since diagnosis and those previously treated with viscosupplementation were also more likely to experience an AE. The product manufacturer sponsored the study; two of their scientists were co-authors.

In a large retrospective cohort study Petrella⁸⁷ compared the safety of avian and non-avian hyaluronic acid for osteoarthritis of the knee. They included 1,726 patients who received avian HA and 1,971 who received non-avian HA at a large center in Canada from 1997 to 2007. Patients had Kellgren-Lawrence grade 1 to 3 evidence of knee OA; mean age was 65 years. There were no significant differences in baseline demographic characteristics or severity between groups. The group receiving avian HA had a significantly higher rate of adverse events (4.8% versus 1.7%) between the second and 10th series than the group receiving non-avian HA. Rates of specific events were not reported; pain, effusion, and erythema were noted as most common. No serious adverse events were reported.

Finally, Waddell and Bricker⁸⁸ published a case series of 1,158 patients in a large orthopedic practice in the US. The primary goal of the study was to assess AEs. The patients received at least one series of three injections of Synvisc. The mean age (65.8 years) and gender composition (60.6% female) were similar to the other two studies. However, the patients' osteoarthritis of the knee was more severe; 70.9% of knees were grade four on the Kellgren-Lawrence scale, and 44.6% of patients had bilateral OA.

The authors provided details on treatment method that were not reported in the other studies. A fluoroscopic technique that confirms accurate needle placement was used. To avoid local AEs, they instructed patients to rest the afternoon of the injection and use an ice pack for two to three hours. In addition, they provided patients with a prescription opioid to use if needed. Finally, they prophylactically administered an intramuscular steroid in patients who had previously experienced knee pain and swelling with injection. Local AEs were reported in 4.7% of patients (1.3% of injections) during Course 1, 13.8% of patients (4.5% of injections) during Course 2, and 17.3% of patients (5.6% of injections) during Course 3. Non-local AEs were not reported. Both authors had received previous funding from the product manufacturer, who provided support for statistical analysis and a medical writer for the manuscript.

Data from the 18 identified AE case reports that included patients age 65 or over are displayed in Table 9. Thirty patients were represented; 77% were female. Over half had received injections of Synvisc, which is considered a high molecular-weight product.

The most commonly reported adverse events involved joint reactions. Pullman-Mooar⁸⁹ reported inflammatory knee effusions in eight patients, ranging in age from 31 to 67 years. Each

of three physicians reported cases of pseudo-septic arthritis.⁹⁰⁻⁹² Acute arthritis, and gout or pseudo-gout were also reported.

Importantly, five cases of sepsis were reported in three articles; one of these patients suffered from staphylococcal scalded skin syndrome.

Other adverse events included systemic reactions in two patients, granulomatous synovitis in two patients, and one case each of saphenous nerve injury, eosinophiluria, erythema, and one case of new-onset herpes zoster.

Table 9. Adverse events described in case reports

Author, Year	AE	N	Age	Sex	Co-morbidities	Brand
Joint Reaction (crystals, etc.)						
Bernardeau, et al., 2001 ⁹³	Acute Arthritis	2	59, 73	F	NR	Synvisc
Idrissi et al., 2012 ⁹²	Pseudo-septic arthritis	1	70	F	NR	Ostenil
Maillefert et al., 1997 ⁹⁴	Pseud- gout (Chondrocalcinosis)	2	62, 83	F	NR	Hyaluron, unspecified
Pullman-Mooar et al., 2002 ⁸⁹	Inflammatory knee effusions	8	31 to 67	3 M, 5 F	NR	Synvisc
Roos et al., 2004 ⁹⁰	Pseudo-septic arthritis	1	70	F	Chondrocalcinosis 2 years earlier	Ostenil
Tahiri et al., 2007 ⁹¹	Pseudo-septic arthritis	1	70	F	Diabetes	Curavisc
Wendling et al., 2007 ⁹⁵	Acute gouty arthritis	1	72	F	Overweight, hypertension	Sinovial
Ali et al., 1999 ⁹⁶	Pseudo-gout	1	74	M	NR	Synvisc
Infections						
Kunugiza et al., 2011 ⁹⁷	Staphylococcal scaled skin syndrome (sepsis)	1	68	F	NR	NR
Lequerre et al., 2002 ⁹⁸	Septic arthritis	1	70	M	NR	Synvisc
Shemesh et al., 2011 ⁹⁹	Septic arthritis	3	64, 70, 75	1 M, 2 F	Hypertension and or hyperlipidemia	NR
Other						
Iizuka et al., 2005 ¹⁰⁰	Saphenous nerve injury	1	68	F	Hypertension, gout	NR
Martens, 2001 ¹⁰¹	Systematic inflammatory reaction	1	70	F	NR	Synvisc
Rees et al., 2001 ¹⁰²	Systemic reaction	1	79	F	Hypertension	Synvisc
Banerjee, 2002 ¹⁰³	Eosinophiluria	1	68	M	Ischemic heart disease, mild renal impairment	Hyalgan
Semih et al., 2009 ¹⁰⁴	Herpes zoster	1	71	M	NR	Sodium hyaluronate
Calvo et al., 2007 ¹⁰⁵	Erythema	1	70	F	Hypertension, pyrazolone allergy	Go-On
Michou et al., 2004 ¹⁰⁶	Granulomatous synovitis	2	71, 72	F	NR	Synvisc

Table 10. McHarm Table

Author, Year	Were the harms pre-defined using standardized or precise definitions?	Was the mode of harms collection specified as active?	Was the potential occurrence of harmful events collected at pre-specified intervals; for example, the occurrence of post-operative complications were evaluated on a daily basis within 30 days of the surgery?	Did the author(s) specify the number for each type of harmful event for each study group?	Was the total number of participants affected by harms specified for each study arm?	If the study reported that there were no serious AEs reported did they define serious AEs?
Altman et al., 1998 ⁶⁰	No	No	Yes	Yes	Yes	Not applicable
Berenbaum et al., 2012 ⁶¹	Yes	No	No	Yes	Yes	Not applicable
Blanco et al., 2008 ⁴³	No	Yes	Yes	No	Yes	Not applicable
Brandt et al., 2001 ⁶²	Yes	Yes	Yes	No	Yes	Not applicable
DeCaria et al., 2012 ⁶³	Unclear	Unclear	No	No	No	No
Dixon et al., 1988 ⁵⁹	No	Yes	Yes	Yes	Yes	Not applicable
Dougados et al., 1993 ⁴¹	Unclear	Unclear	No	Yes	Yes	No
Grecomoro et al., 1987 ⁷⁴	No	Unclear	Yes	Yes	Yes	No
Henderson et al., 1994 ⁷⁵	Unclear	No	Yes	No	Unclear	Not applicable
Huang et al., 2011 ⁶⁴	Unclear	Unclear	Yes	No	Yes	Not applicable
Huskisson et al., 1999 ⁶⁵	Unclear	Unclear	Yes	Yes	Yes	Not applicable
Kahan et al., 2003 ⁶⁶	Unclear	Unclear	Unclear	No	Yes	Not applicable
Karlsson et al., 2002 ⁶⁷	Yes	Unclear	Unclear	Unclear	Yes	Not applicable

Author, Year	Were the harms pre-defined using standardized or precise definitions?	Was the mode of harms collection specified as active?	Was the potential occurrence of harmful events collected at pre-specified intervals; for example, the occurrence of post-operative complications were evaluated on a daily basis within 30 days of the surgery?	Did the author(s) specify the number for each type of harmful event for each study group?	Was the total number of participants affected by harms specified for each study arm?	If the study reported that there were no serious AEs reported did they define serious AEs?
Khanasuk et al., 2012 ⁶⁸	No	No	No	No	Yes	Not applicable
Leopold et al., 2003 ⁷⁶	Unclear	Unclear	Yes	No	Yes	Not applicable
Lundsgaard et al., 2008 ⁷²	No	No	Yes	Yes	Yes	No
Pavelka et al., 2011 ⁶⁹	No	No	Yes	No	Yes	Not applicable
Petrella et al., 2002 ⁷⁰	No	No	No	No	No	No
Petrella et al., 2008 ⁷⁰	No	Unclear	Yes	N/A	Unclear	No
Petrella et al., 2011 ⁷⁸	No	No	No	No	No	No
Pham et al., 2004 ⁷³	No	Yes	Yes	Yes	Yes	Not applicable
Raman et al., 2008 ⁷¹	No	No	Yes	No	Yes	No
Roman et al., 2000 ⁷⁹	No	Unclear	Unclear	Unclear	No	Not applicable
Tamir et al., 2001 ⁸⁰	Yes	No	Unclear	Yes	Yes	Not applicable

Discussion

Key Findings and Strength of Evidence

Intra-articular HA and KR

Three randomized trials and 13 observational studies reported on knee replacement (KR). However, two of the trials did not regard receipt of KR as an outcome (and therefore were not designed specifically to test the hypothesis), the participants in one study had a mean age under 65, and the trials were not powered to compare the rates of KR between HA and comparison groups. A number of observational studies reported rates of KR among HA recipients as approximately 20%. One large observational study that assessed the rates of KR by age group, pain at baseline, and various other factors reported that age was the only factor associated with the likelihood of undergoing KR: OA patients in the 60-69 year old age group were significantly more likely than patients under 50, patients 70-79, and those over 80 to undergo KR.⁴⁸ This study also assessed the time interval between entering care in their practice and undergoing KR. Median time to KR for HA recipients was 1.8 years (14-2,147 days; median followup time in this study was 2.2 years (7-2,222 days); 75% of knees had not had KR by 3.8 years. The authors stated that the average interval between entering care in their practice and undergoing KR for patients not treated with HA was 3 months.

Given the designs of the studies, it is not possible to draw conclusions at this time regarding the effect of HA treatment on delay or avoidance of KR.

The strength of evidence for this question is insufficient to draw any conclusions (see Table 2).

Intra-articular HA and Function

Eighteen randomized trials reported on the effects of HA compared to sham-injected placebo control, another HA, or some other active treatment on function, as measured by the WOMAC, Lequesne index, KOOS, or ADLs, among patients whose average age was 65 or older. Pooling of ten placebo-controlled studies that reported outcomes for the WOMAC or Lequesne, all assessor blinded, revealed a small increase in function in favor of HA (-0.23, 95%CI -0.34, -0.02); however, this difference, which translates to a change of 5.6 units on a 0-100mm VAS scale, did not achieve the MCID of -0.37 (based on the pooled effect size, about 11 percent would have exceeded the MCID in improvement); eight of the ten measured outcomes at 6 months. One study reported placebo to be more effective and one found no difference.

One trial reported on the effects of HA on ADLs. This study found no change from baseline in the HA or placebo group.

No studies reported the proportion of patients who experienced improvement in function alone. However, four double-blind placebo-controlled trials that reported on function reported the proportion of patients who achieved a prespecified level of overall improvement; of these four, three reported a higher proportion of HA-treated patients than placebo-treated patients who achieved either patient- or investigator-reported improvement.

The duration of effect could not be ascertained: few studies followed patients long enough to truly measure durability of effect.

Too few head-to-head trials were identified to be able to draw any conclusions about the superiority of any one product over another.

None of the identified studies stratified findings by age, sex, or any other outcome of interest.

The strength of evidence for the effect of HA compared with placebo is low (trials were not all well designed and two found no effect) but the strength of evidence for head-to-head comparisons is insufficient to draw any conclusions (Table 2).

Intra-articular HA and QoL

Three trials reported on the effects of HA treatment on quality of life. One trial, which compared Hyalgan to treatment with two different volumes of saline, found no change in quality of life from baseline using the KOOS quality-of-life component.⁷² Two head-to-head trials that compared Synvisc with Hyalgan assessed quality of life, one using the SF-36 mental component summary to assess QoL⁶⁸ and one using the EuroQol-5D index to assess HRQoL.⁷¹ The trial that used the SF-36 reported no increase in quality of life for either group, but the trial that used the EuroQol-5D reported a slight increase in QoL for Synvisc from 3 through 12 months but only an increase in HRQoL for patients on Hyalgan at 3 months.

As only three trials reported both QoL and functional outcomes, no conclusions can be drawn about the relationship between these two parameters.

The strength of evidence for any conclusions regarding an effect of HA on quality of life is insufficient.

Intra-articular HA and Pain

A large, comprehensive, relatively good quality 2012 systematic review that compared the effects of HA with sham or non-intervention controls reported that HA injections significantly reduced pain, both statistically and clinically (that is, reaching the MCID) when measured at 3 months; however, this effect was lessened to non-significance when only studies with blinded outcome assessment and at least 100 participants per study arm were included in the analysis. Stratified analysis that compared 54 studies with sham controls with 18 studies with non-blinded controls showed a statistically significant effect of HA on pain in the studies with sham controls that nearly met the MCID. They did not conduct a stratified analysis to assess the effect of age of participants. The authors reported evidence for publication bias, which we did not identify in our pooled analysis for effects on function. Two new trials compared the effects of two different HAs on pain and were not included in prior SRs. One found that single injections of a high- and low-molecular weight were equally effective in reducing pain at 6 months, whereas another found that three injections of an intermediate molecular weight might be superior to low molecular weight HA over 6 months.

Based on the findings of the full sample analysis and the analysis stratified by the use of sham controls in the prior systematic review, we believe that the strength of evidence is low that HA reduces pain, on average, by an amount that approaches the minimum clinically important difference.

Intra-articular HA and AEs

We identified twenty four trials, three large cohort and case series studies, and 18 case reports that reported on the incidence of adverse events among individuals 65 years of age and over who were given HA to treat OA of the knee.

In placebo-controlled trials of HA, serious adverse events were small in number, and their precise frequency cannot be estimated from current data. The rate of non-serious AEs was higher but did not differ between the HA-treated and sham-control groups.

Among three large cohort studies and case series, representing nearly 6,000 recipients of HA (some more than one series), one serious adverse event was reported: severe swelling and synovial fluid accumulation.

Eighteen case reports provided reports of adverse events among 30 individuals 65 years of age or older, including five cases of sepsis (one case of staphylococcus scalded skin syndrome), and one case each of saphenous nerve injury, eosinophiluria, erythema, and new-onset herpes zoster.

These findings suggest that the adverse events associated with intra-articular injections of HA are nearly all at the site of injection or within the joint, largely confined to pain or swelling, and not different from those of patients who received sham injections. The FDA PMA database revealed no post-marketing reports of unexpected adverse events. Information provided by manufacturers about five products was limited to already published data.

The strength of evidence for the conclusion that serious adverse events are rare is moderate. The strength of evidence for a statistically significant difference in SAEs and non SAEs between intervention and placebo groups is low.

Findings in Relation to What is Already Known

To our knowledge, this report represents the first systematic review to attempt to assess the effects of intra-articular HA injections on both delay or avoidance of KR, pain, function, quality of life, and adverse events.

No other systematic reviews have attempted to synthesize the effects of HA on KR, and the present review found insufficient evidence to draw a conclusion about the effects of HA on those outcomes.

Regarding the effect of HA on function, we calculated that the effect size in our study corresponded to an improvement of 5.6 units (on a 0-100mm VAS scale) which was smaller than the minimum clinically important difference of 9 units (which would be comparable to a 10 percent improvement in, e.g., the ability to walk downstairs or to rise from sitting). Our analysis of the effects of HA on function showed no evidence of publication bias.

One large 2012 systematic review assessed the effects of HA on pain, function, and AEs.¹⁴ That review identified a moderate effect of HA on function (-0.33, 95% CI -0.43, -0.22, based on 52 trials) that was no longer considered clinically significant when only large trials (100 or more participants per study arm) with assessor blinding were considered (-0.09, 95% CI -0.17, 0.00, based on 15 trials). However, we believe that limiting the pooled analysis to the larger studies is not methodologically justified, given the small proportion of studies that fit the criteria and the fact that study size is not typically a criterion in assessing study quality/risk of bias. The meta-analysis on the outcome of function conducted for our review included only sham-controlled trials that incorporated assessor blinding, but we did not find any studies that met our inclusion criteria that enrolled more than 100 participants per study arm.

The 2013 American Academy of Orthopedic Surgeons guidelines for the treatment of osteoarthritis of the knee also conducted a systematic review of the literature on the effects of HA on WOMAC-assessed pain, function, and stiffness. These guidelines recommend against the use of hyaluronic acid to treat patients with symptomatic conditions based on the finding that although statistically significant improvement was seen in pain and function with HA compared

to placebo, the improvements did not meet the standard of exceeding the minimum clinically important improvement (in contrast, the 2008 AAOS guidelines had found insufficient evidence to recommend for or against HA, based on an AHRQ review that found evidence of publication bias).¹⁶ The 2012 American College of Rheumatology Guidelines for the treatment of osteoarthritis of the knee also conducted a systematic review of the literature on the effects of HA and other modalities and issued a conditional recommendation for the use of HA for the initial management of patients with knee OA.⁸

The current review is the first to consider only studies of individuals of average age 65 or older. Approximately half of the trials included in the 2012 review by Rutjes and colleagues that assessed the outcome of pain enrolled populations of average age less than 65; and of the 52 trials they included in their analysis of the effects of HA on function, nearly all included participants of average age less than 65.¹⁴ Although patient age might affect the ability to experience (or realize) improved function from a treatment, no evidence exists that would suggest age would affect the ability to experience pain relief. Therefore, we believe the analyses in the prior review that included studies of patients whose average age was less than 65, given the much larger number of included studies, is more adequately powered to assess the effects of HA on pain than would be an analysis that includes a smaller number of studies limited to individuals of average age 65 and over.

The current review found only a small number of serious AEs and in trials, found no differences between treatment and placebo conditions. The 2012 review pooled data on serious AEs from 14 trials that reported on serious AEs and found an increased risk for serious AEs in the HA-treated groups,¹⁴ whereas a 2013 review of 29 studies found no difference between HA and placebo for any AE, in agreement with the present study.⁸¹ To derive a potential explanation for the difference in the risk for serious AEs between the review by Rutjes and colleagues and ours, we reabstracted the data on serious AEs (both those reported by original study authors as being serious, those deemed serious by the criteria of the present study, and those deemed serious by the criteria of the 2012 review). We included only studies that would have met our inclusion criteria (except for age); therefore we eliminated studies that were not assessor blinded, studies in which patients served as their own controls, and conference abstracts, for example. The increase in risk for serious AEs among patients who received HA compared with placebo in the 2012 review appears to be attributable to the difference in the statistical analyses between the two reviews. The criteria used to define SAEs differed between the two reviews, fewer than half of the trials included in the SAE analysis of the review by Rutjes and colleagues¹⁴ actually described specific AEs, and a number of studies that did describe the SAEs they observed had methodological limitations.

Regarding non-serious AEs, the 2012 review limited its assessment to flare-ups (a joint reaction), finding no statistically significant difference between treated and placebo groups.¹⁴ This finding agrees with that of the present review, which found no statistically significant differences between actively treated and sham/placebo-treated groups for non-serious local, joint, and “other” AEs. It is not possible to assess whether the potentially high numbers of these non-serious AEs indicate that a large proportion of study participants experience these AEs because most studies do not report the total numbers of participants who experience at least one AE (so one participant could report many AEs). In addition, the observation that the number of “other” (not joint related and not local, e.g., “headache”) non-serious AEs is far higher than the numbers of local and joint-related non-serious AEs, supports a lack of association between these

occurrences and the intervention and suggests knowledge of such events may not have much of an impact on the decision-making of an individual seeking the chance for relief.

Applicability

To increase potential applicability, we limited studies included in the current review with functional outcomes to those with an average age of 65 or older. Nevertheless, no studies excluded patients younger than 65. Given that the only study that assessed factors that might influence the likelihood of undergoing KR found that age was the only influential factor, age of study participants is likely to be an important consideration for this outcome.

The larger trials included in the assessment of functional outcomes were mostly conducted in academic settings; this typical characteristic of randomized trials tends to limit their applicability to community settings. However a number of the observational studies that addressed the outcome of KR were conducted in private medical practices.

Implications for Clinical and Policy Decision Making

The evidence identified for the current study is insufficient to support a decision either way about the efficacy of intra-articular HA injection based on the delay or avoidance of KR. In addition, the strength of evidence is low regarding the efficacy of HA for improving quality of life or function in a population 65 years of age or older.

Limitations of the Comparative Effectiveness Review Process

Given the constraints of the project, we did not attempt to review studies of populations of average age less than 65 years to determine whether they found improvements in function or quality of life. However, removing the exclusion criterion of age we identified only one randomized trial that reported KR, and it was not considered a primary or even secondary outcome. We also did not contact authors of original research studies to request raw data by patient age and did not attempt to do new pooling of the studies included in the review by Rutjes and colleagues, to include only studies of older populations for reasons explained above.

Limitations of the Evidence Base

The majority of trials identified for the current report were of relatively mediocre quality, with poor reporting. Few trials described their recruitment strategy or method for allocation concealment. A number of studies had dropout rates higher than 20% (no studies addressed differences between dropouts and completers), and although most excluded individuals who had recently received corticosteroids or other courses of an HA, most also did not bar participants from using other modes of pain relief, such as NSAIDs. Further, few or no studies attempted to determine whether response to HA differed between groups of patients stratified by characteristics such as baseline age, disease severity (stage) or type; or duration of treatment, few studies followed patients long enough to truly measure durability of effect, and adverse events were not measured using any standardized method.

Specific to the outcomes of function and knee replacement, no trials measured the duration of effect, no trials measured knee replacement as a primary outcome, and no trials reported the percentage of participants whose function improved (seven studies reported on the percent who

achieved a prespecified level of global improvement, of which four were double-blind placebo-controlled trials).

Research Gaps

Clear research gaps exist regarding studies of the effectiveness of HA among individuals 65 years of age and older and the effect of HA, if any, on delay or avoidance of KR. Two searches for ongoing studies of HA and OA of the knee on Clinicaltrials.gov and review of entries provided by manufacturers revealed no completed, ongoing, or recruiting studies on older individuals with knee OA or with outcomes of KR. The observational studies identified for this review could not definitively answer the question of whether HA delays or prevents the need for KR. However, we advocate analyzing data from any of the large administrative databases maintained by commercial payers, to answer the question as to whether beneficiaries who are treated with intra-articular HA proceed to KR at a slower rate than do those who do not receive HA. We realize that a number of factors might affect the decision to undergo KR, such as age, comorbidities, pain tolerance, activity level, aversion to surgical intervention, and expectations about one's life expectancy; however, at least some of these factors could be controlled for in a large, well-designed case control study. Preliminary findings of such a study were presented at the 2013 meeting of¹⁰⁷ the American College of Rheumatology: using the Truven MarketScan database, researchers matched 7,000 HA recipients (66% female) with 19,627 non-recipients with OA of the knee (propensity score matching with the non-HA cohort was 98%). With one episode of HA treatment, the median times from the initial specialist visit to KR were 199 and 443 days for the non-HA cohort and HA cohort, respectively. Additional treatment episodes increased the median gap by an average 202 days, suggesting true dose-response.

Conclusions

The literature identified for the current review cannot answer the question whether HA delays or prevents the need for KR in older individuals. The literature suggests a small role for HA in improving function among older individuals and an equally small role in reducing pain among adults, of unclear clinical importance with relatively few serious adverse events.

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Abbreviations / Acronyms

ADL	Activities of Daily Living
AEs	Adverse Events
AHRQ	Agency for Healthcare Research and Quality
CMS	Centers for Medicare and Medicaid Services
DJD	Degenerative Joint Disease
FDA	Food and Drug Administration
HA	Hyaluronic acid
HRQoL	Health-Related Quality of life
IADLs	Instrumental Activities of Daily Living
KOOS	Knee Injury and Osteoarthritis Outcomes Score
KR	Knee Replacement
MCID	Minimum clinically important difference
OARSI	Osteoarthritis Research Society International
OMERACT	Outcome Measures in Rheumatology
OR	Odds-Ratio
PICOTs	Participants, Interventions, Comparators, Outcomes, and Timeframes
PMA	Post-Marketing Assessment
QoL	Quality of Life
RCTs	Randomized Controlled Trials
ROB	Risk of Bias
SCEPC	Southern California Evidence-based Practice Center
SD	Standard Deviation
SF-36	Short form-36
SIPS	Scientific Information Packets
SMD	Standardized Mean Difference
SOE	Strength of Evidence
SRC	Scientific Resource Center
TAP	Technology Assessment Program
TKR	Total Knee Replacement
VAS	Visual analog scale
WOMAC	Western Ontario and McMaster Universities Osteoarthritis Index

Appendix A. Search Strategy

DATABASE SEARCHED & TIME PERIOD COVERED:

PubMed – 1/1/1990-10/30/2013

SEARCH STRATEGY:

(1a)

hyaluronic acid OR hyaluronate* OR hyaluronan OR hylan

AND

osteoarthritis, knee OR (knee* AND osteoarthritis) OR (knee* AND arthrit*) OR gonarthrosis

OR

(1b)

hyaluronic acid OR hyaluronate* OR hyaluronan OR hylan

AND

degenerative joint disease

AND

knee OR knees

OR

(1c)

viscosupplement* OR visco-supplement*

AND

osteoarthritis, knee OR (knee* AND osteoarthritis) OR (knee* AND arthrit*) OR gonarthrosis

NUMBER OF RESULTS- 904

NUMBER AFTER REMOVAL OF INTERNAL DUPLICATES: 770

NUMBER AFTER ADDITIONAL REMOVAL OF DUPLICATES BY A.M.: 767

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DATABASE SEARCHED & TIME PERIOD COVERED:

Cochrane Databases – 1/1/1990-11/21/13

SEARCH STRATEGY 1a:

hyaluronic acid OR hyaluronate* OR hyaluronan OR hylan

AND

osteoarthritis, knee OR (knee* AND osteoarthritis) OR (knee* AND arthrit*) OR gonarthrosis

All Results (216)

Cochrane Reviews (5)

Other Reviews (14)

Trials (184)

Methods Studies (1)

Technology Assessments (7)

Economic Evaluations (5)

SEARCH STRATEGY 1b:

hyaluronic acid OR hyaluronate* OR hyaluronan OR hylan
AND
degenerative joint disease
AND
knee OR knees

All Results (8)

Cochrane Reviews (4)
Other Reviews (0)
Trials (4)
Methods Studies (0)
Technology Assessments (0)
Economic Evaluations (0)

SEARCH STRATEGY 1c:

viscosupplement* OR visco-supplement*
AND
osteoarthritis, knee OR (knee* AND osteoarthritis) OR (knee* AND arthrit*) OR gonarthrosis

All Results (57)

Cochrane Reviews (2)
Other Reviews (4)
Trials (45)
Methods Studies (0)
Technology Assessments (5)
Economic Evaluations (1)

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DATABASE SEARCHED & TIME PERIOD COVERED:

Embase – 1/1/1990-11/22/2013

SEARCH STRATEGY:

(1a)

hyaluronic NEAR/2 acid* OR hyaluronate* OR 'hyaluronan'/exp OR hyaluronan OR hylan
AND
osteoarthritis, AND ('knee'/exp OR knee) OR (knee* AND ('osteoarthritis'/exp OR osteoarthritis)) OR
(knee* AND arthrit*) OR 'gonarthrosis'/exp OR gonarthrosis
AND
[humans]/lim
(EXCLUDE MEDLINE RESULTS)

NUMBER OF RESULTS: 1181

(1b)

'degenerative joint disease'/exp OR 'degenerative joint disease' OR 'degenerative joint diseases'
AND
'knee'/exp OR knee OR knees
AND

[humans]/lim
(EXCLUDE MEDLINE RESULTS)

NUMBER OF RESULTS: 1084

(1c)

viscosupplement* OR 'visco supplement' OR 'visco supplements' OR 'visco supplementation'
AND
(knee* AND ('osteoarthritis'/exp OR osteoarthritis)) OR (knee* AND arthrit*) OR 'gonarthrosis'/exp OR
gonarthrosis
AND
[humans]/lim
(EXCLUDE MEDLINE RESULTS)

NUMBER OF RESULTS: 228

TOTAL NUMBER OF RESULTS: 2493

NUMBER AFTER INTERNAL REMOVAL OF DUPLICATES: 1202

NUMBER AFTER REMOVAL OF DUPLICATES WITH OTHER DATABASE RESULTS: 698

NUMBER AFTER ADDITIONAL REMOVAL OF DUPLICATES BY A.M.: 693

DATABASE SEARCHED & TIME PERIOD COVERED:

Web of Science Databases=SCI-EXPANDED, SSCI, A&HCI, CPCI-S, CPCI-SSH – 1/1/1990-
11/22/2013

SEARCH STRATEGY:

Topic=(hyaluronic acid OR hyaluronate* OR hyaluronan OR hylan) AND Topic=(knee OR
knees) AND Topic=(osteoarthritis OR arthrit* OR gonarthrosis)

OR

Topic=(hyaluronic acid OR hyaluronate* OR hyaluronan OR hylan) AND Topic=(knee OR knees) AND
Topic=(degenerative joint disease)

OR

Topic=(viscosupplement* OR visco-supplement*) AND Topic=(knee OR knees) AND
Topic=(osteoarthritis OR arthrit* OR gonarthrosis)

NUMBER OF RESULTS: 1225

NUMBER AFTER REMOVAL OF DUPLICATES WITH OTHER DATABASE RESULTS: 525

NUMBER AFTER ADDITIONAL REMOVAL OF DUPLICATES BY A.M.: 520

DATABASE SEARCHED & TIME PERIOD COVERED:

SCOPUS – 1/1/1990-11/25/2013

SEARCH STRATEGY:

(1a)

hyaluronic acid OR hyaluronate* OR hyaluronan OR hylan

AND

knee OR knees

AND

osteoarthritis OR arthrit* OR gonarthrosis

1481

(1b)

TITLE-ABS-KEY(hyaluronic acid OR hyaluronate* OR hyaluronan OR hylan)

AND

knee OR knees

AND

degenerative joint disease

AND

SUBJAREA(mult OR agri OR bioc OR immu OR neur OR phar OR mult OR medi OR nurs OR vete OR dent OR heal)

65

(1c)

TITLE-ABS-KEY((viscosupplement* OR visco-supplement*))

AND

knee OR knees

AND

osteoarthritis OR arthrit* OR gonarthrosis

AND

SUBJAREA(mult OR agri OR bioc OR immu OR neur OR phar OR mult OR medi OR nurs OR vete OR dent OR heal)

337

TOTAL NUMBER OF RESULTS: 1883

TOTAL AFTER INTERNAL REMOVAL OF DUPLICATES: 1520

TOTAL AFTER REMOVING ALL DUPLICATES WITH OTHER DATABASE RESULTS & IDENTIFIED ANIMAL-ONLY STUDIES: 141

NUMBER AFTER ADDITIONAL REMOVAL OF DUPLICATES BY A.M.: 122

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DATABASE SEARCHED & TIME PERIOD COVERED:

NEW YORK ACADEMY OF MEDICINE GREY LITERATURE REPORT – Earliest dates to 11/26/2013

SEARCH STRATEGY:

Hyaluronic OR hyaluronate OR hyaluronan OR hylan OR viscosupplement OR visco-supplement OR knee OR knees

NUMBER OF RESULTS: 0

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DATABASE SEARCHED & TIME PERIOD COVERED:

CANADIAN AGENCY FOR DRUGS AND TECHNOLOGIES IN HEALTH (CADTH) GREY
MATTERS DATABASE – Earliest to 11/26/2013

SEARCH STRATEGY:

hyaluronic OR hyaluronate OR hyaluronan OR hylan

NUMBER OF RESULTS: 1

viscosupplement OR visco-supplement

NUMBER OF RESULTS: 0

knee OR knees

NUMBER OF RESULTS: 46

Appendix B. List of Excluded Studies

Not English – N=7

1. Auerbach B, Melzer C. [Cross-linked hyaluronic acid in the treatment of osteoarthritis of the knee--results of a prospective randomized trial]. *Zentralbl Chir.* 2002 Oct;127(10):895-9. PMID: 12410458.
2. Bingol U, Yurtkuran M. Comparison of the clinical efficacy and adverse effects of two hyaluronan preparations with different molecular weights and a methyl prednisolone acetate in knee osteoarthritis ORIGINAL (NON-ENGLISH) TITLE Diz Osteoartritinde Iki Farkli {dotless} Molekul Agi {dotless} rli {dotless} kli {dotless} Hyaluronik Asit Preparati {dotless} ve Metil Prednisolon Asetat Preparati {dotless} ni {dotless} n Etki ve Yan Etkilerinin Klinik Olarak Karsi {dotless} lasti {dotless} ri {dotless} lmasi {dotless}. *Turkiye Fiziksel Tip ve Rehabilitasyon Dergisi.* 2013 2013;59(3):189-200. PMID: 2013594380 FULL TEXT LINK <http://dx.doi.org/10.4274/tftr.72687>.
3. Hashemi SM, Madadi F, Razavi S, et al. Intra-articular hyaluronic acid injections Vs. dextrose prolotherapy in the treatment of osteoarthritic knee pain. *Tehran University Medical Journal.* 2012 May;70(2):119-25. PMID: 2012213013.
4. Ostalowska A, Nowak D, Swiechowicz S, et al. Assessment of knee function and biochemical parameters of articular fluid and peripheral blood in gonarthrosis patients following intra-articular administration of hyaluronic acid. *Pol Orthop Traumatol.* 2013;78:173-81. PMID: 23959433.
5. Oswald A, Gachter A. [Acute local reaction after intra-articular injection of HYALAN G-F 20 (Synvisc) for treatment of gonarthrosis onset]. *Praxis (Bern 1994).* 2000 Nov 16;89(46):1929-31. PMID: 11111412.
6. Pavelka K, Trc T, Karpas K, et al. [Intra-articular treatment with Hyalgan in osteoarthrosis of the knee joint: experience in clinical practice in the Czech Republic]. *Acta Chir Orthop Traumatol Cech.* 2002;69(5):302-7. PMID: 12557601.
7. Swiechowicz S, Ostalowska A, Kasperczyk A, et al. Evaluation of hyaluronic acid intra-articular injections in the treatment of primary and secondary osteoarthritis of the knee. *Pol Orthop Traumatol.* 2012;77:105-9. PMID: 23306296.

Study Design – N=78

1. How effective are Hyalgan injections for arthritis? *Johns Hopkins Med Lett Health After 50.* 1998 Mar;10(1):8. PMID: 9600056.
2. How do the new injections for arthritis of the knee work, and who is a good candidate for this treatment? *Johns Hopkins Med Lett Health After 50.* 2000 Jul;12(5):8. PMID: 10879156.

3. Intra-articular injections for osteoarthritis of the knee. *Med Lett Drugs Ther.* 2006 Mar 27;48(1231):25-7. PMID: 16554699.
4. I've read that hyaluronic acid knee injections can be used to postpone knee surgery. Can hyaluronic acid in pill form provide the same relief? *Health News.* 2006 Apr;12(4):16. PMID: 16583498.
5. Summaries for patients. Viscosupplementation for knee osteoarthritis. *Ann Intern Med.* 2012 Aug 7;157(3):I-36. PMID: 22868857.
6. Knee injections offer minimal relief from arthritis pain. *Harv Mens Health Watch.* 2012 Sep;17(2):8. PMID: 23050288.
7. Adams ME. Acute local reactions after intraarticular hylan for osteoarthritis of the knee. *J Rheumatol.* 1996 May;23(5):944-5; author reply 6. PMID: 8724316.
8. Ahadi T, Abtahi M. Platelet-rich plasma versus hyaluronic Acid. *Arthroscopy.* 2012 Nov;28(11):1585; author reply -6. PMID: 23107248.
9. Allard S, O'Regan M. The role of elastoviscosity in the efficacy of viscosupplementation for osteoarthritis of the knee: a comparison of hylan G-F 20 and a lower-molecular-weight hyaluronan. *Clin Ther.* 2000 Jun;22(6):792-5. PMID: 10929925.
10. Atamaz F, Kirazli Y, Akkoc Y. A comparison of two different intra-articular hyaluronan drugs and physical therapy in the management of knee osteoarthritis. *Rheumatol Int.* 2006 Aug;26(10):873-8. PMID: 16416102.
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15. Briem K, Axe MJ, Snyder-Mackler L. Functional and perceived response to intra-articular hyaluronan injection in patients with knee osteoarthritis: persistence of treatment effects over 5 months. *Knee Surg Sports Traumatol Arthrosc.* 2009 Jul;17(7):763-9. PMID: 19296086.

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19. Chen WL, Hsu WC, Lin YJ, et al. Comparison of intra-articular hyaluronic acid injections with transcutaneous electric nerve stimulation for the management of knee osteoarthritis: a randomized controlled trial. *Arch Phys Med Rehabil*. 2013 Aug;94(8):1482-9. PMID: 23628378.
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26. Diracoglu D, Alptekin K, Teksoz B, et al. Knee vs hip single-joint intra-articular hyaluronic acid injection in patients with both hip and knee osteoarthritis: a pilot study. *Clin Rheumatol*. 2009 Sep;28(9):1021-4. PMID: 19455363.
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64. Dreiser R, Rahhali N, Pibourdin JM, et al. Hyaluronic acid management of knee osteoarthritis: Impact on pain. *Value in Health*. 2010 May;13(3):A131.
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Anullri, Denge ve Yasam Kalitesi Uzerine Etkisinin Karsilastirilmesi. *Turkiye Fiziksel Tip ve Rehabilitasyon Dergisi*. 2013 April;59 SUPPL. 1:483.

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67. Kreder HJ, Huskinsson EC, Donnelly S. Is hyaluronic acid effective in patients with osteoarthritis of the knee? *Western Journal of Medicine*. 2000 2000;173(4):252. PMID: 2000366698 MEDLINE PMID 11017989 (<http://www.ncbi.nlm.nih.gov/pubmed/11017989>) FULL TEXT LINK <http://dx.doi.org/10.1136/ewjm.173.4.252>.

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Participants - N=5

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Interventions not of interest - N=4

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Outcomes not of interest - N=75

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5. Arrich J, Piribauer F, Mad P, et al. Intra-articular hyaluronic acid for the treatment of osteoarthritis of the knee: systematic review and meta-analysis. *CMAJ*. 2005 Apr 12;172(8):1039-43. PMID: 15824412.

6. Bannuru RR, Natov NS, Dasi UR, et al. Therapeutic trajectory following intra-articular hyaluronic acid injection in knee osteoarthritis: Meta-analysis. *Osteoarthritis and Cartilage*. 2010 October;18 SUPPL. 2:S242-S3.

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8. Bannuru RR, Natov NS, Obadan IE, et al. Therapeutic trajectory of hyaluronic acid versus corticosteroids in the treatment of knee osteoarthritis: a systematic review and meta-analysis. *Arthritis Rheum*. 2009 Dec 15;61(12):1704-11. PMID: 19950318.

9. Bannuru RR, Natov NS, Obadan IE, et al. Relative efficacy of hyaluronic acid versus corticosteroids in the treatment of knee osteoarthritis: Meta-analysis. *Osteoarthritis and Cartilage*. 2009 September;17 SUPPL. 1:S269-S70.

10. Bellamy N, Campbell J, Robinson V, et al. Viscosupplementation for the treatment of osteoarthritis of the knee. *Cochrane Database Syst Rev.* 2006(2):CD005321. PMID: 16625635.
11. Bellamy N, Campbell J, Robinson V, et al. Intraarticular corticosteroid for treatment of osteoarthritis of the knee. *Cochrane Database Syst Rev.* 2006(2):CD005328. PMID: 16625636.
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17. Cerza F, Carni S, Carcangiu A, et al. Comparison between hyaluronic acid and platelet-rich plasma, intra-articular infiltration in the treatment of gonarthrosis. *Am J Sports Med.* 2012 Dec;40(12):2822-7. PMID: 23104611.
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Appendix C. Evidence Table

Author, Year	Study Location, Years, Name, Design, and Funding	Participants	Inclusion criteria	Exclusion criteria	Comorbidities	Study Arms
Altman et al., 1998 ⁶⁰	US <1998 RCT/CCT parallel Funding: Industry	Age Range: 40-90 Mean age: 64 SD controls: 10 (whole group) Number of participants enrolled: 495 Number of participants in analysis: 333 Number of knees: NR Mean BMI: NR % Female: 57	Diagnosis of osteoarthritis of the knee: ACR(NR) Knee radiograph(Kellgren-Lawrence grade 2 or 3, >=1 osteophyte) Duration of symptoms Knee pain 1 year or more Score(s) on OA assessments VAS for pain on a 50 foot walk: >=20mm WOMAC pain subscale: >=20 on >=1 item out of 5 6-point categorical scale: moderate or marked main Minimum age: 40 Maximum age: 80 No prior IA HA injection within one year No other IA injections, including corticosteroids within preceding 3 months If both knees affected, more serious one was used	NR	NR	Arm 1: N = 115 Mean age: 65 (10) Placebo/sham Acetaminophen up to 4000mg /day permitted as rescue Arm 2: N = 105 Mean age: 62(10) Hyalgan 20mg/2ml Molecular weight: 500-730kD Oral placebo for naproxen twice daily and Acetaminophen up to 4000mg /day permitted as rescue Arm 3: N = 113 Mean age: 63(9) NSAID Total treatments: 5 Time between treatment: 1 week

Author, Year	Study Location, Years, Name, Design, and Funding	Participants	Inclusion criteria	Exclusion criteria	Comorbidities	Study Arms
Berenbaum et al., 2012 ⁶¹	France, Germany 2008-2009 EudraCt no 2008-003875-35 RCT/CCT parallel Funding: Industry	Age Range: NR Mean age: 67 SD controls: NR Number of participants enrolled: 426 Number of participants in analysis: 426 Number of knees: NR Mean BMI: 27.7 (3.1) for Hyalgan % Female: 63	Diagnosis of osteoarthritis of the knee: ACR(NR) Radiologic(Kellgren-Lawrence stage II or III within past 12 months) Duration of symptoms At least 6 months Failure of another treatment modality: Analgesics and/or regular NSAIDs Score(s) on OA assessments Global knee pain VAS: 40mm/100mm WOMAC pain subscale score: 25 or greater on the 0-100 normalized scale Lequesne Index: 4 or greater Minimum age: 49 Maximum age: 81 Intolerance to NSAIDs or weak opioids Radiologic evidence of bilateral OA if global pain VAS in contralateral knee < 30mm	Current or prior receipt of HA in affected knee Current or prior receipt of glucocorticoids in affected knee Use of certain analgesics: Opioids within past month of baseline Other musculoskeletal or joint disease or condition that limits mobility: Inflammatory or other rheumatic diseases Patellofemoral symptomatic OA Secondary OA Symptomatic hip OA ipsilateral to target knee Clinical joint effusion Excessive varus or valgus knee deformity (on physical exam, confirmed radiographically)		Arm 1: N = 209 Mean age: 66.1 (8.1) Hyalgan Molecular weight: 500 kD-730 kD NSAID or paracetamol up to 4g/d as rescue medication Arm 2: N = 217 Mean age: 67.2 (7.8) GO-ON (2.5 ml, 10mg/ml) Molecular weight: 800 kD-1500 kD NSAID or paracetamol up to 4g/d as rescue medication Total treatments: 3 Time between treatment: 3 weeks

Author, Year	Study Location, Years, Name, Design, and Funding	Participants	Inclusion criteria	Exclusion criteria	Comorbidities	Study Arms
Blanco et al., 2008 ⁴³	Spain <2008 RCT/CCT parallel Funding: Industry	Mean age: 68.3 SD controls: (9.1) Number of participants enrolled: 42 Mean BMI: 33 % Female: 76	Diagnosis of osteoarthritis of the knee: WOMAC pain(\geq 150mm) ACR Kellgren-Lawrence(IV) Minimum age: 40 Waiting list for knee replacement	Prior surgical procedure on affected knee Current or prior receipt of HA in affected knee Current or prior receipt of glucocorticoids in affected knee Other musculoskeletal or joint disease or condition that limits mobility Use of glucosamine within prior 3 months Use of an investigational drug within 30 days of study entry CNS impairment, impaired coagulation Known sensitivity to HA, paracetamol, or diclofenac Immune-compromised or receiving immunosuppressive therapy or considered unable to complete treatment or followup	NR	Arm 1: N = 20 Mean age: 68.3(9.1) Placebo/sham Paracetamol and/or diclofenac as rescue analgesics Arm 2: N = 22 Mean age: 67.5(8.1) Adant Molecular weight: 900 kDa Total treatments: 10 (2 cycles of 5 weekly injections, separated by 24 weeks) Time between treatment: 1 week

Author, Year	Study Location, Years, Name, Design, and Funding	Participants	Inclusion criteria	Exclusion criteria	Comorbidities	Study Arms
Brandt et al., 2001 ⁶²	US 1996-1997 RCT/CCT parallel Funding: Industry	Age Range: NR Mean age: NR SD controls: NR Number of participants enrolled: 226 Number of participants in analysis: 226 and 135 Number of knees: NR Mean BMI: HA: 32(6); Saline: 30.1(6.2) % Female: 63	Diagnosis of osteoarthritis of the knee: Kellgren-Lawrence(Grade II or III) Score(s) on OA assessments WOMAC: pain score 13 or greater in knee to be treated knee and less than 13 in contralateral knee Minimum age: 50 Willing to d/c other analgesics and NSAIDs for 5 half-lives of the relevant drug Able to walk 50 feet unassisted Not pregnant or planning pregnancy	Prior surgical procedure on affected knee: Arthroplasty Current or prior receipt of HA in affected knee Current or prior receipt of glucocorticoids in affected knee Initiation of quadriceps exercise program within 4 months of screening Kellgren-Lawrence Grade IV radiographic changes in either knee Tx with anticoagulants, immunosuppressives, or muscle relaxants Inability to tolerate acetaminophen Clinically significant comorbidity (renal or hepatic disease) or abnormality in routine lab tests or allergy to lidocaine	Involvement of both knees: HA: 78% Saline: 88%	Arm 1: N = 112 Mean age: 67(8.4) Placebo/sham Arm 2: N = 114 Mean age: 65(8.4) Orthovisc (2 mL, 15mg/mL) Molecular weight: 1000-2900 kD (considered high MW) Total treatments: 3 Time between treatment: 1 week

Author, Year	Study Location, Years, Name, Design, and Funding	Participants	Inclusion criteria	Exclusion criteria	Comorbidities	Study Arms
DeCaria et al., 2012 ⁶³	Ontario Canada <2012 RCT/CCT parallel Funding: Non-industry	Age Range: 60-80 Mean age: NR SD controls: NR Number of participants enrolled: 30 Number of participants in analysis: na Number of knees: na Mean BMI: HA: 30.48(6.16) Placebo: 29.40(4.11) % Female: 47	Diagnosis of osteoarthritis of the knee: ACR: Kellgren-Lawrence(Grade II-III) ACR clinical criteria for knee pain(NR) Failure of another treatment modality: Multiple years Minimum age: 60 Maximum age: 80	Prior surgical procedure on affected knee: Except for arthroscopy 18 months or more before study commencement Other musculoskeletal or joint disease or condition that limits mobility: Non OA arthritis (e.g., RA, gout), OA in other lower limbs, end-stage knee OA; lower back pathology that limited walking, leg length differential>2cm A neurological or cardiovascular condition that could impair gait function Cognitive impairment Intraarticular injection within 6 months prior to study commencement Chronic use of oral corticosteroids	NR	Arm 1: N = 15 Mean age: 72.93 (5.48) 500 mg acetaminophen to be taken up to 4g/day as rescue medication Placebo/sham 1.2 ml 0.001 mg/ml inert HA Arm 2: Hyaluronic acid (2 ml, 20 mg/ml) Molecular weight: 730 kD 500 mg acetaminophen to be taken up to 4g/day as rescue medication Total treatments: 3 Time between treatment: 1 week
Dixon et al., 1988 ⁵⁹	UK <1988 RCT/CCT parallel Funding: Industry	Age Range: 43-85 Mean age: 68.5 SD controls: NR Number of participants enrolled: 63 Number of participants in analysis: 53 Number of knees: NR Mean BMI: NR % Female: 54	Diagnosis of osteoarthritis of the knee: Symptomatic OA NR	Use of certain analgesics: If other than for OA Other musculoskeletal or joint disease or condition that limits mobility: Hip OA; primary inflammation of the knee (e.g., RA, psoriatic arthropathy, pseudogout, joint infection) Skin conditions overlying the joint Poor general health	NR	Arm 1: N = 33 Mean age: nr Hyalgan 0.2mg/2 ml Molecular weight: NR Placebo/sham Arm 2: N = 30 Mean age: nr Hyalgan 20mg/2 ml Molecular weight: NR Paracetamol was permitted but NSAIDS, corticosteroids, and strong analgesics were not Total treatments: Varied 1 for first 3 weeks and then 2

Author, Year	Study Location, Years, Name, Design, and Funding	Participants	Inclusion criteria	Exclusion criteria	Comorbidities	Study Arms
Dougados et al., 1993 ⁴¹	France <1993 RCT/CCT parallel Funding: NR	Mean age: 69.0 SD controls: 10.6 Number of participants enrolled: 110 Number of participants in analysis: 95 (ITT also done) Mean BMI: NR % Female: 71.0	Diagnosis of osteoarthritis of the knee: ACR Score(s) on OA assessments VAS for pain: >=40 out of 100 Femorotibial localization Knee effusion	Prior surgical procedure on affected knee: Prosthesis or any intra-articular surgery during the preceding 2 years Use of certain analgesics: Dose of NSAIDs or analgesics stable during previous month Other musculoskeletal or joint disease or condition that limits mobility: Secondary osteoarthritis of the knee Serious concomitant medical illness Any arthrocentesis during prior 3 months Stable dose of any basic OA therapy stable for prior 3 months; Stable use of any physiotherapy during the previous month and first 7 weeks of study	NR	Arm 1: Placebo/sham Arm 2: Hyalectin (Hyalgan) Molecular weight: 500-730 kDa Total treatments: 4 Time between treatment: 1 week
Forster et al., 2003 ⁴²	UK <2002 RCT/CCT parallel Funding: NR	Age Range: NR Mean age: 61.5 SD controls: NR Number of participants enrolled: 38 Number of participants in analysis: 32 Mean BMI: NR % Female: NR	Diagnosis of osteoarthritis of the knee: On waiting list for arthroscopic washout Fitness for general or local anesthesia	Prior surgical procedure on affected knee Current or prior receipt of HA in affected knee Current or prior receipt of glucocorticoids in affected knee Mechanical symptoms	NR	Arm 1: N = 19 Mean age: 63 Arthroscopic washout Arm 2: N = 19 Mean age: 60 Hyalgan Molecular weight: 500-730 kD Total treatments: 5 Time between treatment: 1 week

Author, Year	Study Location, Years, Name, Design, and Funding	Participants	Inclusion criteria	Exclusion criteria	Comorbidities	Study Arms
Grecomoro et al., 1987 ⁷⁴	Italy <1987 RCT/CCT parallel Funding: NR	Age Range: 43-92 Mean age: 64.88 SD controls: 10.94 Number of participants enrolled: 34 Number of knees: 40 % Female: 19/34	Diagnosis of osteoarthritis of the knee: Not reported Knee pain with movement	NR	Involvement of both knees: 6/34	Arm 1: N = 20 knees Mean age: NR Placebo/sham Arm 2: N = 20 knees Mean age: NR Hyalgan Molecular weight: 500K-750K Total treatments: 3 Time between treatment: 1 week
Henderson et al., 1994 ⁷⁵	UK <1994 RCT/CCT parallel Funding: NR	Age Range: NR Mean age: NR SD controls: NR Number of participants enrolled: 91 Number of participants in analysis: 84 Number of knees: NR Mean BMI: NR % Female: 69	Diagnosis of osteoarthritis of the knee: Clinical history and radiological evidence Kellgren-Lawrence(Grades I and II: severity group 1; Grades III and IV: severity group 2) Score(s) on OA assessments VAS scale for pain evoked by activities: minimum score of 30 mm out of 100mm	Other musculoskeletal or joint disease or condition that limits mobility: Inflammatory joint disease, metabolic bone disease, anserine bursitis, pain referred from other structures	Involvement of both knees: >99%	Arm 1: N = 20 (Severity group I) Mean age: 60.0(1.9) Placebo/sham Arm 2: N = 26 Severity Group 2 Second placebo group Arm 3: N = 18 Severity Group 1 Mean age: 63.9(1.9) Hyalgan (20mg/2mL) Molecular weight: NR Arm 4: N = 26 Severity Group 2 Mean age: 67.0(1.7) Hyalgan Total treatments: 5 Time between treatment: 1 week

Author, Year	Study Location, Years, Name, Design, and Funding	Participants	Inclusion criteria	Exclusion criteria	Comorbidities	Study Arms
Huang et al., 2011 ⁶⁴	Taiwan <2011 RCT/CCT parallel Funding: Industry	Age Range: nr Mean age: 65.0 SD controls: 8.3 Number of participants enrolled: 200 Number of participants in analysis: 198 Number of knees: NR Mean BMI: 25.6(3.6) % Female: 76	Diagnosis of osteoarthritis of the knee: ACR (knee pain with one or more of the following conditions: age>50, crepitus, or morning stiffness<30 minutes duration Radiographic evidence(Kellgren Lawrence score II and III, predominance in tibio-femoral compartment) VAS pain scores on 50-foot walking test(>=40mm) Minimum age: 50 Any acute disease or trauma leading to secondary OA had to have occurred at least 5 years before study entry	Current or prior receipt of glucocorticoids in affected knee Other musculoskeletal or joint disease or condition that limits mobility Severe degeneration of knee joint with marked joint narrowing, varus, or valgus deformity of the knee (>12") or other joint deformities or other joint disorders Joint or skin infections Joint prostheses of lower limb or symptomatic hip Inflammatory joint disease, specific arthropathy, severe axis deviations or instabilities,	NR	Arm 1: N = 100 Mean age: 64.2(8.4) Placebo/sham Arm 2: N = 100 Mean age: 65.9(8.1) Hyalgan (20mg/2ml) Total treatments: 5 Time between treatment: 1 week

Author, Year	Study Location, Years, Name, Design, and Funding	Participants	Inclusion criteria	Exclusion criteria	Comorbidities	Study Arms
Huskisson et al., 1999 ⁶⁵	United Kingdom <1997 RCT/CCT parallel Funding: NR	Age Range: nr Mean age: nr SD controls: nr Number of participants enrolled: 100 Number of participants in analysis: 81 Number of knees: NR Mean BMI: nr % Female: 67	Diagnosis of osteoarthritis of the knee: ARA Criteria Kellgren-Lawrence(II or III) Consistent pain for 3 months Moderate to severe pain on walking	Current or prior receipt of glucocorticoids in affected knee Other musculoskeletal or joint disease or condition that limits mobility: Serious functional impairment at the knee, hip OA, other related joint OA, psoriasis, sacroiliitis, painful knee conditions other than OA Kellgren Lawrence IV Known or suspected joint infection Poor general health or other conditions which would prevent regular hospital attendance Skin conditions overlying the joint Severe intercurrent hepatic or renal disease or major general medical conditions		Arm 1: N = 50 Mean age: 64.8 (9.3) Placebo/sham Arm 2: N = 50 Mean age: 65.8 (8.8) Hyalgan Molecular weight: 500-730 kDa Total treatments: 5 Time between treatment: 1 week
Kahan et al., 2003 ⁶⁶	France 10/1998-2/2000 RCT/CCT parallel Funding: NR	Mean age: 66 SD controls: 10 Number of participants enrolled: 506 Number of participants in analysis: 506 Mean BMI: 28 % Female: 67.5	Diagnosis of osteoarthritis of the knee: ACR Kellgren-Lawrence(any) Failure of another treatment modality: Two courses of NSAID therapy, each at least 10 d long, within the last 3 months and/or a symptomatic slowacting drug taken continuously during the last 2 months Score(s) on OA assessments Pain VAS: ≥ 40 mm / 100 mm Minimum age: 18	Prior surgical procedure on affected knee: Arthroscopy, lavage, meniscectomy, etc.) within the last year; TKR ever Current or prior receipt of HA in affected knee Current or prior receipt of glucocorticoids in affected knee Inflammatory flare in the target knee (effusion with nocturnal pain, local heat or redness, morning stiffness for longer than 45 min or greater than 50% increase in the VAS pain score as compared to the previous week) Synovectomy, tibial osteotomy Surgery scheduled within last 9 months	Involvement of both knees: 74	Arm 1: N = 253 Mean age: 66 (10) Conventional treatment Arm 2: N = 253 Mean age: 66 (10) Synvisc Molecular weight: NR Total treatments: 3 Time between treatment: 1 week

Author, Year	Study Location, Years, Name, Design, and Funding	Participants	Inclusion criteria	Exclusion criteria	Comorbidities	Study Arms
Karlsson et al., 2002 ⁶⁷	<p>Sweden</p> <p><2002</p> <p>RCT/CCT parallel</p> <p>Funding: Industry</p>	<p>Age Range: NR</p> <p>Mean age: reported by arm below</p> <p>SD controls: reported by arm below</p> <p>Number of participants enrolled: 246</p> <p>Number of participants in analysis: ITT: 246 PP: 210</p> <p>Number of knees: NR</p> <p>Mean BMI: 28</p> <p>% Female: 61</p>	<p>Score(s) on OA assessments</p> <p>Lequesne algofunctional index: ≥ 10</p> <p>Weight-bearing pain VAS: ≥ 40mm</p> <p>Minimum age: 60</p> <p>Normal general physical exam</p>	<p>Prior surgical procedure on affected knee: Arthroscopy, arthrography, surgery less than 6 months prior to inclusion</p> <p>Current or prior receipt of HA in affected knee</p> <p>Current or prior receipt of glucocorticoids in affected knee</p> <p>Other musculoskeletal or joint disease or condition that limits mobility: RA or other inflammatory joint disease (ACR criteria)</p> <p>Any disabling problem of the musculoskeletal system or other organ system which could interfere with the assessment of efficacy</p> <p>Bone attrition in either knee (Ahlback III or IV), previous intra-articular fracture of the knee</p> <p>Alcohol or drug abuse</p> <p>Known allergy to any substance related to the study</p> <p>Clinically relevant hematological or known clinical chemistry values outside the reference values at the time of inclusion</p> <p>Any disabling problem with any other organ system that could interfere with the assessment of efficacy</p>	NR	<p>Arm 1: N = 66 (57 PP) Mean age: 71(6) Placebo/sham</p> <p>Arm 2: N = 92 (76 PP) Mean age: 72(7) Artzal (2.5 ml 1% hyaluronan) Molecular weight: 1,000 kDa</p> <p>Arm 3: N = 88 (77 PP) Mean age: 70(7) Synvisc (2 ml 0.8%) Molecular weight: 7,000 kDa</p> <p>Total treatments: 3 Time between treatment: 1 day</p>

Author, Year	Study Location, Years, Name, Design, and Funding	Participants	Inclusion criteria	Exclusion criteria	Comorbidities	Study Arms
Khanasuk et al., 2012 ⁶⁸	Thailand 2011-2012 RCT/CCT parallel Funding: NR	Mean age: NR SD controls: NR Number of participants enrolled: 32 Number of participants in analysis: 30 Number of knees: NR Mean BMI: 26 % Female: 80	Diagnosis of osteoarthritis of the knee: ACR for primary OA of the knee(NR) Pain VAS($\geq 3/10$) Kellgren-Lawrence radiological grading(\geq Grade II) Minimum age: 45	Current or prior receipt of HA in affected knee Intention to take pain medication after injection History of allergy to avian products	NR	Arm 1: N = 15 Mean age: 65.1(9.6) Hylan GF-20 (Synvisc)(single 6 ml injection) Molecular weight: Reported as High Arm 2: N = 15 Mean age: 67.0(9.5) Hyalgan (single injection) Molecular weight: Reported as Low Total treatments: 1
Leopold et al., 2003 ⁷⁶	US 2000-2002 RCT/CCT parallel Funding: Non-industry	Age Range: 39-83 Mean age: NR SD controls: NR Number of participants enrolled: 100 Number of participants in analysis: 80 Number of knees: NR Mean BMI: CS: 29.3 HA:28.8 % Female: CS: 56 HA: 52	Diagnosis of osteoarthritis of the knee: Radiographic evidence of symptomatic knee OA(NR) Minimum age: 18 Dissatisfaction with prior attempts at nonoperative management modalities	Current or prior receipt of HA in affected knee Other musculoskeletal or joint disease or condition that limits mobility Pregnant or lactating Radiographic evidence of bone on bone arthritis or Chodrocalcinosis Insufficiency of the collateral ligament, of the ACL or PCL with concomitant symptomatic giving way of the affected extremity or a current infection in the affected extremity as demonstrated on physical exam History of crystalline arthropathy or neuropathic arthropathy Allergy or hypersensitivity to any of the study medications or to poultry products	NR	Arm 1: N = 42 Mean age: 64 Arm 2: N = 38 Mean age: 66 Hylan G-F 20 (16mg/2ml) Total treatments: 3 HA 1CS Time between treatment: 1 week

Author, Year	Study Location, Years, Name, Design, and Funding	Participants	Inclusion criteria	Exclusion criteria	Comorbidities	Study Arms
Lundsgaard et al., 2008 ⁷²	Denmark <2008 NCT00144820 RCT/CCT parallel Funding: Non-industry	Age Range: NR Mean age: 69.6 SD controls: 7.27 Number of participants enrolled: 251 Number of participants in analysis: 243 Mean BMI: 29.3 % Female: 52.4	Score(s) on OA assessments Daily knee pain on VAS (that did not respond to analgesics): 20mm/100mm Minimum age: 59 Daily	Prior surgical procedure on affected knee: Invasive procedures within past 6 months Current or prior receipt of glucocorticoids in affected knee Other musculoskeletal or joint disease or condition that limits mobility: RA or other inflammatory arthritis Contra-indication to hyaluronate Contra-indication to knee injection Medications that could interfere with intervention Comorbidity, e.g. psychosis or dementia that could interfere Knee infection or uric acid crystals	NR	Arm 1: Saline 2ml Arm 2: Saline 20 mL, no hyaluronate Arm 3: Hyalgan Molecular weight: NR Total treatments: 4 Time between treatment: 1 week

Author, Year	Study Location, Years, Name, Design, and Funding	Participants	Inclusion criteria	Exclusion criteria	Comorbidities	Study Arms
Pavelka et al., 2011 ⁶⁹	Czech Republic, France, Italy, Switzerland, the Slovak Republic and Germany November 2007 - January 2009 NCT00556608 RCT/CCT parallel Funding: Industry	Age Range: 41-80 Mean age: 65 SD controls: 9 Number of participants enrolled: 381 Number of participants in analysis: 354 Mean BMI: 27 % Female: 72.9	Diagnosis of osteoarthritis of the knee: ACR Kellgren-Lawrence(2 or 3) Duration of symptoms 3 months Failure of another treatment modality: NSAIDS Score(s) on OA assessments WOMAC pain: include 40 - 80 Minimum age: 40	Prior surgical procedure on affected knee: TKR, arthroplasty Current or prior receipt of HA in affected knee Current or prior receipt of glucocorticoids in affected knee Use of certain analgesics: Chronic use of NSAIDS, analgesics or narcotics Other musculoskeletal or joint disease or condition that limits mobility: Pain mainly related to femoral patellar syndrome at the target knee, no remaining joint space width at the target knee, symptomatic hip osteoarthritis or other condition that would interfere with study assessments, severe varus/valgus deformity in the target knee, history or current evidence of other joint diseases, such as inflammatory, infective or metabolic joint disease, concomitant rheumatic disease, significant injur Lymphatic stasis in the relevant limb, skin infection, disease or trauma at the injection site Initiation of target knee physical therapy in the past 3 months, initiation/ change in dose of symptomatic slow-acting drugs for osteoarthritis BMI >=32	Involvement of both knees: 66%	Arm 1: N = 192 Mean age: 65.1 (9.1) Synovial Molecular weight: 800 - 1,200 kD Arm 2: N = 188 Mean age: 64.9 Synvisc Molecular weight: 6,000 kD Total treatments: 3 Time between treatment: 1 week

Author, Year	Study Location, Years, Name, Design, and Funding	Participants	Inclusion criteria	Exclusion criteria	Comorbidities	Study Arms
Petrella et al., 2002 ⁷⁰	Canada < 2002 RCT/CCT parallel Funding: Industry	Age Range: NR Mean age: 65.5 SD controls: 9.5 Number of participants enrolled: 120 Number of participants in analysis: 108 Mean BMI: 30.7 % Female: 45.8	Diagnosis of osteoarthritis of the knee: Kellgren-Lawrence(1 to 3 included) Score(s) on OA assessments VAS pain 0-10 scale: 3+ Unilateral OA	Current or prior receipt of HA in affected knee Current or prior receipt of glucocorticoids in affected knee NSAID intolerance Bilateral symmetric inflammatory reaction	Involvement of both knees: 0%	Arm 1: N = 28 Mean age: 62.6 (9.5) Placebo/sham Arm 2: N = 25 Mean age: 67.3 (8.9) Suplasyn Molecular weight: NR Placebo pill Arm 3: N = 29 Mean age: 65.0 (9.7) Suplasyn Molecular weight: NR NSAID Arm 4: N = 26 Mean age: 66.3 (8.8) NSAID Total treatments: 3 Time between treatment: 1 week

Author, Year	Study Location, Years, Name, Design, and Funding	Participants	Inclusion criteria	Exclusion criteria	Comorbidities	Study Arms
Petrella et al., 2008 ⁷⁷	Canada <2008 RCT/CCT parallel Funding: Non-industry	Age Range: nr Mean age: 71 SD controls: 8 Number of participants enrolled: 200 Number of participants in analysis: nr Mean BMI: 27.2 % Female: 30	Diagnosis of osteoarthritis of the knee: Medial compartment OA Radiographic grade(1-3) Did not exhibit non-arthritis-related disease	Current or prior receipt of HA in affected knee Current or prior receipt of glucocorticoids in affected knee End-stage OA in affected knee	NR	Arm 1: N = 50 Mean age: 71+/-8 Placebo/sham Arm 2: N = 50 Mean age: 68+/-6 HA dual molecular weight Molecular weight: 580–780 kDa+1.2 to 2.0 million kDa Arm 3: N = 50 Mean age: 69+/-5 HA low molecular weight Molecular weight: 500–730 kDa Arm 4: N = 50 Mean age: 71+/-9 HA high molecular weight Molecular weight: 6 million kDa Total treatments: 3 Time between treatment: 1 week

Author, Year	Study Location, Years, Name, Design, and Funding	Participants	Inclusion criteria	Exclusion criteria	Comorbidities	Study Arms
Petrella et al., 2011 ⁷⁸	Canada < 2011 ISRCTN986303 31 RCT/CCT parallel Funding: NR	Age Range: NR Mean age: 70 SD controls: 8 31 Number of participants enrolled: 200 Number of participants in analysis: Unclear Mean BMI: 27 % Female: 57	Diagnosis of osteoarthritis of the knee: Kellgren-Lawrence(1 to 3 included) Score(s) on OA assessments VAS pain: 45+	Current or prior receipt of HA in affected knee Current or prior receipt of glucocorticoids in affected knee Use of certain analgesics: Dosage of glucosamine and/or chondroitin sulfate, and/or NSAIDs that has been stable over the preceding three months with the dosage remaining constant during the study Other musculoskeletal or joint disease or condition that limits mobility: End stage OA Active skin disease or infection in the area of the injection site Any condition/ disease which in the opinion of the investigator could interfere with patient compliance and/ or interfere with the interpretation of the treatment results Contra-indication to intra-articular injection or known hypersensitivity to Sodium Hyaluronate Planned surgery on knee	NR	Arm 1: N = 50 Mean age: 71 (8) Placebo/sham Arm 2: N = 50 Mean age: 68 (6) sodium hyaluronate Molecular weight: Combined high & low weight Arm 3: N = 50 Mean age: 69 (5) sodium hyaluronate - low weight Molecular weight: 500-730 KDa Arm 4: N = 50 Mean age: 71 (9) sodium hyaluronate - high weight Molecular weight: 6000 KDa Total treatments: 3 Time between treatment: 1 week

Author, Year	Study Location, Years, Name, Design, and Funding	Participants	Inclusion criteria	Exclusion criteria	Comorbidities	Study Arms
Pham et al., 2004 ⁷³	France <2004 RCT/CCT parallel Funding: NR	Age Range: 50+ Mean age: 64.9 SD controls: 7.7 Number of participants enrolled: 301 % Female: 65 average	Diagnosis of osteoarthritis of the knee: Presence of a symptomatic primary painful medial femorotibial knee OA defined by a daily pain visual analogue scale (VAS) score .30 mm in the previous month VAS for pain(>30mm in prior month) Joint space(>2mm)	Current or prior receipt of HA in affected knee Current or prior receipt of glucocorticoids in affected knee Use of certain analgesics: Diacerein or other antiinflammatories Other musculoskeletal or joint disease or condition that limits mobility: Severe OA (joint space <2mm), secondary knee OA, Paget's Contraindications to HA Need for surgery	NR	Arm 1: N = 85 Mean age: 64.9 (7.7) Placebo/sham Arm 2: N = 131 Mean age: 71.0 NRD101 Molecular weight: 1.900 kDa Arm 3: N = 85 Mean age: 64.5 Diacerein Total treatments: 12? (3 course every 3 months for a year) Time between treatment: 1 week
Raman et al., 2008 ⁷¹	UK < 2008 RCT/CCT parallel Funding: Non-industry	Age Range: 42-82 Mean age: 67.2 SD controls: NR Number of participants enrolled: 392 Number of participants in analysis: 380 Mean BMI: NR % Female: 68	Diagnosis of osteoarthritis of the knee: Score(s) on OA assessments VAS (10 point scale): 6+ Preferred tx strategy was viscosupplementation	Prior surgical procedure on affected knee Current or prior receipt of HA in affected knee Current or prior receipt of glucocorticoids in affected knee Bilateral OA	NR	Arm 1: N = 199 Mean age: NR Synvisc (Hylan GF 20) Molecular weight: 6000 kD Arm 2: N = 193 Mean age: NR Hyalgan Molecular weight: 500 - 730 kD Total treatments: 3 for Synvisc, 5 for Hyalgan Time between treatment: 1 week

Author, Year	Study Location, Years, Name, Design, and Funding	Participants	Inclusion criteria	Exclusion criteria	Comorbidities	Study Arms
Roman et al., 2000 ⁷⁹	Spain < 2000 RCT/CCT parallel Funding: NR	Age Range: 41-86 Mean age: 65.14 SD controls: 9.77 Number of participants enrolled: 49 Mean BMI: NR % Female: 83.7	Diagnosis of osteoarthritis of the knee: Kellgren-Lawrence(2 or 3 included)	NR	NR	Arm 1: N = 30 Mean age: NR Adant Molecular weight: 900 kD Arm 2: N = 19 Mean age: NR Hyalgan Molecular weight: 800 kD Total treatments: 5 Time between treatment: 1 week
Tamir et al., 2001 ⁸⁰	Israel < 2001 RCT/CCT parallel Funding: NR	Age Range: NR Mean age: 71 SD controls: NR Number of participants enrolled: 49 Number of participants in analysis: Unclear Mean BMI: NR % Female: 73.5	Diagnosis of osteoarthritis of the knee: Altman Kellgren-Lawrence(2 to 4 included) Minimum age: 60 Maximum age: 85	Prior surgical procedure on affected knee: No surgery ever, no arthroscopy within 6 months Current or prior receipt of HA in affected knee Current or prior receipt of glucocorticoids in affected knee Other musculoskeletal or joint disease or condition that limits mobility: RA, other inflammatory arthritis, OA of hip, OA from fracture of knee Skin conditions on knee	NR	Arm 1: N = 24 Mean age: 70 Placebo/sham Arm 2: N = 25 Mean age: 71 Bio-Hy Molecular weight: 3000 kDa Total treatments: 5 Time between treatment: 1 week

Appendix D. Data Abstraction Tools

- 1. DJD Data Abstraction Tool**
- 2. Cochrane Risk of Bias Tool for Randomized Controlled Trials, Adapted**
- 3. Ottawa-Newcastle Risk of Bias Assessment for Observational Studies, Adapted**
- 4. Assessment of Reporting of Adverse Events (Questions from McHarms)**
- 5. AMSTAR Assessment of Reporting Quality for Systematic Reviews**

1. DJD Data Abstraction Tool

Should this article have been previously excluded based on the exclusion criteria?

Do you need another article to complete this form?

Yes (stop until Aneesa links the article; specify reference number)

No

[Clear Response](#)

Does this article report on part of a larger study or a follow-up to a previous study?

Yes No [Clear Response](#)

Does the larger study have a name?

Yes No [Clear Response](#)

When did this study occur? (e.g. dates or year of recruitment to date of completion)

Years (specify)

NR

[Clear Response](#)

Location(s):

- US
- Not US (specify country)
- Multi-country

[Clear Response](#)

Study Design (choose one):

- RCT/CCT parallel
- RCT/CCT crossover
- Open or uncontrolled trial
- Population-based prospective cohort study
- Case control study
- Case study
- Case series
- Database analysis

[Clear Response](#)

Does this study report on AE outcomes?

- Yes No [Clear Response](#)
-

Participants:

If not reported, please indicate "NR"

- Age range: ___ to ___ (specify range)
 - Mean age (whole group if reported) (specify mean)
 - Standard Deviation (SD) controls (specify SD)
 - Number of participants enrolled (specify number)
 - Number of participants in analysis if different from enrolled (specify number)
 - Number of knees if reported that way (specify)
 - Mean BMI (specify)
 - % female (specify %)
 - Not Reported
-

Inclusion criteria for participation in the study:

- Diagnosis of osteoarthritis of the knee (specify diagnostic modality and cutoff scores, if relevant)
 - Duration of symptoms
 - Failure of another treatment modality (specify)
 - Score(s) on OA assessments
 - Age \geq ___ (specify inclusion of age)
 - Age $<$ ___ (specify inclusion of age)
 - Other 1 (specify)
 - Other 2 (specify)
 - Other 3 (specify)
 - Other 4 (specify)
 - Other 5 (specify)
 - Not Reported
-

Exclusion criteria for the study:

- Prior surgical procedure on affected knee (specify type)
 - Current or prior receipt of HA in affected knee
 - Current or prior receipt of glucocorticoids in affected knee
 - Use of certain analgesics (specify the analgesics)
 - Other musculoskeletal or joint disease or condition that limits mobility (rheumatoid arthritis, osteoporosis, hip OA)(specify)
 - Other chronic disease that limits mobility (advanced CVD, advanced COPD, Parkinsons...)
 - Obesity
 - Age > ___ (specify exclusion of age)
 - Age < ___ (specify exclusion of age)
 - Other 1 (specify)
 - Other 2 (specify)
 - Other 3 (specify)
 - Other 4 (specify)
 - Other 5 (specify)
 - Not Reported
-

Comorbidities:

- Obesity (specify % of participants)
- Involvement of both knees (specify % of participants)
- Diabetes (specify % of participants)
- Other 1 (specify)
- Other 2 (specify)

Other 3 (specify)

Not Reported

Intervention

How many arms are there?

Control group (Arm 1)

Number of participants (specify number)

Mean age (SD) (specify number)

HA Brand or chemical name [indicate name]

Additional treatment

None

Placebo/sham

NSAID

Opioid pain medications

Corticosteroid injection

Corticosteroid oral

Plasma enriched with growth factors

Other (specify)

Intervention (Arm 2)

Number of participants (specify number)

Mean age (SD) (specify number)

HA Brand or chemical name [indicate name]

Additional treatment

Intervention (Arm 3)

- Number of participants (specify number)
- Mean age (SD) (specify number)
- HA Brand or chemical name [indicate name]
- Additional treatment

Intervention (Arm 4)

- Number of participants (specify number)
- Mean age (SD) (specify number)
- HA Brand or chemical name [indicate name]
- Additional treatment

Intervention (Arm 5)

- Number of participants (specify number)
- Mean age (SD) (specify number)
- HA Brand or chemical name [indicate name]
- Additional treatment

How many total treatments did participants receive?

If more than one treatment, how far apart?

Number

Unit

Outcomes (choose all that apply):

Arthroplasty (or time to arthroplasty or delay to arthroplasty or avoidance of...)

Function:

Quality of life:

Adverse events/harms

Other included outcomes 1 (specify outcome)

Other included outcomes 2 (specify outcome)

Other included outcomes 3 (specify outcome)

Other included outcomes 4 (specify outcome)

Other included outcomes 5 (specify outcome)

Other included outcomes 6 (specify outcome)

Funding:

Industry

Non Industry

Not Reported

Did the authors have any conflict of interest?

Yes

No

NR

[Clear Response](#)

Does this article need another form to be completed for the same article (i.e., article reports more than one study)?

Yes (please complete another form) No [Clear Response](#)

Reference Mining

Yes (specify reference number) No [Clear Response](#)

Needs to discuss

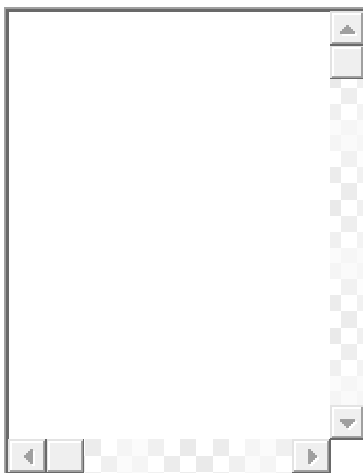
Yes No [Clear Response](#)

Has this form been reconciled?*

*Indicate "yes" only if this form has been reconciled. Programmer will pull data from this form.

Yes No [Clear Response](#)

Comments



2. Cochrane Risk of Bias Tool for Randomized Controlled Trials, Adapted

1. **Sequence Generation:** Describe the method used to generate the allocation sequence in sufficient detail to allow an assessment of whether it should produce comparable groups.

Was the participant recruitment and assignment to condition (allocation sequence) adequately generated? (a “no” would mean, e.g., that care providers assigned patients to treatment arms or allowed patients to self-select treatment arms).

- Low risk
(yes)
- High risk (no)
- Unclear

[Clear Response](#)

2. **Allocation concealment:** Describe the method used to conceal the allocation sequence in sufficient detail to determine whether intervention allocations could have been foreseen in advance of, or during, enrolment.

Did the study report a reasonable plan for concealment of allocation? (e.g., use of an opaque envelope to store the allocation key).

- Low risk
- High risk
- Unclear

[Clear Response](#)

3. **Blinding of participants, personnel and outcome assessors** *Assessments should be made for each main outcome (or class of outcomes):* Describe all measures used, if any, to blind study participants and personnel from knowledge of which intervention a participant received. Provide any information relating to whether the intended blinding was effective

3a. Did the study report adequate blinding of participants (was the control group appropriate for the intervention)?

- Low risk
- High risk
- Unclear

[Clear Response](#)

3b. Did the study report adequate blinding of care providers (if different from outcome assessors)

(including assessors of AEs)?

- Low risk
- High risk
- Unclear

[Clear Response](#)

3c. Did the study report adequate blinding of outcome assessors (including assessors of AEs)?

- Low risk
- High risk
- Unclear

[Clear Response](#)

4. **Incomplete outcome data** *Assessments should be made for each main outcome (or class of outcomes)*

4a. Was the loss to follow-up less than 20%?

- Low risk
- High risk
- Unclear

[Clear Response](#)

4b. Were loss-to-follow-up or other missing data explained?

- Low risk
- High risk
- Unclear

[Clear Response](#)

4c. Did the analysis include:

- a) all participants randomized to particular groups
- b) only those who completed the treatment regimen
- c) were crossovers counted as participants in the group they crossed into

- N/A
- Unclear

[Clear Response](#)

5. **Selective outcome reporting:** Did the authors describe measuring outcomes for which they then reported no actual results?

- Low risk
- High risk
- Unclear

[Clear Response](#)

6. **Other sources of bias:** State any important concerns about bias not addressed in the other domains in the tool

6a. Were findings reported as percent who responded (vs. change in assessment score from baseline)?

- Yes
- No
- Unclear
- N/A

[Clear Response](#)

6b. Was a **standardized measurement tool** used (i.e., WOMAC, IALs/ADLs, etc)

- Low risk
- High risk
- Unclear

[Clear Response](#)

6c. Did the authors describe a **washout period** of at least 3 months for steroid injections or 6 months for Hyaluronic acid?

- Low risk
- High risk
- Unclear

[Clear Response](#)

6d. Were co-interventions either avoided in the trial design or did the authors ensure that they were similar between the index and control groups?

- Low risk
- High risk
- Unclear

[Clear Response](#)

Have you reconciled this form with the second reviewer?

- Yes
- No

[Clear Response](#)

3. Ottawa-Newcastle Risk of Bias Assessment for Observational Studies, Adapted

Risk of Bias Assessment for Observational Studies

1. Representativeness/appropriateness of participant selection

Random or consecutive recruitment=Y

Convenience sample=N

Not reported or unclear

2. Control for baseline differences in cohorts

Similarity of groups at baseline or adjustment in analyses=Y

No attempt to control or adjust=N

Not reported=NR

3. Loss to followup

Explanation provided for loss of participants and/or intention to treat=Y

No explanation or no mention of original number=N

4. Masking of exposure to outcomes assessor

Description of masking=Y

No masking or no description =N

5. Ascertainment of condition

Description of ascertainment/diagnostic criteria=Y

No description or patient self-report=N

6. Documentation of other treatment modalities

Documentation=Y

No documentation=N

7. Extent to which valid outcomes are described

Adequate description of outcome=Y

Insufficient detail regarding outcome or follow-up time=N

8. Prespecification of harms, mode of harms collection

Description of a list of harms assessed or monitoring=Y

No such description or passive harms collection=N

No AE collection=NA

9. Financial COI

Funding source described and not manufacturer=Y

Funding source described as manufacturer=N

No funding source mention=NR

10 Investigator COI reported?

No COI=Y

COI=N

Not reported=NR

4. Adverse Events (Questions from McHarms)

1. Were the harms PRE-DEFINED using standardized or precise definitions?

Harms can be defined as the totality of adverse consequences of an intervention or therapy. Harms are the opposite of benefits, against which they are directly compared. The balance between the benefit(s) and harm(s) of an intervention (i.e. drug or surgery) is ideally used to determine its efficacy or effectiveness.

Pre-defined indicates that the harms that were expected are explicitly defined prior to the collection of these expected events. For example, if bleeding is listed as a harmful event, the criteria by which they determine the bleeding (i.e. body location, type, or amount of blood loss that counts as an event, etc) should be specified.

Standardized classification of harms can be derived from any of the following:

1) reference to standard terminology or classifications of harms from a recognized external organization(s)(such as government regulatory or health agencies. Examples of standardized terminology for harms includes, WHO-ART, MEDra, HTA report on the Measurement and Monitoring of Surgical Adverse Events)

2) previously explicitly defined classifications of harms in the literature, or

3) based on pre-specified clinical criteria, or

4) pre-specified laboratory test (may not need to have a specific cut-off level specified in all cases)

In some instances only some of the harms identified in a study will be precisely defined. In

this case, there must be some judgement.

- Yes
- No
- Unclear

[Clear Response](#)

2. Was the mode of harms collection specified as ACTIVE?

Active ascertainment of harms indicates that participants are asked about the occurrence of specific harms in structured questionnaires or interviews or pre-defined laboratory or diagnostic tests and usually performed at pre-specified time intervals.

Passive ascertainment of harms indicates that study participants spontaneously report (on their own initiatives) or are allowed to report harmful events not probed with active ascertainment.

- Yes
- No
- Unclear

[Clear Response](#)

3. Was the potential occurrence of harmful events collected at pre-specified intervals; for example, the occurrence of post-operative complications were evaluated on a daily basis within 30 days of the surgery?

- Yes
- No
- Unclear

[Clear Response](#)

4. Did the author(s) specify the NUMBER for each TYPE of harmful event for each study group?

For example, the study reported 3 types of harmful events (nausea, vomiting, and bleeding); for each of these events the frequency was reported for each study group.

- Yes
- No
- Unclear

[Clear Response](#)

5. Was the TOTAL NUMBER of participants affected by harms specified for each study arm?

- Yes
- No
- Unclear

[Clear Response](#)

6. If the study reported that there were no serious AE's reported did they define serious AEs?

- Yes
- No
- Unclear
- N/A

[Clear Response](#)

Have you reconciled this form with the second reviewer?

- Yes
- No

[Clear Response](#)

5. AMSTAR Assessment of Reporting Quality for Systematic Reviews

1. Was an 'a priori' design provided?

The research question and inclusion criteria should be established before the conduct of the review.

Note: Need to refer to a protocol, ethics approval, or pre-determined/a priori published research objectives to score a “yes.”

- Yes
- No
- Can't answer
- Not applicable

2. Was there duplicate study selection and data extraction?

There should be at least two independent data extractors and a consensus procedure for disagreements should be in place.

Note: 2 people do study selection, 2 people do data extraction, consensus process or one person checks the other's work.

- Yes
- No
- Can't answer
- Not applicable

3. Was a comprehensive literature search performed?

At least two electronic sources should be searched. The report must include years and databases used (e.g., Central, EMBASE, and MEDLINE). Key words and/or MESH terms must be stated and where feasible the search strategy should be provided. All searches should be supplemented by consulting current contents, reviews, textbooks, specialized registers, or experts in the particular field of study, and by reviewing the references in the studies found.

Note: If at least 2 sources + one supplementary strategy used, select “yes” (Cochrane register/Central counts as 2 sources; a grey literature search counts as supplementary).

- Yes
- No
- Can't answer
- Not applicable

4. Was the status of publication (i.e. grey literature) used as an inclusion criterion?

The authors should state that they searched for reports regardless of their publication type. The authors should state whether or not they excluded any reports (from the systematic review), based on their publication status, language etc.

Note: If review indicates that there was a search for “grey literature” or “unpublished literature,” indicate “yes.” SIGLE database, dissertations, conference proceedings, and trial registries are all considered grey for this purpose. If searching a source that contains both grey and non-grey, must specify that they were searching for grey/unpublished lit.

- Yes
- No
- Can't answer
- Not applicable

5. Was a list of studies (included and excluded) provided?
A list of included and excluded studies should be provided.

Note: Acceptable if the excluded studies are referenced. If there is an electronic link to the list but the link is dead, select “no.”

- Yes
- No
- Can't answer
- Not applicable

6. Were the characteristics of the included studies provided?
In an aggregated form such as a table, data from the original studies should be provided on the participants, interventions and outcomes. The ranges of characteristics in all the studies analyzed e.g., age, race, sex, relevant socioeconomic data, disease status, duration, severity, or other diseases should be reported.

Note: Acceptable if not in table format as long as they are described as above.

- Yes
- No
- Can't answer
- Not applicable

7. Was the scientific quality of the included studies assessed and documented?
'A priori' methods of assessment should be provided (e.g., for effectiveness studies if the author(s) chose to include only randomized, double-blind, placebo controlled studies, or allocation concealment as inclusion criteria); for other types of studies alternative items will be relevant.

Note: Can include use of a quality scoring tool or checklist, e.g., Jadad scale, risk of bias, sensitivity analysis, etc., or a description of quality items, with some kind of result for EACH study (“low” or “high” is fine, as long as it is clear which studies scored “low” and which scored “high”; a summary score/range for all studies is not acceptable).

- Yes
- No
- Can't answer
- Not applicable

8. Was the scientific quality of the included studies used appropriately in formulating conclusions?

The results of the methodological rigor and scientific quality should be considered in the analysis and the conclusions of the review, and explicitly stated in formulating recommendations.

Note: Might say something such as “the results should be interpreted with caution due to poor quality of included studies.” Cannot score “yes” for this question if scored “no” for question 7.

- Yes
- No
- Can't answer
- Not applicable

9. Were the methods used to combine the findings of studies appropriate?

For the pooled results, a test should be done to ensure the studies were combinable, to assess their homogeneity (i.e., Chi-squared test for homogeneity, I²). If heterogeneity exists a random effects model should be used and/or the clinical appropriateness of combining should be taken into consideration (i.e., is it sensible to combine?).

Note: Indicate “yes” if they mention or describe heterogeneity, i.e., if they explain that they cannot pool because of heterogeneity/variability between interventions.

- Yes
- No
- Can't answer
- Not applicable

10. Was the likelihood of publication bias assessed?

An assessment of publication bias should include a combination of graphical aids (e.g., funnel plot, other available tests) and/or statistical tests (e.g., Egger regression test, Hedges-Olken).

Note: If no test values or funnel plot included, score “no”. Score “yes” if mentions that publication bias could not be assessed because there were fewer than 10 included studies.

- Yes
- No
- Can't answer
- Not applicable

11. Was the conflict of interest included?

Potential sources of support should be clearly acknowledged in both the systematic review and the included studies.

Note: To get a “yes,” must indicate source of funding or support for the systematic

review AND for each of the included studies.

- Yes
- No
- Can't answer
- Not applicable

Shea et al. BMC Medical Research Methodology 2007 7:10 doi:10.1186/1471-2288-7-10

Additional notes (in italics) made by Michelle Weir, Julia Worswick, and Carolyn Wayne based on conversations with Bev Shea and/or Jeremy Grimshaw in June and October 2008 and July and September 2010.

Appendix E. Non-English Language Article Abstracts Reviewed

Non-English Language Articles with English Abstracts: Assessment of a Random Selection

ID/ Author, year, language	Design	Intervention	N, participant demographics	Outcomes
161/Not reported, 2012, Finnish	Care guidelines	Multiple	Not applicable (NA)	NA
180/Alhoff, 1998, German	CCT	HA vs. std care, 6 months	179 gonarthrosis patients	Cost-effectiveness in terms of treatment cost and productivity, Lequesne and Euroquol for pain and mobility 92.4% of all patients under HYA achieved optimum values of Euroquol for general satisfaction vs. 42.9% in the reference group
254/Borras-Verdera, 2012, Spanish	Open uncontrolled trial	1 injection HA + mannitol, periodic followup (FU) for 6 months	79 pts. with painful knee OA	VAS WOMAC for pain and joint function, safety, need for rescue medication: % of patients who improved + effect A significant reduction in joint pain, stiffness and functional disability compared with baseline was observed at every follow-up visit (P<.001). Joint function improved by 38.7% on Day 30, reaching 47.5% on Day 180
296/Chen, 2002, Chinese	Open uncontrolled trial	3 weekly HA injections, 1-6 month FU	96 pts	Lysholm scoring, clinical signs, mobility, safety: % of patients who improved + outcome obvious improvements in the signs and function of knee in 39 patients (40.6%), only some improvements in 48 patients (50.0%), and no obvious

				improvements in other 9 patients (9.4%). The total effectiveness rate was 74.0%
335/Dai, 2002, Chinese	controlled trial	Weekly HA injections, variable number	310 postop pts (arthroscopy or open)	Average VAS score for pain, time to maximum painless ROM after arthroscopy + effect: The VAS score of patients in the treatment group was significant lower than that of the control group. The period to the maximal painless ROM of the joint was 6 days in the treatment group after open operation, while 9 days in the control group
342/Diehl, 2013, German	review	Knee OA: Multiple treatment modalities	NA	NA (no real conclusions except that HA is safe and provide shortterm symptom relief)
348/Dougados, 1994/French	Evaluation of arthroscopy to assess cartilage lesions and changes due to treatment (chondroscopy)	Preliminary study of repeated HA injections to test applicability, sensitivity of chondroscopy to visualize changes in cartilage	Not reported	Not relevant
379/Fukuda, 2004, Japanese	Non-systematic review	HA injection	Findings suggest HA effective for joint cellular and immune function but insufficient evidence on its effect on progression	
380/Gadek, 2011, Polish	No study details	HA injection (Suplasyn)	Not reported	Study "reconfirmed effectiveness and safety..." No data in abstract
381/Galus, 2006, Polish	Non-systematic review on uses of HA			No mention of efficacy
409/Gu, 2011, Chinese	Non-systematic review on use of HA			Mentions evidence from insurers
422/He, 2012	Case control study (really a trial) of HA + exercise vs. HA			No useful findings for this report, as HA was control
431/Heybeli 2008	Post arthroscopic HA vs. no treatment	Post-surgical Orthovisc injection	67 patients 40-65 years of age	Improvement in pain scores at 6 weeks did not differ between the two groups (HA 21%,

				control 16%; p=0.478), whereas improvement in function scores was significantly higher in the HA group (23% vs 9.2%; p=0.018)
443/ Hu 2006	RCT	HA vs. ligustrazine, 5 tx, 63 month followup	71 cases (82 knees)	There was significant decrease in Lequesne's index in SH group after the treatment (P<0.01), but not in LI group (P>0.05). Three weeks later, there was significant decrease in Lequesne's index in both groups after the treatment (P<0.01), with no significant difference between SH and LI group (P>0.05). After the 5-week treatment, the efficacy rate of the LI group was 82.1%, and that of the SH group was 87.2%
466/ Ishikawa 2002 Japanese	NSR on HA for knee and shoulder			NR
517/Krocker 2006 German	Uncontrolled trial	Single injection of Durolane, synthetic HA, 24 weeks followup	50 patients with primary OA	KOOS, VAS, and EQ-5D, as well as motion of the knee. At 2 wks: the subjective function of knee and quality of life had increased significantly. At 24 wks, all parameters increased significantly (quality of life and activity +19%; range of motion active 109 vs. 115 degrees ; pain, 55 vs. 41 mm (VAS); all p<0.01)
520/Kuiper-Geertsma 2000 Dutch	NSR			NR
542/Li 2011 Chinese	RCT	Comparison of PRP and HA: 3 injections at 3-week intervals, 6-month followup	30 patients	International Knee Documentation Committee (IKDC) score, WOMAC score, and Lequesne index significant differences in IKDC score, WOMAC score, and

				Lequesne index between pre- and post-injection in 2 groups ($P < 0.05$); no significant difference was found between different time points (3, 4, and 6 months) in test group ($P > 0.05$), while significant differences were found between the postoperative 6th month and the postoperative 3rd and 4th months in control group ($P < 0.05$). There was no significant difference in IKDC score, WOMAC score, and Lequesne index between 2 groups within 4 months ($P > 0.05$), but the effectiveness of test group was significantly better than that of control group at 6 months after injection ($P < 0.05$)
544/ Li 2009, Chinese	Uncontrolled trial of acupuncture effect on HA			NR
545/Liang 2010	Double blind placebo controlled RCT	HA vs. CS? , duration not reported	Sample size unknown	Findings unclear: HA better than CS?
ID #546 Ling 2002, IDs #563, 568,	NSR NSRs			NA
ID#578 Mar 2013 Spanish	Dataset analysis and modeling of 10-year budget impact	HA injection	Patients awaiting knee replacement	Modeling estimates that HA can delay TKR by 2.67 years. Leading to significant cost saving
ID# 587 Marson 2007 Italian	NSR			
ID# 602 Menshikova 2007 Russian	Uncontrolled trial	ostenil (HA)	60 OA patients, mean age 65	Significant improvement was seen in 60% patients. Pain and stiffness in the knee joint relieved 2-fold. The function improved less. OA severity by Leken's index decreased by two degrees. 20% patients stopped

				intake of NAD, 32% had no need in taking NAD regularly. Subjective and objective assessment (by the patient and by the doctor) of the symptoms severity improved twice. Twelve months later the
ID# 616 Mitner 2001 German	Controlled trial (patients were own controls: blinding unclear)	HA, 5 weekly injections	43 patients with bilateral knee OA	In knees treated with hyaluronic acid the mean peak torque of the knee extensor was 57 +/- 26.15/32 +/- 19.63 Nm vs. 77.17 +/- 32.54/47.83 +/- 21.43 Nm after (p < 0.01), the mean peak torque of the knee flexor was 40.44 +/- 21.58/22.89 +/- 16.64 Nm vs. 53.55 +/- 24.26/34.05 +/- 17.37 Nm after treatment (p < 0.01) at the angular velocities of 60 degrees/s and 180 degrees/s. Significant differences (p > 0.01) between treated and untreated knee were found for total work of the extensor and flexor of the knee. The pain at rest decreased from 3.83 +/- 1.72 cm to 1.36 +/- 1.42 cm and the pain under load decreased from 7.57 +/- 1.34 cm to 3.75 +/- 1.32 cm in the treated knee group (p < 0.01)
634/Navarro 2006 Spanish	Uncontrolled trial	HA, 5 weekly injections	111 patients	Significant improvement in all efficacy variables
642/Noain 2002 Spanish	Case reports			2 reports of acute local reactions
644/Nozaki 2002 Japanese	NSR			
647/Okuda 1994 Japanese	Not OA, not study of HA			

Appendix F. Table Hyaluronic Acid Products Indicated for Treatment of OA of the Knee but Not Approved in the US

Product Name	Molecular Weight	Source	US Equivalent	Manufacturer
Adant	900 kD	Synthetic *	None	Meiji Seika Pharma Co., Ltd. Japan
Artz	620-1170kD	Avian	Supartz	Seikagaku Corporation Japan
BioHy	600-3000kD	Synthetic	Euflexxa	Biotechnology General Corp./Savient
Durolane	1000kD	Avian	None	Q-Med
Go-on	800-1500kD	Synthetic	None	Rottapharm Madaus, Monza, Italy
Hyaject	1500kD	Synthetic	Unclear	Ormed Gmbh Germany
Hyalart	750kD	Avian	Hyalgan?	MEDA Manufacturing GmbH
Hyalubrix	1500-3200kD	Synthetic	None	Fidia
Hylan GF-20	600kD	Avian	Synvisc	
Hyruan	3000kD	n/a	None	LG Life Science
Ostenil	1200-1400kD	Synthetic	None	TRB Chemedica Ltd. UK
Sinovial	800-1200kD	Avian	None	IBSA Gulf Kingdom of Saudi Arabia
Suplasyn	500-730kD	Synthetic	Hyalgan	Alveda/Mylan

*Purified from a cultured strain of Streptococcus via fermentation

Appendix G. Strength of Evidence Assessment Required Domains: Definitions and Scores

Appendix Table. Grading the strength of a body of evidence: Required domains and their definitions*

Domain	Definition and Elements	Score and Application
Study Limitations	<p>Study limitations are the degree to which the included studies for a given outcome or comparison have a high likelihood of adequate protection against bias (i.e., good internal validity), assessed through two main elements:</p> <ul style="list-style-type: none"> • Study design (e.g., RCTs or observational studies) • Aggregate quality of the studies under consideration. <p>Information for this determination comes from the rating of quality (good/fair/poor) done for individual studies</p>	<p>Use one of three levels of, separately by type of study design:</p> <ul style="list-style-type: none"> • Low level of study limitations • Medium level of study limitations • High level of study limitations
Consistency	<p>The principal definition of consistency is the degree to which reported effect sizes from included studies appear to have the same direction of effect. This can be assessed through two main elements:</p> <ul style="list-style-type: none"> • Effect sizes have the same sign (that is, are on the same side of “no effect”) • The range of effect sizes is narrow. 	<p>Use one of three levels of consistency:</p> <ul style="list-style-type: none"> • Consistent (i.e., no inconsistency) • Inconsistent • Unknown or not applicable (e.g., single study) <p>As noted in the text, single-study evidence bases (even mega-trials) cannot be judged with respect to consistency. In that instance, use “Consistency unknown (single study).”</p>

Domain	Definition and Elements	Score and Application
Directness	<p>The rating of directness relates to whether the evidence links the interventions directly to health outcomes. For a comparison of two treatments, directness implies that head-to-head trials measure the most important health or ultimate outcomes.</p> <p>Two types of directness, which can coexist, may be of concern: Evidence is indirect if:</p> <ul style="list-style-type: none"> • It uses intermediate or surrogate outcomes instead of health outcomes. In this case, one body of evidence links the intervention to intermediate outcomes and another body of evidence links the intermediate to most important (health or ultimate) outcomes. • It uses two or more bodies of evidence to compare interventions A and B -- e.g., studies of A vs. placebo and B vs. placebo, or studies of A vs. C and B vs. C but not A vs. B. <p>Indirectness always implies that more than one body of evidence is required to link interventions to the most important health outcomes.</p> <p>Directness may be contingent on the outcomes of interest. EPC authors are expected to make clear the outcomes involved when assessing this domain.</p>	<p>Score dichotomously as one of two levels directness</p> <ul style="list-style-type: none"> • Direct • Indirect <p>If indirect, specify which of the two types of indirectness account for the rating (or both, if that is the case) -- namely, use of intermediate/surrogate outcomes rather than health outcomes, and use of indirect comparisons. Comment on the potential weaknesses caused by, or inherent in, the indirect analysis. The EPC should note if both direct and indirect evidence was available, particularly when indirect evidence supports a small body of direct evidence.</p>
Precision	<p>Precision is the degree of certainty surrounding an effect estimate with respect to a given outcome (i.e., for each outcome separately)</p> <p>If a meta-analysis was performed, this will be the confidence interval around the summary effect size.</p>	<p>Score dichotomously as one of two levels of precision:</p> <ul style="list-style-type: none"> • Precise • Imprecise <p>A precise estimate is an estimate that would allow a clinically useful conclusion. An imprecise estimate is one for which the confidence interval is wide enough to include clinically distinct conclusions. For example, results may be statistically compatible with both clinically important superiority and inferiority (i.e., the direction of effect is unknown), a circumstance that will preclude a valid conclusion.</p>
	<p>Reporting bias results from selectively publishing or reporting research findings based on the favorability of direction or magnitude of effect. It includes:</p> <ul style="list-style-type: none"> • Study publication bias, i.e., nonreporting of the full study. • Selective outcome reporting bias, i.e., nonreporting (or incomplete reporting) of planned outcomes or reporting of unplanned outcomes. • Selective analysis reporting bias, i.e., reporting of one or more favorable analyses for a given outcome while not reporting other, less favorable analyses. <p>Assessment of reporting bias for individual studies depends on</p>	<p>Score as one of two levels:</p> <ul style="list-style-type: none"> • Suspected • Undetected <p>Reporting bias is suspected when:</p> <ul style="list-style-type: none"> • Testing for funnel plot asymmetry demonstrates a substantial likelihood of bias, <p>And/or</p> <ul style="list-style-type: none"> • A qualitative assessment suggests the likelihood of missing studies,

Domain	Definition and Elements	Score and Application
	<p>many factors—e.g. availability of study protocols, unpublished study documents, and patient-level data. Detecting such bias is likely with access to all relevant documentation and data pertaining to a journal publication, but such access is rarely available.</p> <p>Because methods to detect reporting bias in observational studies are less certain, this guidance does not require EPCs to assess it for such studies</p>	<p>analyses, or outcomes data that may alter the conclusions from the reported evidence.</p> <p>Undetected reporting bias includes all alternative scenarios</p>

*Adapted from Berkman, N. D., et al. (2008). Grading the Strength of a Body of Evidence When Assessing Health Care Interventions for the Effective Health Care Program of the Agency for Healthcare Research and Quality: An Update. Methods Guide for Effectiveness and Comparative Effectiveness Reviews. Rockville (MD).

Appendix H. Tools to Measure Function

Index of Severity for Osteoarthritis of the Hip by Lequesne et al.

Overview:

Lequesne et al developed an index of severity for osteoarthritis for the hip (ISH). This can be used to assess the effectiveness of therapeutic interventions.

Sections for index:

(1) pain or discomfort

(2) maximum distance walked

(3) activities of daily living

I Pain or Discomfort

Parameter	Finding	Points
pain or discomfort during nocturnal bedrest	none	0
	only on movement or in certain positions	1
	without movement	2
duration of morning stiffness or pain after getting up	none	0
	< 15 minutes	1
	>= 15 minutes	2
remaining standing for 30 minutes increases pain	no	0
	yes	1
pain on walking	none	0
	only after walking some distance	1
	early after starting	2
pain or discomfort in sitting position for 2 hours	no	0
	yes	1

where:

- A modification of a 1991 version was to have the duration of morning stiffness scored 0 if it was 1 minute or less and 1 if it was from 1 to less than 15 minutes.
- Pain on walking in a 1991 version expanded "early after starting" to "after initial ambulation and increasingly with continued ambulation"

II. Maximum Distance Walked

Parameter	Finding	Points
maximum distance walked	unlimited	0
	> 1 kilometer but limited	1
	about 1 kilometer (about 15 minutes)	2
	about 500 - 900 meters (about 8-15 minutes)	3
	from 300 - 500 meters	4
	from 100 - 300 meters	5
walking aids required	< 100 meters	6
	none	0
	1 walking stick or crutch	1
	2 walking sticks or crutches	2

III. Activities of Daily Living

Parameter	Finding	Points
Can you put on socks by bending forward?	easily	0
	with mild difficulty	0.5
	with moderate difficulty	1.0
	with marked difficulty	1.5
	impossible	2.0
Can you pick up an object from the floor?	easily	0
	with mild difficulty	0.5
	with moderate difficulty	1.0
	with marked difficulty	1.5
	impossible	2.0
Can you go up and down a standard flight of stairs?	easily	0
	with mild difficulty	0.5
	with moderate difficulty	1.0
	with marked difficulty	1.5
	impossible	2.0
Can you get into and out of a car?	easily	0

	with mild difficulty	0.5
	with moderate difficulty	1.0
	with marked difficulty	1.5
	impossible	2.0

index of severity =

= SUM(points for all parameters)

Interpretation:

- minimum points for each section: 0
- maximum points for each section: 8
- minimum index score: 0
- maximum index score: 24

Index Score	Handicap
0	none
1 - 4	mild
5 - 7	moderate
8 - 10	severe
11 - 13	very severe
>= 14	extremely severe

Modifications to Index

The index was modified in 1991 (Table 2) by the addition of a question for sexual activity in sexually active women being evaluated for hip prosthesis. This was graded as for the activities of daily living. This results in a maximum index score of 26.

The index was modified in 1997 with some minor changes to morning stiffness and termed the "algofunctional index".

References:

Lequesne M Mery C et al. Indexes of severity for osteoarthritis of the hip and knee. Scand J Rheumatology. 1987; Supplement 65: 85-89.

Lequesne M. Indices of severity and disease activity for osteoarthritis. Seminars in Arthritis and Rheumatism. 1991; 20 (supplement 2): 48-54.

Lequesne MG. The algofunctional indices for hip and knee osteoarthritis. J Rheumatol. 1997; 24: 779-781.



Health Questionnaire

***English version for the UK
(validated for Ireland)***

SAMPLE

By placing a tick in one box in each group below, please indicate which statements best describe your own health state today.

Mobility

- I have no problems in walking about
- I have some problems in walking about
- I am confined to bed

Self-Care

- I have no problems with self-care
- I have some problems washing or dressing myself
- I am unable to wash or dress myself

Usual Activities (e.g. work, study, housework, family or leisure activities)

- I have no problems with performing my usual activities
- I have some problems with performing my usual activities
- I am unable to perform my usual activities

Pain/Discomfort

- I have no pain or discomfort
- I have moderate pain or discomfort
- I have extreme pain or discomfort

Anxiety/Depression

- I am not anxious or depressed
- I am moderately anxious or depressed
- I am extremely anxious or depressed

Best
imaginable
health state

100



90

80

70

60

50

40

30

20

10

0

Worst
imaginable
health state

To help people say how good or bad a health state is, we have drawn a scale (rather like a thermometer) on which the best state you can imagine is marked 100 and the worst state you can imagine is marked 0.

We would like you to indicate on this scale how good or bad your own health is today, in your opinion. Please do this by drawing a line from the box below to whichever point on the scale indicates how good or bad your health state is today.

**Your own
health state
today**

SAMPLE



RAND » RAND Health » Surveys and Tools » Medical Outcomes Study » 36-Item Short Form Survey Instrument

Medical Outcomes Study: 36-Item Short Form Survey Instrument

RAND 36-Item Health Survey 1.0 Questionnaire Items

Unformatted version

1. In general, would you say your health is:	
Excellent	1
Very good	2
Good	3
Fair	4
Poor	5

2. Compared to one year ago, how would you rate your health in general now?	
Much better now than one year ago	1
Somewhat better now than one year ago	2
About the same	3
Somewhat worse now than one year ago	4
Much worse now than one year ago	5

The following items are about activities you might do during a typical day. Does **your health now limit you** in these activities? If so, how much?

(Circle One Number on Each Line)

	Yes, Limited a Lot	Yes, Limited a Little	No, Not limited at All
3. Vigorous activities , such as running, lifting heavy objects, participating in strenuous sports	[1]	[2]	[3]
4. Moderate activities , such as moving a table, pushing a vacuum cleaner, bowling, or playing golf	[1]	[2]	[3]
5. Lifting or carrying groceries	[1]	[2]	[3]
6. Climbing several flights of stairs	[1]	[2]	[3]
7. Climbing one flight of stairs	[1]	[2]	[3]
8. Bending, kneeling, or stooping	[1]	[2]	[3]
9. Walking more than a mile	[1]	[2]	[3]
10. Walking several blocks	[1]	[2]	[3]
11. Walking one block	[1]	[2]	[3]
12. Bathing or dressing yourself	[1]	[2]	[3]

During the **past 4 weeks**, have you had any of the following problems with your work or other regular daily activities as a result of your **physical health**?

(Circle One Number on Each Line)

	Yes	No
13. Cut down the amount of time you spent on work or other activities	1	2
14. Accomplished less than you would like	1	2
15. Were limited in the kind of work or other activities	1	2
16. Had difficulty performing the work or other activities (for example, it took extra effort)	1	2

During the **past 4 weeks**, have you had any of the following problems with your work or other regular daily activities as a result of any **emotional problems** (such as feeling depressed or **anxious**)?

(Circle One Number on Each Line)

	Yes	No
17. Cut down the amount of time you spent on work or other activities	1	2
18. Accomplished less than you would like	1	2
19. Didn't do work or other activities as carefully as usual	1	2

20. During the **past 4 weeks**, to what extent has your physical health or emotional problems interfered with your normal social activities with family, friends, neighbors, or groups?

(Circle One Number)

Not at all 1

Slightly 2

Moderately 3

Quite a bit 4

Extremely 5

21. How much **bodily pain** have you had during the **past 4 weeks**?

(Circle One Number)

None 1

Very mild 2

Mild 3

Moderate 4

Severe 5

Very severe 6

22. During the **past 4 weeks**, how much did **pain** interfere with your normal work (including both work outside the home and housework)?

(Circle One Number)

Not at all 1

A little bit 2

Moderately 3

Quite a bit 4

Extremely 5

These questions are about how you feel and how things have been with you **during the past 4 weeks**. For each question, please give the one answer that comes closest to the way you have been feeling.

How much of the time during the **past 4 weeks** . . .

(Circle One Number on Each Line)

	All of the Time	Most of the Time	A Good Bit of the Time	Some of the Time	A Little of the Time	None of the Time
23. Did you feel full of pep?	1	2	3	4	5	6
24. Have you been a very nervous person?	1	2	3	4	5	6
25. Have you felt so down in the dumps that nothing could cheer you up?	1	2	3	4	5	6
26. Have you felt calm and peaceful?	1	2	3	4	5	6
27. Did you have a lot of energy?	1	2	3	4	5	6
28. Have you felt downhearted and blue?	1	2	3	4	5	6
29. Did you feel worn out?	1	2	3	4	5	6
30. Have you been a happy person?	1	2	3	4	5	6
31. Did you feel tired?	1	2	3	4	5	6

32. During the **past 4 weeks**, how much of the time has your **physical health or emotional problems** interfered with your social activities (like visiting with friends, relatives, etc.)?

(Circle One Number)

All of the time 1

Most of the time 2

Some of the time 3

A little of the time 4

None of the time 5

How TRUE or FALSE is each of the following statements for you.


(Circle One Number on Each Line)

	Definitely True	Mostly True	Don't Know	Mostly False	Definitely False
33. I seem to get sick a little easier than other people	1	2	3	4	5
34. I am as healthy as anybody I know	1	2	3	4	5
35. I expect my health to get worse	1	2	3	4	5
36. My health is excellent	1	2	3	4	5

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WOMAC OSTEOARTHRITIS INDEX VERSION LK3.0**INSTRUCTIONS TO PATIENTS**

In Sections A, B and C questions will be asked in the following format and you should give your answers by putting an "X" in one of the boxes.

NOTE:

1. If you put your "X" in the left-hand box, i.e.

None	Mild	Moderate	Severe	Extreme
<input checked="" type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>

then you are indicating that you have no pain.

2. If you put your "X" in the right-hand box, i.e.

None	Mild	Moderate	Severe	Extreme
<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input checked="" type="checkbox"/>

then you are indicating that your pain is extreme.

3. Please note:

- that the further to the right you place your "X" the more pain you are experiencing.
- that the further to the left you place your "X" the less pain you are experiencing.
- please do not place your "X" outside the box.

You will be asked to indicate on this type of scale the amount of pain, stiffness or disability you have experienced in the last 48 hours.

Remember the further you place your "X" to the right, the more pain, stiffness or disability you are indicating that you experienced. Finally, please note that you are to complete the questionnaire with respect to your study joint(s). You should think about your study joint(s) when answering the questionnaire, i.e., you should indicate the severity of your pain, stiffness and physical disability that you feel is caused by arthritis in your study joint(s). Your study joint(s) has been identified for you by your health care professional. If you are unsure which joint(s) is your study joint, please ask before completing the questionnaire.

Section A

INSTRUCTIONS TO PATIENTS

The following questions concern the amount of pain you have experienced due to arthritis in your study joint(s). For each situation please enter the amount of pain experienced in the last 48 hours. (Please mark your answers with an "X".)

QUESTION: How much pain do you have?

1. Walking on a flat surface.

None	Mild	Moderate	Severe	Extreme
<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>

2. Going up or down stairs.

None	Mild	Moderate	Severe	Extreme
<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>

3. At night while in bed.

None	Mild	Moderate	Severe	Extreme
<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>

4. Sitting or lying.

None	Mild	Moderate	Severe	Extreme
<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>

5. Standing upright.

None	Mild	Moderate	Severe	Extreme
<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>



Section B

INSTRUCTIONS TO PATIENTS

The following questions concern the amount of joint stiffness (not pain) you have experienced in the last 48 hours in your study joint(s). Stiffness is a sensation of restriction or slowness in the ease with which you move your joints. (Please mark your answers with an "X".)

6. How severe is your stiffness after first wakening in the morning?

None	Mild	Moderate	Severe	Extreme
<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>

7. How severe is your stiffness after sitting, lying or resting later in the day?

None	Mild	Moderate	Severe	Extreme
<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>



Section C

INSTRUCTIONS TO PATIENTS

The following questions concern your physical function. By this we mean your ability to move around and to look after yourself. For each of the following activities, please indicate the degree of difficulty you have experienced in the last 48 hours due to arthritis in your study joint(s). (Please mark your answers with an "X".)

QUESTION: What degree of difficulty do you have?

- | | | | | | |
|----------------------------|--------------------------|--------------------------|--------------------------|--------------------------|--------------------------|
| 8. Descending stairs. | None | Mild | Moderate | Severe | Extreme |
| | <input type="checkbox"/> | <input type="checkbox"/> | <input type="checkbox"/> | <input type="checkbox"/> | <input type="checkbox"/> |
| 9. Ascending stairs. | None | Mild | Moderate | Severe | Extreme |
| | <input type="checkbox"/> | <input type="checkbox"/> | <input type="checkbox"/> | <input type="checkbox"/> | <input type="checkbox"/> |
| 10. Rising from sitting. | None | Mild | Moderate | Severe | Extreme |
| | <input type="checkbox"/> | <input type="checkbox"/> | <input type="checkbox"/> | <input type="checkbox"/> | <input type="checkbox"/> |
| 11. Standing. | None | Mild | Moderate | Severe | Extreme |
| | <input type="checkbox"/> | <input type="checkbox"/> | <input type="checkbox"/> | <input type="checkbox"/> | <input type="checkbox"/> |
| 12. Bending to floor. | None | Mild | Moderate | Severe | Extreme |
| | <input type="checkbox"/> | <input type="checkbox"/> | <input type="checkbox"/> | <input type="checkbox"/> | <input type="checkbox"/> |
| 13. Walking on flat. | None | Mild | Moderate | Severe | Extreme |
| | <input type="checkbox"/> | <input type="checkbox"/> | <input type="checkbox"/> | <input type="checkbox"/> | <input type="checkbox"/> |
| 14. Getting in/out of car. | None | Mild | Moderate | Severe | Extreme |
| | <input type="checkbox"/> | <input type="checkbox"/> | <input type="checkbox"/> | <input type="checkbox"/> | <input type="checkbox"/> |
| 15. Going shopping. | None | Mild | Moderate | Severe | Extreme |
| | <input type="checkbox"/> | <input type="checkbox"/> | <input type="checkbox"/> | <input type="checkbox"/> | <input type="checkbox"/> |



16. Putting on socks/stockings.
 None Mild Moderate Severe Extreme

17. Rising from bed.
 None Mild Moderate Severe Extreme

18. Taking off socks/stockings.
 None Mild Moderate Severe Extreme

19. Lying in bed.
 None Mild Moderate Severe Extreme

20. Getting in/out of bath.
 None Mild Moderate Severe Extreme

21. Sitting.
 None Mild Moderate Severe Extreme

22. Getting on/off toilet.
 None Mild Moderate Severe Extreme

23. Heavy domestic duties.
 None Mild Moderate Severe Extreme

24. Light domestic duties.
 None Mild Moderate Severe Extreme

PFTN16 _____

PFTN17 _____

PFTN18 _____

PFTN19 _____

PFTN20 _____

PFTN21 _____

PFTN22 _____

PFTN23 _____

PFTN24 _____

THANK YOU FOR COMPLETING THE QUESTIONNAIRE