

Evidence scan:

Hyaluronic acid injections for osteoarthritis of the knee

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1 Purpose & background

Hyaluronic acid (HA) is a polymer with viscoelastic properties. It is present in the synovial fluid of the knee and other joints. Intra-articular injections of HA are sometimes used to treat pain associated with osteoarthritis (OA) of the knee. This treatment is also known as *viscosupplementation*.

ACC's 2005 interventional pain management (IPM) guidance recommended that intra-articular HA injections may be considered for patients with knee OA that has not responded to corticosteroid injectionsⁱ. The evidence on which the 2005 recommendation was based was graded "B", which means it was of "fair" or medium quality.

Several HA products are now available and there is currently no reliable evidence that any one brand is superior to others. In New Zealand, Synvisc (Hylan G-F 20) appears to be the most commonly used HA product. ACC funds a small number of claims for Synvisc, i.e. up to ten claims per year. Requests to fund Synvisc and other HA products are increasing, but the volume of requests is still relatively low. Most requests are made by orthopaedic surgeons. An HA injection costs ACC around \$650 excluding GST.

The Evidence Based Healthcare team has been asked to examine the recent evidence for this intervention and develop up to date recommendations. The purposes of this pragmatic, rapid evidence scan are therefore to:

1. Identify and summarise recent, high quality evidence on the effectiveness of intra-articular HA injections for pain associated with OA of the knee.
2. Outline current guideline recommendations and payer policies on use and funding of this intervention.
3. Determine whether ACC's current recommendation on this intervention needs to change to reflect current evidence and guidelines.
4. Propose a purchasing recommendation for this intervention.

2 Methods

2.1 Literature search

To identify recent evidence, a search of the following sources was carried out in June 2016. Details of the search strategies are included in Appendix 6.1.

- Cochrane Library, <http://www.cochranelibrary.com/>
- Medline In-Process (Ovid platform)
- CRD databases, <http://www.crd.york.ac.uk/CRDWeb/>
- DynaMed Plus
- Medline (Ovid platform)
- Embase (Ovid platform)
- TRIP database, <https://www.tripdatabase.com/index.html>

2.2 Selection criteria

For evidence on effectiveness in reducing pain and improving function and on product safety, a pragmatic approach focusing on the most recent, highest quality evidence was taken. Inclusion was therefore limited to systematic reviews, meta-analyses and health technology assessments published in or after 2013. Studies that compared HA injections with therapies considered experimental, e.g. platelet rich plasma (PRP), were excluded.

Relevant clinical guidelines were included if developed using an evidence based methodology and published in or after 2013. Their methods and key recommendations on HA injections are summarised below.

Current overseas payer policies on HA injections for OA of the knee were identified for information on whether and in what circumstances other insurers fund this intervention.

ⁱ See *Hyaluronic acid for knee pain*, http://www.acc.co.nz/for-providers/clinical-best-practice/interventional-pain-management/interventions/intervention-index/WCM1_033946

3 Findings

3.1 Systematic reviews, meta-analyses and health technology assessments

Eleven systematic reviews and/or meta-analyses and one health technology assessment were identified. They are summarised in Table 1 below, A to Z by author:

Table 1: systematic reviews, meta-analyses & health technology assessments		
Study details	Findings & conclusions	Comments
<p>Agency for Healthcare Research and Quality (AHRQ). Systematic review of HA in the treatment of severe degenerative joint disease of the knee (2015)¹</p> <p>Includes reviews, randomised controlled trials (RCTs), observational studies & unpublished data</p> <p>Commissioned by the US Department of Health as part of AHRQ's technology assessment program</p>	<ul style="list-style-type: none"> Based on 2 systematic reviews, 25 RCTs, 20 case series or prospective studies and 18 case reports There is moderate strength evidence that HA reduces pain, on average, by an amount roughly equivalent to the minimum clinically important difference (based on two good quality systematic reviews^{2 3}) There is low strength evidence that HA modestly improves function compared to placebo: <i>"Trials enrolling older participants show a small, statistically significant effect of HA on function. Whether this effect is clinically meaningful is less clear"</i> There is moderate strength evidence that serious adverse events with HA are rare The strength of the evidence is insufficient to draw conclusions on whether HA can delay or avoid the need for total knee replacement There is insufficient evidence from head-to-head trials to say whether one HA product is better than another The strength of the evidence is insufficient to draw conclusions on HA's overall effect on quality of life 	<p>Robust methodology</p> <p>First review to synthesize the evidence on HA & delay/avoidance of knee replacement surgery</p> <p>Conclusions on function focused on people aged 65 plus; applicability to patients aged under 65 may therefore be limited</p> <p>Noted that the majority of HA trials identified were of mediocre quality & failed to meet criteria for low risk of bias, primarily due to inadequate reporting</p>
<p>Altman et al (2015)⁴</p> <p>Systematic review comparing the methodology & recommendations of clinical practice guidelines on HA injections for knee OA</p>	<p>Ten guidelines were identified and appraised using the AGREE II instrument⁵. Their methodology was found to vary with regard to inclusion criteria, analysis of evidence, formulation of recommendations and guideline group composition. As a result, their recommendations are highly inconsistent:</p> <ul style="list-style-type: none"> Three recommend against HA for knee OA. Three say the intervention is appropriate in specified circumstances Four are uncertain or make no recommendation <p>Conclusion: inconsistent guideline recommendations make it difficult for clinicians to judge the appropriateness of HA injections for knee OA</p>	<p>Confirms what was already suspected re guideline variability</p> <p>Search and appraisal methodology appear robust</p> <p>Review was industry sponsored</p> <p>The four most recent guidelines are included in this evidence scan & are summarised in Table 2 below</p>

<p>Bannuru et al (2015)²</p> <p>Systematic review & meta-analysis of oral and intra-articular (IA) pharmacological interventions for knee OA</p> <p>Used network meta-analysis to estimate comparative efficacy of all interventions relative to each other</p>	<p>Identified 137 RCTs involving 33,000+ participants; for HA; 52 studies compared HA to IA placebo and 12 compared HA to IA corticosteroids (n=4806). Analysis at three months found that:</p> <ul style="list-style-type: none"> • Pain: all interventions (except paracetamol) significantly out-performed oral placebo • HA injection was the most efficacious pain intervention with an effect size of 0.63 (95% credible interval [CI] 0.39 to 0.88) vs. oral placebo, 0.34 (95% CI 0.26 to 0.42) vs. IA placebo and 0.02 (95% CI -0.12 to 0.17) vs. IA corticosteroids • Function: all interventions except IA corticosteroids significantly out-performed oral placebo. Stiffness: there were no significant differences between interventions <p>Conclusion: IA interventions were superior to oral non-steroidal anti-inflammatory drugs (NSAIDs), possibly due to the integrated IA placebo effect</p>	<p>Noted a lack of long term data, inadequate reporting of safety data, possible publication bias and few head-to-head comparisons</p> <p>Suggested that effect sizes of IA interventions may have been boosted by placebo effects associated with IA delivery</p> <p>Review funded by AHRQ</p>
<p>Bannuru et al (2014)⁶</p> <p>Systematic review and meta-analysis of HA vs. NSAIDs for knee OA</p>	<p>Focused on HA vs. NSAIDs. Identified five relevant RCTs (n=712)</p> <p>Conclusion: in terms of pain scores, HA was not significantly different from continuous oral NSAIDs at 4 weeks or 12 weeks</p> <p>Safety was difficult to assess due to variations in reporting. However, the authors suggested HA might be a viable alternative to NSAIDs, <i>“especially for older patients at greater risk for systemic adverse events”</i></p>	<p>The five RCTs had only short follow up duration & only one was judged to have low risk of bias</p> <p>All were sponsored by HA manufacturers</p> <p>Review funded by AHRQ</p>
<p>Blue Cross Blue Shield’s technology assessment of HA for knee OA (2014)⁷</p> <p>Investigates whether HA offers clinically meaningful improvement over placebo</p>	<ul style="list-style-type: none"> • There is a large body of RCTs <u>but</u> evidence of defined meaningful clinical improvement over placebo is still lacking & adverse events have been poorly reported • The identified study and publication biases imply that an unbiased effect estimate would be lower than any pooled result <p>Conclusion: a large body of evidence comparing the effects of HA with placebo does not demonstrate HA improves net health outcomes in patients with knee OA</p>	<p>‘Best evidence’ assessment of 5 meta-analyses & 3 RCTs published 2011 – 2014</p> <p>Based on this assessment, knee HA does <u>not</u> meet the Blue Cross Blue Shield evaluation criteriaⁱⁱ</p>
<p>Campbell et al (2015)⁸</p> <p>Systematic review of overlapping meta-analyses of HA vs. other therapies</p>	<p>Found 14 meta-analyses (n=20,049) of HA vs. NSAIDs, IA therapies or IA placebo. Based on 2 highest quality analyses (identified using Jadad decision algorithm), concluded that:</p> <ul style="list-style-type: none"> • Highest level of evidence suggests HA is a viable option for knee OA • Improvements in pain & function can persist for up to 26 weeks; safety profile is good • HA should be considered in patients with early knee OA 	<p>Benefits vs. placebo described as <i>“small but clinically relevant”</i>; no major benefits vs. NSAIDs, but HA had fewer side effects. Two highest quality MAs were a 2006 Cochrane review⁹ & a study focused on PRP¹⁰</p>

ⁱⁱ Blue Cross Blue Shield has ceased funding HA injections for knee OA in some US states, see Section 3.3.

<p>Jevsevar et al (2015)¹¹</p> <p>Systematic review & meta-analysis to determine the clinical significance of HA for knee OA</p>	<p>Included 19 RCTs of HA vs. control¹¹ with (i) ≥30 participants in each arm and (ii) specified outcome measures for which minimally important difference (MID) has been established:</p> <ul style="list-style-type: none"> • Double blind, IA placebo-controlled trials showed much smaller treatment effects • In these trials, overall treatment effect was less than half the MID for pain, function & stiffness <p>Conclusions: meta-analysis of just the double blind, sham controlled trials showed no clinically important difference of HA over placebo. When all trials were added, the overall effect was greater, but this was biased due to the influence of non- or improperly blinded trials. The best evidence does not support the use of HA</p>	<p>“Best evidence” approach & meta-analysis suggested that treatment effects are inflated in trials where blinding is inadequate</p> <p>The first named author is also a co-author of the American Academy of Orthopaedic Surgeons guideline (2013)¹² summarised below</p>
<p>Miller & Block (2013)¹³</p> <p>Systematic review & meta-analysis of US-approved HA products vs. IA saline control for knee OA</p> <p>An extended version with more detail about the methodology was published as Strand et al (2015)¹⁴</p>	<p>Included 29 RCTs (n=4,866). Participants were typically in their early 60s, overweight or obese & diagnosed with OA of moderate radiographic severity (up to grade 3 on Kellgren-Lawrence scale). Two thirds were female. RCTs were appraised using Jadad quality tool.</p> <p>HA injections had very large treatment effects (calculated as standardised mean differences or SMDs)* compared to pre-injection values:</p> <ul style="list-style-type: none"> • Pain: SMDs were 1.37 at 4-13 weeks and 1.14 at 14-26 weeks (both p<0.001) • Function: SMDs were 1.16 at 4-13 weeks and 1.07 at 14-26 weeks (both p<0.001) <p>Treatment effects for HA compared to IA saline controls were medium:</p> <ul style="list-style-type: none"> • Pain: SMDs were 0.43 at 4-13 weeks and 0.38 at 14-26 weeks (both p<0.001) • Function: SMDs were 0.34 4-13 weeks and 0.32 at 14-26 weeks (both p<0.001) <p>Heterogeneity among studies was high for pain and moderate for function outcomes</p> <p>HA & saline did not differ significantly with respect to safety outcomes</p> <p>Conclusion: HA injection with US-approved products is safe and efficacious through to 26 weeks in patients with symptomatic knee OA</p> <p>* Effect sizes of 0.2, 0.5, 0.8 and 1.0 are respectively considered small, moderate, large and very large</p>	<p>The RCTs were of overall medium quality (median Jadad score of 3)</p> <p>Pre- to post-treatment effect sizes were not calculated for controls</p> <p>Pain outcomes were inconsistent across RCTs; HA treatment effects were smaller in higher quality RCTs</p> <p>Evidence of publication bias</p> <p>Vast majority of RCTs, plus review itself, were industry-sponsored</p> <p>The majority of RCTs excluded patients with most severe knee OA</p> <p>CRD reviewed this study & found that its conclusion cannot be considered reliable, as it did not sufficiently consider variability in effectiveness or potential biases in the evidence base¹⁵</p>
<p>Pai et al (2014)¹⁶</p> <p>Systematic review & meta-analysis of Hylan G-F 20 (Synvisc) vs. IA placebo for</p>	<p>Identified six RCTs (n=680). Two (n=269) met criteria for meta-analysis, which showed no significant difference between HA and placebo injections in terms of reduction in visual analogue scale (VAS) scores for weight bearing pain at six months. Authors identified a significant placebo effect for patients receiving IA injections & suggested that withdrawal of</p>	<p>There was “marked heterogeneity” between the six trials</p> <p>The two included in the meta-analysis were well conducted (rated</p>

<p>painful knee OA</p>	<p>fluid from the affected knee prior to injection may itself have additional benefits</p> <p>Conclusion: although Hylan G-F 20 may reduce VAS scores for weight bearing pain at six months, patients should be informed that this improvement may be equivalent to that seen with placebo injections</p>	<p>4/5 or 5/5 on Jadad scale)</p> <p>The review's conclusion was based on a relatively small cohort</p>
<p>Richette et al (2015)¹⁷</p> <p>Systematic review & meta-analysis of HA vs. IA placebo based on trials with low risk of bias</p>	<p>Identified eight RCTs (n=2,199) with low risk of bias (i.e. adequate randomisation & concealment plus double-blind design). The RCTs showed no heterogeneity. Meta-analysis found that HA significantly reduced pain intensity (8 RCTs, SMD -0.21, 95% CI [confidence interval] -0.32 to -0.10) and improved function (5 RCTs, SMD -0.12, 95% CI -0.22 to -0.02) at three months.</p> <p>Conclusion: meta-analysis of high quality trials shows that HA provides a moderate but real benefit for patients with knee OA</p>	<p>Seven RCTs were industry funded</p> <p>Reviewers described effect size for pain as “<i>moderate but clinically relevant on an individual patient basis</i>” & suggested HA be considered for patients with comorbidities on safety grounds</p>
<p>Trigkilidas & Anand (2013)¹⁸</p> <p>Systematic review of HA vs. IA corticosteroids or IA placebo</p>	<p>14 RCTs met the inclusion criteria (n=2,282). Of the 12 that compared HA to IA placebo:</p> <ul style="list-style-type: none"> • Five found no statistically significant difference between the two groups • Two favoured HA at either one year or six months, <u>but</u> were of poor quality • Three found a statistically significant superiority for HA in the short term (≤18 weeks) • Two found a modest effect in favour of HA at six months for pain, but not for function <p>Of the two studies comparing HA to IA corticosteroids: one showed no difference between treatments; the other suggested HA superiority at 6 months, but had a high dropout rate.</p> <p>Conclusion: there is weak evidence that HA has a modest effect vs. placebo on early to moderate knee OA. The effect peaks at around 6–8 weeks, with a doubtful effect at 6 months. The evidence for HA vs. corticosteroids is even weaker.</p>	<p>The search was fairly limited, so studies may have been missed; no attempt to pool study results</p> <p>The authors noted that many RCTs reported a high placebo effect from arthrocentesis (removal of a small volume of synovial fluid prior to therapeutic injection), with placebo groups reporting significant improvements from baseline</p>
<p>Trojan et al (2016)¹⁹</p> <p>American Medical Society for Sports Medicine (AMSSM) position statement on viscosupplementation for knee OA</p>	<p>Based on a network meta-analysis of 11 RCTs comparing HA to IA steroid or IA placebo. Analysis compared numbers of patients in each treatment arm who responded according to <i>Outcome Measures in Rheumatoid Arthritis Clinical Trials – OA Research Society International</i> (OMERACT-OARSI) criteria for pain, function & stiffness.</p> <p>Found evidence of “small but statistically significant improvement” with HA: at 26 weeks subjects receiving HA were respectively 15% or 11% more likely to respond according to OMERACT-OARSI criteria than those receiving steroid or placebo injections (p<0.05).</p> <p>Conclusion: HA is suggested for knee OA in appropriate patients aged <60, based on moderate quality evidence of treatment response in those aged >60.</p>	<p>High degree of heterogeneity between RCTs</p> <p>Poor reporting & issues with blinding were chief sources of bias</p> <p>Reviewers found substantial variation in individual responses to HA and noted that predictors of positive response have yet to be identified</p>

3.2 Evidence based guidelines

Four evidence based guidelines were identified. They are summarised in Table 2 below, A to Z by author:

Table 2: evidence based guidelines		
Guideline details	Key recommendations	Comments
<p>American Academy of Orthopaedic Surgeons (AAOS). Treatment of osteoarthritis of the knee 2nd edition (2013)</p> <p>Summary¹² and full version²⁰ available</p> <p>Replaces AAOS's 2008 guideline²¹, which was revised earlier than planned due to concerns over methodology</p>	<p>Recommendation: we cannot recommend using HA for patients with symptomatic OA of the knee</p> <ul style="list-style-type: none"> Strength of recommendation is “strong”, i.e. it is based on two or more high strength studies with consistent findings for or against the intervention. A strong recommendation means that the quality of the supporting evidence is high Implication: <i>“practitioners should follow a strong recommendation unless there is a clear and compelling rationale for an alternative approach”</i> <p>Note: this represents the only significant recommendation change from the 2008 guideline, which stated that <i>“We cannot recommend for or against the use of IA HA for patients with mild to moderate symptomatic OA of the knee”</i>.</p> <ul style="list-style-type: none"> The 2008 recommendation on HA was based on level I and II evidence and was graded “inconclusive” 	<p>Used more rigorous “best evidence” approach to select and evaluate evidence, e.g. includes only original research (RCTs) meeting minimum sample size & follow up duration criteria; excludes secondary analyses (systematic reviews)</p> <p>Use of “minimum clinically important improvement” (MCII) thresholds and other aspects of the guideline’s methodology have been criticised^{19 22 23}</p>
<p>National Institute for Health and Care Excellence (NICE). Osteoarthritis: care and management in adults CG177 (2014)</p> <p>UK national guideline on all types of OA in adults</p> <p>Summary²⁴ and full version (describing methods and evidence in detail) available²⁵</p>	<p>Recommendation: do not offer IA hyaluronan injections for the management of osteoarthritis</p> <p>Based on a 2006 Cochrane review⁹ which included 76 studies, plus 20 additional & more recent studies, the findings on pain relief were as follows:</p> <ul style="list-style-type: none"> Studies of two licensed HA preparations used for knee OA (Synvisc and Orthovisc) demonstrated clinically important pain reductions compared to placebo; however, <i>“all these effects were surrounded by uncertainty and the quality ranged from low to very low”</i>. Studies of two unlicensed preparations found no clinically important difference compared to placebo. <p>Findings on other clinical outcomes:</p> <ul style="list-style-type: none"> Quality of life data was only reported for one licensed preparation (there was no clinically important difference over placebo). 	<p>Update of a previous osteoarthritis guideline (CG59, 2008)</p> <p>Developed according to rigorous & approved NICE methodology²⁵</p> <p>The guideline development group found uncertainty and varying quality throughout the HA evidence</p> <p>Evidence on licensed HA products was of low or very low quality</p> <p>Evidence on unlicensed HA products was mostly of moderate to very low quality (there was some high quality evidence comparing</p>

	<ul style="list-style-type: none"> Two licensed & one unlicensed preparation had higher rates of adverse events compared to placebo No included studies reported on time to joint replacement <p>Findings on cost effectiveness:</p> <ul style="list-style-type: none"> HA injections are unlikely to be cost effective 	<p>unlicensed products to each other or to placebo)</p> <p>Evidence was lacking on whether specific groups of patients respond better to HA injections</p>
<p>Osteoarthritis Research Society International (OARSI). Guidelines on non-surgical management of knee OA (2014)²⁶</p> <p>Recommendations were stratified according to OA subtype</p>	<p>Recommendations: IA HA injection is (i) of uncertain appropriateness for knee-only OA subtype; and (ii) not appropriate for multiple joint OA subtype</p> <p>There were inconsistent conclusions on effectiveness from the meta-analyses and conflicting results on safety from the guideline panel's consensus development process</p> <p>Level of evidence: systematic review and meta-analysis of RCTs</p> <p>Quality of evidence: good (i.e. there was good evidence of uncertainty)</p>	<p>'Best evidence' update of OARSI's previous (2010) guideline, based on recent RCTs, meta-analyses & systematic reviews only; recommendations reached through consensus</p> <p>Evidence on knee OA came from three systematic reviews</p>
<p>Veterans Affairs & Department of Defense (VA/DoD). Clinical practice guideline for the non-surgical management of hip & knee OA (2014)²⁷</p> <p>US guideline for primary care providers treating adults eligible for VA or DoD health programmes</p>	<p>Recommendation: There is insufficient evidence to recommend for or against the use of intra-articular HA injection in patients with OA of the knee; however it may be considered for patients who have not responded adequately to non-pharmacologic measures and who have an inadequate response, intolerable adverse events, or contraindications to other pharmacologic therapies</p> <p>The strength of this recommendation is classified "I", which means that:</p> <ol style="list-style-type: none"> The current evidence is insufficient to assess the balance of benefits and harms, because evidence is lacking, of poor quality, or conflicting If the treatment is offered, patients should understand this uncertainty 	<p>Found many knee studies were of low quality due to small size or flawed methodology/data analysis</p> <p>Noted that negative results from unpublished trials have led to concerns about publication bias</p> <p>Altman's assessment⁴ (see Table 1 above) scored this guideline the lowest quality of the four included in this evidence scan</p>

3.3 Overseas payer policies on HA injections for knee OA

A number of US payers and insurers fund HA injections for knee OA in specified circumstances.

According to the AHRQ review (2015) outlined above, the US Centers for Medicaid and Medicare Services (CMS) covers HA injections for elderly Medicare recipients under certain conditions¹. Medicare funds HA for the knee only and requires x-ray evidence of OA²⁸.

Aetna funds HA for members with knee OA who meet stated criteria²⁹. The criteria include a requirement to try conservative therapy (e.g. physical therapy, NSAIDs) and IA corticosteroids first unless contraindicated. Aetna differentiates on cost and will only fund more expensive HA products (e.g. Synvisc) for members with documented contraindications or intolerance of cheaper brands.

Cigna's coverage policy³⁰ is similar. Cigna has a list of preferred viscosupplementation products (Monovisc, Orthovisc, Synvisc and Synvisc-One) and will only fund other HA brands for members with contraindications or intolerance of the preferred products. More detailed information on Cigna and Aetna HA funding policies are available in Appendix 6.2.

Blue Cross Blue Shield (BCBS) makes coverage decisions on a state by state basis. In response to the recommendation change in the second edition of the AAOS guideline outlined in Table 2 above²⁰, BCBS companies in several states (e.g. Florida) are eliminating coverage for knee OA injections³¹. The technology assessment carried out by the BCBS Association's own Technology Evaluation Center⁷ in 2014 (see Table 1 above) concluded that HA injections for knee OA do not meet the BCBS Association Technology Evaluation Center (TEC) criteria to determine whether a technology improves health outcomes.

No information was found on whether any workers' compensation authorities fund the intervention, or on the funding situation in Australia.

4 Discussion

4.1 Summary: reviews & guidelines differ, effectiveness is uncertain

Eleven systematic reviews, meta-analyses or health technology assessments of the effectiveness of HA for knee OA were included in this evidence scan.

The included reviews reached different conclusions. Seven found that HA offered some pain relief benefits over placebo or control treatment^{1 2 8 13 14 17-19}. Benefits were typically described as modest or small to moderate. Some reviews noted that the evidence was of low to moderate quality^{1 18 19}. Four reviews found that HA offered no significant pain relief benefits over placebo or control treatment^{6 7 11 16}.

Five reviews found that HA improved function to some extent^{1 2 8 13 14 19}. Effect sizes tended to be smaller and evidence tended to be weaker for functional improvements than for pain relief.

One review found moderate evidence that serious adverse events associated with HA are rare¹. Safety was on the whole not reported on in detail. HA does however appear to be regarded as a relatively safe treatment option.

There is currently no strong evidence around the relative performance of different HA products or on which patients are most likely to benefit (see Section 4.3).

Guideline recommendations also varied. Four evidence based guidelines were included in the scan: two recommended against HA^{20 25} and two were uncertain^{26 27}. This inconsistency is echoed by a recent systematic review of HA guidelines, which identified a further six guidelines and concluded that the recommendations across all ten were highly inconsistent⁴. One guideline also concluded that HA injections are unlikely to be cost effective²⁵.

The major US payers currently fund HA for knee OA, but BCBS has stopped funding it in some states in response to the negative recommendation in the latest edition of the AAOS guideline²⁰.

4.2 Issues with evidence quality in included reviews & guidelines

Several methodological and quality issues in the included reviews and guidelines, and also in the wider evidence base (mostly RCTs), have been identified. These include:

- Inadequate blinding in some RCTs^{11 19}
- Significant placebo effects from IA delivery/arthrocentesis^{2 16 18}
- A tendency for authors to focus on statistically rather than clinically significant outcomes and controversy over how clinical relevance is defined^{1 7 11 19 20 22}
- Lack of long term follow up^{2 6 8}
- Inadequate reporting of safety data^{2 7}
- General mediocre to low quality or poor reporting in RCTs^{1 6 7 19 25 27}
- Publication bias^{2 7 13 14 27}
- Industry sponsorship^{6 13 14 17}

Other authors have also raised concerns about conflicts of interest in the primary evidence base, noting an association between RCTs with favourable conclusions and industry sponsorship³².

4.3 Evidence gap around predicting response to HA

Reviews have typically found a high degree of variability in individual response to HA injections and some have remarked on the need to identify predictors of positive response¹⁹. The developers of the UK NICE guideline identified this as an evidence gap and recommended further research to determine which subgroups of patients respond best to HA and other OA interventions²⁵.

Research presented at a recent rheumatology conference has reported that obesity and more severe OA with more joint space narrowing are significantly associated with lack of response to HA injections³³. These findings come from a retrospective analysis of 166 participants in a French RCT and have yet to be confirmed in other studies.

5 Conclusions & recommendations

Based on the reviews and guidelines included in this evidence scan, the effectiveness of HA injections for knee OA appears to be uncertain. Reviews reach different conclusions and guideline recommendations are inconsistent. In addition, a number of methodological shortcomings and quality issues have been identified in several of the reviews and also in the primary research on which the reviews are based.

This conclusion is echoed elsewhere. The DynaMed evidence based clinical reference tool concludes that *“The effectiveness of IA HA (viscosupplementation) is uncertain”*³⁴ and other authors have noted that differences in methodology have caused systematic reviews and meta-analyses of HA for knee OA to reach different and sometimes conflicting conclusions even though they draw on the same primary research base^{35 36}.

In light of this uncertainty, it is proposed that ACC revise its 2005 position and adopt the following purchasing recommendationⁱⁱⁱ:

Do not purchase intra-articular injections of hyaluronic acid to treat pain associated with osteoarthritis of the knee

This recommendation may be revisited if good quality research on which individuals are most likely to respond to HA injections becomes available in the future.

ⁱⁱⁱ This *do not purchase* recommendation was ratified by the Clinical Governance Committee & adopted as official ACC purchasing policy in September 2016.

6 References

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7 Appendices

7.1 Search strategies

Cochrane Library, <http://www.cochranelibrary.com/>

1. hyaluron*
2. knee
3. #1 and #2
4. viscosupplement*
5. #2 and #4
6. #3 or #5
7. (hyalgan or synvisc or hylan) and #2
8. #6 or #7

TRIP, <https://www.tripdatabase.com/index.html>

1. (synvisc or hylan* or viscosupplement* or hyaluron*) and knee*
2. Limit to all secondary evidence

CRD Databases, <http://www.crd.york.ac.uk/CRDWeb/>

1. (synvisc or hylan* or viscosupplement* or hyaluron*) and knee*

Medline & Epub Ahead of Print on the Ovid platform

1. *Hyaluronic Acid/
2. *Osteoarthritis, Knee/
3. 1 and 2
4. limit 3 to (english language and humans and yr="2005 - Current")
5. limit 4 to "review articles"
6. limit 4 to "reviews (best balance of sensitivity and specificity)"
7. limit 4 to (consensus development conference or consensus development conference, nih or evaluation studies or government publications or guideline or meta analysis or practice guideline or systematic reviews)
8. or/5-7

Medline In-Process on the Ovid platform

1. ((synvisc or hylan* or viscosupplement* or hyaluron*) and ((knee* adj3 osteoarthritis*) and pain*)).mp.
2. limit 1 to yr="2005 -Current"
3. limit 2 to english language

Embase on the Ovid platform

1. hyaluronic acid/ or viscosupplementation/
2. knee osteoarthritis/
3. 1 and 2
4. limit 3 to (human and english language and yr="2010 - Current")
5. "systematic review"/
6. meta analysis/
7. exp practice guideline/
8. or/5-7
9. 4 and 8
10. limit 4 to (meta analysis or "systematic review")
11. limit 4 to "reviews (maximizes specificity)"
12. or/9-11

7.2 Aetna & Cigna coverage policies

Payer policy: Aetna (major US managed health care company & insurance provider)

According to policy no.0179 (2015)²⁹, **Aetna considers viscosupplementation medically necessary** for members with osteoarthritis of the tibiofemoral articulation of the knee who meet all of the following criteria:

- A. Conservative therapy (e.g. physical therapy, non-steroidal anti-inflammatory drugs) has not resulted in functional improvement after at least 3 months or the member is unable to tolerate conservative therapy because of adverse side effects,
- B. The clinical diagnosis is supported by radiologic evidence of osteoarthritis of the knee (e.g. joint space narrowing, subchondral sclerosis) or the member has documented symptomatic osteoarthritis of the knee according to American College of Rheumatology clinical and laboratory criteria.
- C. The member has failed to adequately respond to aspiration and injection of intra-articular steroids
- D. The member reports pain which interferes with functional activities (e.g. ambulation, prolonged standing)
- E. The pain cannot be attributed to other forms of joint disease
- F. The member is not scheduled to undergo a total knee replacement within six months of starting treatment
- G. There are no contraindications to the injections (e.g., active joint infection, bleeding disorder, skin infections at the injection site).

Note: Aetna considers ultrasound guidance for viscosupplementation injections experimental and investigational because it has not been established that this approach will improve health outcomes.

Additional series of injections for members who have responded to previous series are considered medically necessary under the following circumstances:

- A. At least three months has elapsed since the prior series of injections
- B. The medical record demonstrates a reduction in the dose of NSAIDs (or other analgesics or anti-inflammatory medication) during the three month period following the previous series of injections (note: a dose reduction is not required if the member requires these medications for a comorbid medical condition in addition to knee osteoarthritis)
- C. The medical record objectively documents significant improvement in pain and function as the result of the previous injections.

Reliable evidence on the relative effectiveness of different brands of viscosupplement is lacking. Aetna will therefore only fund the more costly brands (Hyalgan, Supartz, Gel-One, Synvisc and Synvisc-One [hylan G-F 20]) if a member has a documented contraindication to or intolerance of the cheaper products (Euflexxa, Monovisc and Orthovisc).

Aetna considers viscosupplementation experimental and investigational for all other indications because effectiveness has not been established.

Payer policy: Cigna (major managed health care company & insurance provider; US-based, but operates globally)

According to policy no. 1405 (2015)³⁰, Cigna covers preferred viscosupplementation products (Monovisc, Orthovisc, Synvisc and Synvisc-One) as **medically necessary** when all of the following criteria are met:

- Diagnosis of symptomatic osteoarthritis of the knee affecting activities of daily living
- Failure to respond, contraindication or intolerance to all of the following treatment options:
 - Non-pharmacologic (e.g. exercise, physical therapy, weight loss if indicated)
 - Non-narcotic analgesics (e.g. acetaminophen, tramadol)
 - Non-steroidal anti-inflammatory drugs
 - Intra-articular corticosteroids

Cigna covers non-preferred products (Euflexxa, Gel-One, Hyalgan and Supartz) as **medically necessary** when all of the following criteria are met:

- Diagnosis of symptomatic osteoarthritis of the knee affecting activities of daily living

- Failure to respond, contraindication or intolerance to all of the treatment options listed above
- Contraindication or intolerance to the preferred products listed above

Cigna covers additional treatment courses of viscosupplementation when all the following criteria are met:

- Initial criteria for use of the requested product were met
- History of clinical beneficial response with previous treatment course, e.g. an improvement in an objective measurement of pain and/or functional status (such as Visual Analog Scale [VAS], WOMAC Index or other validated objective measure)
- At least 6 months have lapsed since the completion of the prior treatment course

Dosage, frequency and duration of therapy should be reasonable, clinically appropriate and supported by evidence based literature. It should be adjusted according to severity, alternative available treatments and previous response to viscosupplementation.

Cigna does not cover viscosupplementation for osteoarthritis in sites other than the knee because it is considered experimental, investigational or unproven.