How effective is glucosamine in the treatment of osteoarthritis compared to placebo and chondroitin? A review of the best evidence

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Introduction

Osteoarthritis (OA) is the most common form of arthritis and is a source of chronic pain, disability and decreased quality of life for many people, particularly adults over 50.1,2 It affects more than 1.3 million Australians and affects females to males in a 3 to 1 ratio.1,2 Management of OA is a challenge for health care professionals. There are a wide range of management options that have varying levels of evidence for their efficacy. These include exercise, ambulatory aids, weight loss, pharmaceuticals, surgery, intra-articular injections and complementary medicines (CAM). In 2004-5, the Australian Bureau of Statistics National Health Survey (ABS NHS) established that 40% of Australians with OA use pharmaceuticals and 46% use dietary supplements.3 One of the most common supplements taken in Australia is glucosamine. It is also available in a combination tablet with chondroitin. Twenty six per cent of females and 21% of males with OA in the ABS NHS reported taking glucosamine.4

Mechanism of action of glucosamine and chondroitin

Glucosamine comes in two forms: glucosamine sulphate (GS) and glucosamine hydrochloride (GH). GS and chondroitin sulphate (CS) are building blocks of the important components of articular cartilage called proteoglycans.3,4 The predominant proteoglycan present in articular cartilage is aggrecan, which is rich in chondroitin sulphate.5 Aggre can has osmotic properties which help combat the compressive loads placed on the articular cartilage between joints.3,4 It is proposed that glucosamine is a substrate for the biosynthesis of proteoglycans and glycosaminoglycans (GAGs).3 Glucosamine is synthesised by chondrocytes from glucose to produce GAGs and this in turn stimulates proteoglycan production.7 The rationale for use of glucosamine in OA is based mostly on animal and in-vitro models where promising results were seen, including a rebuilding of experimentally damaged cartilage, normalisation of cartilage metabolism and some anti-inflammatory effect.3,8 It has been suggested that some of the dose of oral chondroitin and glucosamine (tablets or powder) reach the joint as both complementary and alternative medicines (CAMs) are partially absorbed in the intestine.9 The recommended doses are: 1500-2000 mg daily for GS, and 800-1200 mg daily for CS.4 Some research suggests that glucosamine and chondroitin have a slow onset of action and patients may not see improvements in symptoms for 6-8 weeks from when they start taking either CAM. The authors also stated that there could be a carryover effect, with relief of symptoms persisting two months after discontinuing the supplement.9 Richy et al. stated that minimum time reported for the onset of a significant action was two weeks for both glucosamine and chondroitin; however the authors excluded trials with a treatment period of less than four weeks.4

There is considerable controversy regarding the analgesic and disease modifying efficacy of glucosamine in OA.3,10 This uncertainty trickles down to a consumer level. Data from three national and one state-wide pharmacist-operated medicines call centres, indicate that many consumers were asking questions about glucosamine, including questions surrounding its efficacy.11

To address this uncertainty the question, “What is the efficacy of glucosamine in treating osteoarthritis in adults, compared to placebo and chondroitin?” was posed to inform a literature search for reviews on this question. The databases used were Cochrane Library, Medline and Pubmed. This yielded 13 relevant reviews. Ten of these were not analysed because the reviews had a publication date before 2003,12-14 or number of studies15,16 contained results of low quality studies and did not focus on the question at hand.17 This left three recent systematic reviews for critical appraisal.

Critical appraisal of Cochrane review by Towheed et al.

This Cochrane review, of which the latest version was published in 2009, investigated the effectiveness and toxicity of glucosamine in OA.3 Their literature search was extensive and included studies published by January 2008, with no language or age restrictions set.

Their inclusion criteria were outlined and included randomised controlled trials (RCTs) of OA at any site, excluding temporo-mandibular joint (TMJ) disorders.3 This Cochrane review allowed RCTs that administered glucosamine by any route. All of the 25 RCTs included were double blinded. They utilised the GRADE criteria to critique the RCTs and assess whether the design and quality of RCTs was sufficient for inclusion in the review. The mean trial duration was almost six months (25.5 weeks) and the mean number of participants randomised in each of the 25 randomised parallel-group trials was 198, with a total of 4963 participants being captured in this review.3 Most of the studies (80%) investigated OA of the knee exclusively. A strength of the systematic review was
that it presented results both collectively (data from all 25 RCTs) and exclusively; using only data from higher-quality studies in which an appropriate method of allocation concealment had been described by the authors of the RCT. Just over half of the studies were rated as having adequate allocation concealment (13 RCTs, 52%).

Twelve of these 13 RCTs were included in a post-hoc sensitivity analysis. The reviewers decided that the remaining 48% had either insufficient or unclear concealment of allocation. One high-quality review was excluded due to a unique comparator.

The particular product or brand used in the RCTs may impact on results and therefore may be a confounding factor. It has been postulated by some researchers that glucosamine hydrochloride is ineffective, whereas GS has shown more promising results. Therefore it may have been useful if the results of this Cochrane review by Towheed et al. also presented the data regarding GS and GH analysed separately. Of the 12 studies included in the sensitivity analysis, seven exclusively investigated GS, whereas the other five investigated GS or GH supplementation.

The alternative was a comparison of Rotta brand versus non-Rotta brand glucosamine. This can be viewed as both a strength and weakness of the systematic review. The inclusion of this comparison is advantageous because RottaPharm is an Italian manufacturer and in Italy and throughout the rest of Europe, glucosamine is considered a pharmaceutical and therefore is more highly regulated, in comparison to countries such as North America and Australia. In these countries it is not classed as a pharmaceutical and is instead seen as a complementary medicine or dietary supplement. In Australia, glucosamine undergoes basic quality and safety assessments. However there is no evaluation of efficacy or bioavailability of any of the glucosamine products available for consumer purchase. A Canadian study by Russell et al. (discussed by Towheed) found that the actual dosage (in mg) of GS varied from 59% to 138% of the dose stated on the label. This variability in dose could alone account for the heterogeneity amongst studies of the efficacy of glucosamine.

The positive results of GS, limited to the Rotta brand, raises questions about affiliations with the manufacturer, as 56% of the RCTs had some form of affiliation with RottaPharm (by evaluating Rotta brand or other relationship).

There is evidence that research funded by pharmaceutical companies is more likely to have results favouring the sponsor, when compared to research with funding from other sources. This positive publication bias may be due to the failure of pharmaceutical companies to publish negative results and may have been a factor in this review. However there is no evidence that the studies funded by pharmaceutical companies were of lower quality than those funded from other sources.

Results of Cochrane review by Towheed et al.

Of the 25 studies that met the inclusion criteria (including low quality and older studies), 18 studies were pooled for the outcome variable of reduction of pain. Towheed et al. found that glucosamine (GS or GH) improved pain more than placebo and this result was statistically significant (summary SMD [standardised mean difference] -0.47; 95% CI -0.72 to -0.23). The authors concluded that this corresponded to a 22% improvement in pain from baseline. Towheed et al. did note that there was variability amongst the results and there was not a positive consensus regarding glucosamine among all of the RCTs. Towheed et al. also analysed 11 high-quality studies exclusively and concluded that there was no statistically significant difference in reported pain by participants compared to placebo. These patients were assigned to at least six months of treatment with glucosamine (GS or GH) at 1500 mg daily. The summary SMD (random-effects model) was -0.16 (95% CI -0.36 to 0.04).

The Lequesne Index was another outcome that was analysed by Towheed and fellow researchers. Lequesne Index score was developed by Lequesne et al. and has been used since 1987 to evaluate the effectiveness of therapeutic interventions regarding OA. It is a questionnaire regarding pain or discomfort, maximum distance walked and activities of daily living. For this outcome, Towheed et al. found similar results from pooling all of the data (five RCTs) and data from the sensitivity analysis for adequate allocation and concealment (four RCTs).

For the five RCTs, Towheed et al. found that glucosamine was significantly superior to placebo in terms of its ability to improve Lequesne index scores. The summary SMD (random-effects model) was -0.47 (95% CI -0.82 to -0.12). For the sensitivity analysis, the summary SMD was -0.54 (95% CI -0.96 to -0.12). The authors noted that a negative SMD in these cases was indicative of a positive effect of glucosamine. Towheed et al. concluded that the results from the sensitivity analysis regarding Lequesne Index corresponded to an 11% improvement in function from baseline. Many other outcomes were analysed by this Cochrane review and WOMAC pain, function and stiffness outcomes did not reach statistical significance.

A total of 14 (56%) of the RCTs used Rotta brand GS as the only preparation that was used. A subgroup analysis of Rotta preparation was performed by Towheed et al. and a statistically significant benefit for GS over placebo was found for four outcomes: reduction in pain, Lequesne Index and WOMAC pain and function subscale scores. These results were based on different numbers of RCTs, being eight, five, seven and six respectively. The summary SMD value for reduction in pain was -1.11 (95% CI -1.66 to -0.57) and for Lequesne index this value was -0.47 (95% CI -0.82 to -0.12). A negative SMD for these outcomes corresponded to glucosamine being significantly superior to placebo. This subgroup analysis, which reported positive effects of glucosamine compared to placebo, was derived from data of both high and low quality RCTs, and most of the RCTs solely investigated OA of the knee (62.5%) and the remainder either didn’t specify site (25%) or studied multiples sites (12.5%).

Towheed et al. also reported on joint space narrowing (JSN) based on the results from two RCTs. Towheed et al. found the summary mean difference measuring minimum joint space width for the knee or hip was 0.32 (95% CI 0.05 to 0.58) after administration of 1500 mg daily for three consecutive years. The authors state this is statistically significant in favour of glucosamine and therefore glucosamine may have an effect on the radiological progression of OA.

Critical appraisal of meta-analysis by Richy et al.

A comprehensive meta-analysis published by Richy et al. in 2003 investigated the structural and symptomatic efficacy of glucosamine and chondroitin in knee OA. Their extensive literature search included publication dates from 1980 to March 2002, with no limitations on language or age group and the two independent reviewers were blinded to sources and authors. Their inclusion criteria were reasonable; however their minimum time frame was set at four weeks. This is a short time frame for a treatment intervention. This meta-analysis included only studies
where the administration was oral. This is more relevant to the question at hand and differs from the Cochrane review by Towheed et al., which allowed RCTs where the administration of glucosamine was oral, intravenous, intra-articular, intramuscular or multiple routes. However it is important to note that in the review by Towheed et al., 72% (21 of 29 studies before final exclusion) were exclusively oral administration. The review by Richy and fellow researchers analysed 15 studies with a total of 1775 patients. The authors described that their quality assessment was carried out using a validated instrument and the process was explained. Quality criteria included randomisation, blinding, and the inclusion of reasons for participant withdrawals/dropouts. The assessment of quality was blinded and carried out by the same two independent reviewers, and differences were resolved by consensus. There were seven trials on glucosamine and the mean quality score of the glucosamine trials was 90%. There were eight trials on chondroitin and the mean quality score was lower at 68.4%.

**Results of review by Richy et al.**

The review by Richy et al. looked at several outcomes or effects of these two complementary therapies. These include one quantitative measure, joint space narrowing (JSN) and several qualitative measures: Lequesne Index (LI), WOMAC (Western Ontario MacMaster University Osteoarthritis Index), visual analogue scale (VAS) for pain, and it also investigated the safety profile of these therapies. Joint space narrowing from glucosamine was evaluated using data from two three-year trials (212 and 202 patients). When converted to natural units, the potential minimal joint space narrowing difference (JSN) and several qualitative outcomes (Lequesne index, WOMAC, VAS and mobility) for glucosamine when compared with baseline and with VAS and mobility for chondroitin. No placebo group reached significance in any of these outcomes. In regards to pain reduction assessed by VAS, the global effect size for glucosamine and chondroitin was modest at 0.49 (95% CI, 0.31-0.67; P for association <.0001).

Richy et al. found a relative risk of being a responder when allocated to glucosamine or chondroitin versus placebo was 1.6 (95% CI 1.38-1.82). Being a responder was defined by the authors of each RCT or based on global assessment by Richy and fellow researchers. Secondary calculation of the relative risk of response gives a figure of 1.7 for chondroitin and 1.3 for glucosamine.

In all 15 trials in this meta-analysis, rescue analgesia with NSAIDs was permitted. The authors stated that in most of the trials there was a cumulative low dose of NSAIDs. Specific data on the doses and frequency of rescue analgesia were not presented by Richy and fellow authors. As rescue analgesia was likely to be a confounding factor in measures of pain reported by the patients, these data should have been made available in the review. The authors stated that both the placebo group and groups assigned to chondroitin or glucosamine were allowed rescue medication. This shows the groups were treated equally; however there would have been wide ranging differences in patient’s self administration of NSAIDs. Richy et al. found that those assigned to glucosamine or chondroitin used a lower quantity of rescue analgesia over the study period compared to participants taking placebo. Despite this lower consumption of pain relief, those assigned to either active ingredient still reported less pain than those people receiving placebo. The Cochrane review and a network meta-analysis by Wandel et al. did not discuss rescue analgesia at all in their papers. This is a major weakness as it is a confounding factor and it is likely that some if not most RCTs in their reviews allowed rescue analgesia. Wandel et al. did make recommendations for further trials including the careful control and monitoring of analgesic co-interventions; however more indepth discussion was warranted.

**Critical appraisal of network meta-analysis by Wandel et al.**

In 2010, Wandel et al. published a network meta-analysis analysing the effects of glucosamine, chondroitin or placebo in patients with osteoarthritis of the hip or knee. The review evaluated 10 trials with a total of 3803 participants. Out of the three reviews critically appraised, Wandel had the second highest number of participants after Towheed. Similar to Towheed, 80% of trials investigated OA of the knee exclusively (8 of 10 RCTs). The inclusion criteria of Wandel et al. were similar to the other two reviews which have been discussed. However they excluded trials with less than an average of 100 patients per arm. This study also included RCTs which were published until June 2009, making it the most up to date of the three reviews. It also searched as far back as inception (like Towheed) whereas Richy et al. restricted RCTs to those published from 1980. This network meta-analysis carried out a quality assessment, where two of the four reviewers independently assessed concealment of allocation, blinding and adequacy of analyses. However, the quality assessment did not state that the reviewers were blinded to author, title and other identifying details of the RCTs; therefore it must be assumed that blinding was not carried out. This review required that RCTs had either used a formally approved preparation of the CAM or had confirmation of its contents from laboratory analysis. This quality control measure is a strength of this meta-analysis.
Results of network meta-analysis by Wandel et al.

Wandel et al. included six trials which investigated joint space narrowing (JSN) in their review. Three investigated glucosamine sulphate solely, two chondroitin and one investigated a combination of glucosamine hydrochloride and chondroitin sulphate. The two trials on JSN included in the review by Richy et al. and Towheed et al. were also included in this review. Wandel et al. found minute effects for all preparations (glucosamine, chondroitin and combination) on joint space narrowing compared to placebo. The difference reported for glucosamine was -0.2 mm (-0.3 to 0.0 mm) in favour of glucosamine, which corresponds to an effect size of -0.16 (-0.25 to 0.0). Heterogeneity between trials was reported as low. With a lower end of the 95% confidence interval (CI) equalling zero or the line of no effect, Wandel et al. concluded that the effects of glucosamine on joint space narrowing are minimal. This differs to the results of Richy et al. who used global effect size as a measure, and found the effect of glucosamine to be low to medium. Richy et al. chose to look upon these results more favourably by focussing on the actual change in mm, which was 0.27 mm, and the CI did not cross the line of no effect (zero). Wandel et al. found differences reported for chondroitin and the combination were still in favour for these active ingredients compared to placebo; however the effect sizes were lower than that of glucosamine and both 95% CIs overlapped zero. Considering there were only three RCTs investigating glucosamine and JSN published by June 2009 that met inclusion criteria for this review, more high-quality, longer-term studies are needed.

For pain outcomes, Wandel et al. took a slightly different approach to the other reviews. The authors refer to a hierarchy of pain outcome measures published in 2006 by Juni et al. with global pain scale being the highest in the hierarchy. When more than one pain outcome was reported in an RCT, only the highest ranked measure was included in the meta-analysis. Using this method, Wandel et al. found that there was no clinically significant difference in global pain score (VAS) with glucosamine, chondroitin, or the combination compared to placebo. The authors did state that there was abundant statistical power in VAS figures; however a pre-specified minimal clinically important difference of 0.9 cm on a 10 cm VAS was not reached by any of the pooled estimates. The overall difference in reported VAS with supplement versus placebo was −0.4 cm (95% CI −0.7 to −0.1 cm) on a 10 cm VAS for glucosamine, −0.3 cm (95% CI −0.7 to 0.0 cm) for chondroitin, and −0.5 cm (95% CI −0.9 to 0.0 cm) for the combination of glucosamine and chondroitin. The biggest difference was seen with combination, followed by glucosamine and then chondroitin.

As mentioned earlier, there are possible confounding factors that may lower our confidence in the results of trials or reviews on the efficacy of glucosamine. Wandel et al. carried out tests for interaction, which help examine whether an effect is modified by another variable. Confounding factors that were tested included: quality of the RCTs, type of joint (knee, hip, etc.), type of glucosamine (GH or GS), presence or absence of quality control measures for supplements. The authors found that the tests for interaction were negative for these four variables (P ≥ 0.20 for interaction). The inclusion of this statistical analysis was a strength of the review.

Safety profile

All three reviews found no significant difference in the number of side effects reported by those on glucosamine compared to placebo. The Cochrane review reported that side effects mainly included stomach upset and other joint pain. A study by Reginster (2001) included in all three reviews found that the four most commonly reported adverse effects were abdominal pain, indigestion, diarrhoea and increased blood pressure. The percentage of patients assigned to glucosamine reporting these symptoms was either equal to or lower than those reporting these side effects in the placebo group. Other research suggests that extra caution and closer monitoring may be necessary for people with:

- significant shellfish allergies, as glucosamine is prepared from shellfish and therefore may cause an allergic reaction;
- diabetes, as glucosamine may increase glucose levels in patients with suboptimal glucose tolerance, making close blood sugar level monitoring advisable; and
- warfarin use, as there have been 22 cases reported to the World Health Organisation of increased bleeding or bruising with the combination of glucosamine and warfarin.

Conclusions

All three reviews are classed as Level I evidence and the strengths and weaknesses of each have been discussed. Due to differences in the spectrum of studies included in each review and the differing benchmarks set for positive results, there is not a clear consensus amongst the reviews on the efficacy of glucosamine for OA. The review by Richy et al. showed significantly better results for glucosamine over placebo for the Lequesne index, WOMAC, VAS pain and mobility. However the results reported by Wandel et al. regarding VAS were not found to reach a pre-specified minimal clinically important difference and therefore the authors’ recommendations were that it should not be prescribed to patients, who have not received these treatments before. When Towheed et al. analysed only high-quality studies, this review found that glucosamine was not significantly more effective than placebo in reducing pain in OA sufferers. However, it did find efficacy for glucosamine for reducing pain when both high- and lower-quality RCTs were analysed and when Rotta brand GS was investigated exclusively. The subgroup analysis of Rotta preparation found statistically significant benefit of GS over placebo on four outcomes: reduction in pain, Lequesne Index and WOMAC pain and function subscale scores. This adds strength to the viewpoint that GS may be superior to GH. As Rotta is manufactured in Europe, where GS is a pharmaceutical, it is also more likely that the dose and formulation is as the label reads. GS is not considered a pharmaceutical in countries such as Australia, United States of America and Canada. When analysing the results of this Cochrane review, publication bias due to pharmaceutical company involvement should be considered and may decrease confidence in the validity of these results.

Recommendations

The lack of consensus amongst reviews makes clear recommendations difficult, but patients considering the use of glucosamine could be informed that uncertainty remains as to whether glucosamine reduces the pain and disability of osteoarthritis and preserves cartilage compared with placebo. The advantages glucosamine may have are generally small and of a size that may not justify its cost. However it does seem to be safe, but care should be taken in patients with diabetes, those taking warfarin and those with allergies to shellfish. In patients who have been taking glucosamine and...
have found it to be beneficial, there could be a case to continue it. There may be a difference in the effectiveness in different preparations of glucosamine, with the strongest evidence being for glucosamine sulphate preparations taken at a dose of at least 1500 mg per day.

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References


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


### Table 1. Results of the three systematic reviews on glucosamine

<table>
<thead>
<tr>
<th>CAM investigated</th>
<th>OAsite investigated</th>
<th>Number of RCTS</th>
<th>Number of participants (mean per trial)</th>
<th>Trial duration</th>
<th>Publication dates incl. in literature search</th>
<th>Pain</th>
<th>Function</th>
<th>Joint space narrowing (glucosamine)</th>
<th>Joint space narrowing (chondroitin)</th>
<th>Joint space narrowing (combination)</th>
<th>Relative risk of being a responder</th>
<th>Absolute risk difference and NNT</th>
<th>Safety</th>
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</thead>
<tbody>
<tr>
<td>GS and GH versus placebo</td>
<td>Knee OA exclusively</td>
<td>25</td>
<td>4963 (198)</td>
<td>Mean was 25.5 weeks</td>
<td>Inception to January 2008</td>
<td>VAS (12/15 RCTs); Global effect size (random effects) was 0.49 (95% CI, 0.31–0.67; P for association &lt;0.001)</td>
<td>11% improvement in function reported by authors (based on the most representative study) (LI)</td>
<td>2 RCTs (Pavelka 2002; Registerin 2001) using Rotta preparation SMD measuring minimum JS width for the knee or hip was 0.32 (95% CI 0.05 to 0.58) after administration of 1500 mg daily for three consecutive years. Authors state statistically significant in favour of glucosamine and therefore glucosamine may have an effect on the radiological progression of OA.</td>
<td>NA</td>
<td>1.6 (when treated with glucosamine or chondroitin, 1.6 times more likely to have a positive response to treatment compared to placebo) (1.38–1.82)</td>
<td>Glucosamine was as safe as placebo in terms of the number of participants reporting adverse reactions (RR 0.99; 95% CI 0.91 to 1.07) placebo group 4.7% were withdrawn because of toxicity 39% reported an adverse reaction glucosamine group 3.3% were withdrawn because of toxicity 30% reported an adverse reaction</td>
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<tr>
<td>GS, chondroitin versus placebo</td>
<td>Knee OA exclusively</td>
<td>15</td>
<td>1775 (118*) (1020 glucosamine; 755 chondroitin)</td>
<td>Mean for glucosamine: 51.4 weeks* [calculated from Table 2'] Mean for CS: 25.9 weeks* [calculated from Table 3']</td>
<td>January 1980 to March 2002</td>
<td>VAS (10/10 RCTs) No clinically significant difference in global pain score (VAS) with glucosamine, chondroitin, or the combination compared to placebo. The overall difference in reported VAS with supplement versus placebo was −0.4 cm (95% CI −0.7 to −0.1 cm) on a 10 cm VAS for glucosamine, −0.3 cm (95% CI −0.7 to 0.0 cm) for chondroitin, and −0.5 cm (95% CI −0.9 to 0.0 cm) for the combination of glucosamine and chondroitin</td>
<td>NA</td>
<td>2 RCTs (Pavelka 2002; Registerin 2001) using Rotta preparation potential minimal JSN difference between GS and placebo was found to be 0.27 mm (95% CI, 0.13–0.41 mm) after administration of 1500 mg daily for 3 consecutive years Authors state highly significant (P=0.001) effect on minimum JSN</td>
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<tr>
<td>GS, GH, chondroitin, combination versus placebo</td>
<td>80% RCTs studied knee</td>
<td>10</td>
<td>3803 (380*)</td>
<td>Trial duration ranged from: 4 weeks to 156 weeks. Data were extracted as multiple time points; therefore mean could not be calculated. See table 1.</td>
<td>Inception to June 2009</td>
<td>VAS (10/10 RCTs) No clinically significant difference in global pain score (VAS) with glucosamine, chondroitin, or the combination compared to placebo. The overall difference in reported VAS with supplement versus placebo was −0.4 cm (95% CI −0.7 to −0.1 cm) on a 10 cm VAS for glucosamine, −0.3 cm (95% CI −0.7 to 0.0 cm) for chondroitin, and −0.5 cm (95% CI −0.9 to 0.0 cm) for the combination of glucosamine and chondroitin</td>
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Key: CI = confidence interval; LI = Lequesne Index; NA = not applicable; JSN = joint space narrowing; NNT = number needed to treat; SMD = standardised mean difference; WOMAC = Western Ontario MacMaster University Osteoarthritis Index

*calculated, not stated in review

Please note that in the network meta-analysis, Wandel et al. uses the terms “credible interval” and “confidence interval” interchangeably as these terms are analogous to each another