SUPPLEMENTARY APPENDIX 2: Evidence Report

ACR/AF 2019 Guideline for the Management of Osteoarthritis of the Hand, Hip and Knee

Osteoarthritis – Evidence Report

Prepared for: American College of Rheumatology

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Introduction

Critical outcomes

- Each table reports the summary of findings from randomized trials and/or systematic reviews reporting the critical outcomes. The critical outcomes, as chosen by the Core Team, differed somewhat for assessment of hand OA and assessment of hip or knee OA.
- For hand OA, critical outcomes included measures of pain (AUSCAN, DASH, MHQ, PRWE, QuickDASH, VAS), self-reported function (AUSCAN, Cochin, DASH, FIHOA, MHQ, PRWE, QuickDASH), performance-based function (AHFT, COPM, GAT, grip strength, pinch strength, JFHT, MAM), and serious adverse events.
- For hip or knee OA, critical outcomes included measures of pain (WOMAC, KOOS, HOOS, VAS, SF-36 bodily pain, HAQ, AIMS, KSPS, McGill pain questionnaire, NRS), self-reported function (WOMAC, KOOS, HOOS, SF-36 physical function, PCS, HAQ [disability], PDI, ASES), performance-based function (chair stand test, gait speed [short distance], stair negotiation, timed up and go test, 6 minute walk test), and serious adverse events.
- Note that serious adverse events are very rare, and thus it is quite difficult to achieve a statistically significant difference between groups for this outcome in randomized trials powered for efficacy outcomes that occur much more often.
- Included studies examined one or more critical outcomes. Each outcome was analyzed separately.

Interventions

- The following interventions were within the scope of this guideline:
    - Pharmacologic – oral (acetaminophen, anti-depressants, bisphosphonates, chondroitin, colchicine, fish oil, glucosamine, glucosamine/chondroitin, hydroxychloroquine, methotrexate, non-tramadol opioids, oral NSAIDs, tramadol, vitamin D)
    - Pharmacologic – topical (capsaicin, lidocaine, NSAIDs)
    - Pharmacologic – biologics (anti-nerve growth factor, tumor necrosis factor inhibitor, interleukin-1 receptor antagonist)
    - Pharmacologic – intra-articular (corticosteroids [long or short-acting, high or low dose], hyaluronic acid, platelet rich plasma, prolotherapy, mesenchymal stem cells, botulinum toxin, saline, anesthetic)
    - Non-pharmacologic (acupuncture, assistive devices, chiropractic manipulation, electrical stimulation, TENS, exercise, gloves, iontophoresis, joint stabilization, kinesiotape, nerve ablation, occupational therapy, orthoses, osteopathic manipulation, paraffin, patient education, physical activity, physical therapy, relaxation techniques, strengthening, therapeutic cooling, therapeutic heat [including ultrasound], work modification, cognitive behavioral therapy, manual therapy, massage therapy, mind-body practices, patellofemoral taping, pulsed vibration therapy, self-efficacy/self-management, walking, weight loss)
    - Usual care was defined as maximally tolerable therapeutic doses of acetaminophen or NSAIDs

Systematic Literature Review

- Randomized controlled trials (RCTs) were the preferred source of evidence. We used systematic reviews as an additional resource to identify relevant RCTs, but if a systematic review focused solely on RCTs it was not used in the evidence base. Instead, we tabled data from individual RCTs in RevMan to perform our own independent meta-analyses. In some instances, evidence from systematic reviews was used as supplementary evidence if it provided data from RCTs and observational studies or observational study data alone that was particularly relevant.

Quality Assessment

- Quality assessment was performed separately for each outcome using the GRADE system, which results in one of four possible evidence grades that reflect level of confidence in the effect estimate: high, moderate, low, and very low.
- Study design is the starting point for quality assessment: randomized controlled trials (RCTs) start at high quality and observational studies start at low quality.
- Five factors can lower the quality of evidence grade: risk of bias, inconsistency, indirectness, imprecision, and publication bias.
- Risk of bias refers to limitations in study design or execution (e.g. lack of allocation concealment or blinding).
- Inconsistency refers to unexplained heterogeneity in results of studies evaluating the same outcome.
- Indirectness refers to lack of direct comparisons of interventions of interest (e.g. studies comparing drug A vs. placebo and drug B vs. placebo when the comparison of interest is drug A vs. drug B), lack of applicability in the interventions or populations being evaluated, or use of indirect (surrogate) outcome measures.
- Imprecision refers to uncertainty in the estimate of effect due to very low numbers of patients or events and/or wide 95% confidence intervals that cross a clinical decision threshold (i.e. between recommending and not recommending treatment).
- Publication bias refers to selective publication of studies that show greater treatment effects (i.e. negative studies are suppressed).
- Quality of evidence can vary from outcome to outcome. The final quality assessment for the PICO question is based on the critical outcome with the lowest quality assessment.
- The level of evidence listed in this report for either an individual paper or a group of papers is not meant to be an absolute statement about the quality of the study (or studies) under consideration. Rather, the intention is to rate the paper(s) *in relation to the question being asked in this guideline*. Because of this, a very well conducted study might actually be rated down in this evidence report, possible reasons including that the population or intervention being studied does not completely match the population or intervention being examined by the PICO question in this guideline (in other words, downgrading for indirectness). The level of evidence may also be downgraded due to imprecision in the effect estimate (wide confidence intervals that cross the line of no effect, or a low number of patients or events). A combination of these factors may result in quality of evidence from a well-conducted study being rated as low.

Presentation of effects

- The treatment effects from continuous outcomes are presented as mean difference (MD) or standardized mean difference (SMD). The latter measure was used in instances where different measuring scales were combined in the analysis. For consistency of presentation, in some instances SMD was also used for evidence from single study comparisons in the same table where SMD was used for combined study comparisons.
- The treatment effects from binary (yes or no) outcomes are presented as relative effects and absolute effects.
- Relative effects capture the difference between intervention and control in relative terms. For example, a 10% event rate in controls and a 5% event rate in the intervention represents a 50% relative risk reduction (10% - 5%/ 10%)
- The same difference represents a 5% absolute risk reduction (10% - 5% = 5%). In general, for patients, the absolute effect is the most important.
- Relative effects for dichotomous outcomes in the tables are expressed as odds ratios (OR).
- In the tables, when OR is specified, the first intervention (e.g. NSAID or acetaminophen or placebo) is the reference intervention.

Evidence Summaries including Summary of Findings (= Tables under each PICO question, except some PICO questions for which no evidence was available)

- Whenever possible, data from different studies was combined and presented in GRADE summary-of-findings tables.
- A random effects meta-analysis (conducted in Review Manager) was performed to combine data from two or more studies
- Direct comparisons are situations where trials directly compare drug A to drug B within one of the patient subgroups covered in this guideline.
- Indirect comparisons: Some studies do not include a direct comparison of drugs or interventions specified in a given PICO question. For example, if a question specifies duloxetine versus NSAIDs as the comparison of interest, a trial that compares duloxetine plus NSAIDs to placebo plus NSAIDs indirectly addresses the question.
- Data from some studies could not be presented in GRADE summary-of-findings tables. This was usually because the studies did not report measures of dispersion (e.g. standard deviation, 95% confidence interval) that are necessary for calculation of between-group effect size estimates. In such instances we summarized the data in Word tables that follow the GRADE evidence tables under a given PICO question.

Interpreting the evidence

- It is important to take into account the information presented specifically as it relates to the question of interest. For example, when the only evidence for a given PICO question is indirect due to the comparison or patient population, it appropriately gets downgraded for indirectness as shown under the column labeled “indirectness.” Also, if the 95% confidence interval around an effect size is wide and

crosses the line of no difference between treatments, the evidence for that outcome is downgraded due to imprecision. Study design and risk of bias also may result in downgrades in the quality of evidence. The overall quality of evidence takes all these factors into account, and is appropriately rated as high, moderate, low or very low. This quality of evidence is key to your decisions.

Moving from evidence to recommendations

- In GRADE, recommendations can be either strong or conditional. Generally, strong recommendations are restricted to high or moderate quality evidence. Low quality evidence almost invariably mandates a weak recommendation.
- There are, however, situations in which low quality evidence can lead to strong recommendations. For instance, if there is low quality evidence favoring an intervention but high quality evidence of important harm then a strong recommendation against the intervention may be appropriate.

Bibliography of included studies

- A complete list of studies included as evidence for this report will appear at the end of this document upon completion of the literature search update. Shorter lists of studies included for each PICO question with an evidence base appear at the end of the summaries for each question

Hip and/or Knee Osteoarthritis

PICO 1: Aerobic training vs. usual care for knee and/or hip OA

Summary: Sixteen RCTs[1-16] of adults with knee OA and one RCT of adults with hip OA[17] evaluated aerobic training as treatment for knee OA compared to usual care. In samples with knee OA, eight studies[1-6,14-16] evaluated an intervention that consisted primarily of aerobic exercise, while the other seven studies[7-13] investigated interventions of aerobic exercise combined with strength training. Most interventions were 6-12 weeks, while others were 12-18 months[4,10,14].

In studies testing aerobic exercise only interventions, the meta-analysis indicated that the intervention group reported greater improvement in pain and self-reported function after a 6-12 week intervention[1-3,15], however these differences in pain were not sustained one year later[5]. There was no long term follow-up for self-reported function. There were no differences in pain and self-reported function between groups after a 1 year intervention, however the confidence in this result is low due to wide confidence intervals around the effect estimates.[4,14] The intervention group also demonstrated greater improvements for the 6MWT[6] and stair climbing[6]. There were mixed results for gait speed and the chair stand test, and the level of confidence of these outcomes were low as they were each only assessed in one study with a small sample size.[1,2]

In studies testing combined aerobic and strength training interventions, the results were mixed. The intervention group reported greater improvements in pain at short-term (3 month) follow-up[7]. There were no differences reported for pain or self-reported function after a 8-24 week[7-9,11] or 18 month intervention[10], however there is low confidence in these estimates due to wide confidence intervals. The results were also mixed for performance-based function. Those in the intervention group demonstrated greater improvements in the 6MWT after an 18 month intervention[10], on the 6MWT, TUG, and stair descent at short-term (3-6 month) follow-up.[7,12] There were no differences observed for the outcomes at other time points; however, imprecision was high due to wide confidence intervals around the effect estimates.

Teirlinck et al.[17] investigated aerobic exercise for people with hip OA. They observed that the intervention group had greater improvements in self-reported function after the intervention and in self-reported and performance-based function (TUG) at follow up. There were no significant between-group differences in pain; however, the confidence in the pain estimates is low due to wide confidence intervals around the effect estimates.

A literature search update in August 2018 identified two additional RCTs that addressed this comparison.[18,19] The findings of these studies did not alter the overall findings presented in the tables below.

Quality of evidence across all critical outcomes: Moderate

Table 1. Aerobic exercise compared to Usual care for Knee OA

Certainty assessment							Summary of findings				
№ of participants (studies) Follow-up	**Risk of bias**	**Inconsistency**	**Indirectness**	**Imprecision**	**Publication bias**	**Overall certainty of evidence**	**Number of participants**		**Relative effect (95% CI)**	**Anticipated absolute effects**	
							With Usual care for Knee OA	**With Aerobic exercise**		**Risk with Usual care for Knee OA**	**Risk difference with Aerobic exercise**
Pain - pre/post 6-12 week intervention (lower scores indicate improvement)											
261 (5 RCTs)	serious [a]	not serious	not serious	not serious	none	⨁⨁⨁◯ MODERATE	115	146	-	-	SMD **0.45 lower** (0.88 lower to 0.02 lower) **Favors aerobic**
Pain - 1 year follow up (6-12 wk intervention) (lower scores indicate improvement)											
52 (1 RCT)	serious [a]	not serious	not serious	serious [b]	none	⨁⨁◯◯ LOW	23	29	-	-	SMD **0.4 lower** (0.95 lower to 0.16 higher)
Pain - pre/post 1 year intervention (lower scores indicate improvement)											
160 (2 RCTs)	serious [a]	not serious	not serious	serious [b]	none	⨁⨁◯◯ LOW	81	79	-	-	SMD **0.11 lower** (0.42 lower to 0.2 higher)

Table 1. Aerobic exercise compared to Usual care for Knee OA											
Certainty assessment							Summary of findings				
Pain - 6 month follow up (1 year intervention) (lower scores indicate improvement)											
78 (1 RCT)	serious [a]	not serious	not serious	serious [b]	none	⨁⨁◯◯ LOW	35	43	-	-	SMD **0.01 higher** (0.44 lower to 0.45 higher)
Self-reported function - pre/post 6-12 week follow-up (lower scores indicate better function)											
56 (2 RCTs)	serious [a]	not serious	not serious	not serious	none	⨁⨁⨁◯ MODERATE	29	27	-	-	SMD **0.81 lower** (1.36 lower to 0.26 lower) **Favors aerobic**
Self-reported function - pre/post 1 year intervention (lower scores indicate improvement)											
160 (2 RCTs)	serious [a]	not serious	not serious	serious [b]	none	⨁⨁◯◯ LOW	80	80	-	-	SMD **0.23 lower** (0.6 lower to 0.15 higher)
Self-reported function - 6 month follow up (1 year intervention) (lower scores indicate improvement)											
78 (1 RCT)	serious [a]	not serious	not serious	serious [b]	none	⨁⨁◯◯ LOW	35	43	-	-	SMD **0.08 lower** (0.52 lower to 0.37 higher)

Table 1. Aerobic exercise compared to Usual care for Knee OA											
Certainty assessment							**Summary of findings**				
6-min walk test (higher numbers indicate improvement)											
412 (3 RCTs)	serious [a]	not serious	not serious	not serious	none	⨁⨁⨁◯ MODERATE	207	205	-	-	MD **98.65 higher** (23.57 lhigher to 173.73 higher) **Favors aerobic**
Stair climbing time (lower scores indicate improvement)											
293 (1 RCT)	serious [a]	not serious	not serious	not serious	none	⨁⨁⨁◯ MODERATE	149	144	-	-	MD **1.2 lower** (2.31 lower to 0.09 lower) **Favors aerobic**
Chair stand											
27 (1 RCT)	serious [a]	not serious	not serious	serious [c]	none	⨁⨁◯◯ LOW	13	14	-	-	MD **1.03 lower** (3.8 lower to 1.74 higher)
Gait speed – preferred (higher numbers indicate improvement)											

Table 1. Aerobic exercise compared to Usual care for Knee OA											
Certainty assessment							**Summary of findings**				
28 (1 RCT)	serious [a]	not serious	not serious	serious [c]	none	⨁⨁◯◯ LOW	15	13	-	-	MD **8.7 higher** (3.06 higher to 14.34 higher) **Favors aerobic**
Gait speed – max (higher numbers indicate improvement)											
28 (1 RCT)	serious [a]	not serious	not serious	serious [c]	none	⨁⨁◯◯ LOW	15	13	-	-	MD **9.4 higher** (2.5 lower to 21.4 higher)

CI: Confidence interval; **SMD:** Standardized mean difference; **MD:** Mean difference

Explanations

a. Participants not blinded, unclear if outcome assessors were blinded

b. Wide CI that crosses line of no effect

c. Single study, small sample size

Table 2. Aerobic exercise + strength training compared to usual care for knee OA									
Certainty assessment							**Summary of findings**		
№ of participants		**Inconsistency**	**Indirectness**	**Imprecision**	**Publication bias**	**Overall certainty**	**Number of participants**		**Anticipated absolute effects**

Table 2. Aerobic exercise + strength training compared to usual care for knee OA

Certainty assessment							Summary of findings				
(studies) Follow-up	**Risk of bias**					**of evidence**	**With usual care for knee OA**	**With Aerobic exercise + strength training**	**Relative effect (95% CI)**	**Risk with usual care for knee OA**	**Risk difference with Aerobic exercise + strength training**
Pain - 8-24 week intervention (lower scores indicate improvement)											
318 (4 RCTs)	serious [a]	not serious	not serious	serious [b]	none	⨁⨁◯◯ LOW	156	162	-	-	SMD **0.37 lower** (0.75 lower to 0.01 higher)
Pain - 18 month intervention (lower scores indicate improvement)											
158 (1 RCT)	serious [a]	not serious	not serious	serious [b]	none	⨁⨁◯◯ LOW	78	80	-	-	SMD **0.21 higher** (0.11 lower to 0.52 higher)
Pain - 3-month follow up (lower scores indicate improvement)											
107 (1 RCT)	serious [a]	not serious	not serious	not serious	none	⨁⨁⨁◯ MODERATE	56	51	-	-	SMD **0.76 lower** (1.15 lower to 0.37 lower) **Favors exercise**
Self-reported function - 8-24 week intervention (lower scores indicate improvement)											

Table 2. Aerobic exercise + strength training compared to usual care for knee OA											
Certainty assessment							**Summary of findings**				
220 (4 RCTs)	serious [a]	not serious	not serious	serious [b]	none	⨁⨁◯◯ LOW	104	116	-	-	SMD **0.3 lower** (0.82 lower to 0.22 higher)
Self-reported function - 18 month intervention (lower scores indicate improvement)											
158 (1 RCT)	serious [a]	not serious	not serious	serious [b]	none	⨁⨁◯◯ LOW	78	80	-	-	SMD **0.03 higher** (0.28 lower to 0.35 higher)
Self-reported function - 3-6mo follow up (lower scores indicate improvement)											
133 (2 RCTs)	serious [a]	not serious	not serious	serious [b]	none	⨁⨁◯◯ LOW	69	64	-	-	SMD **0.66 lower** (1.36 lower to 0.03 higher)
TUG - 20 week intervention (lower scores indicate improvement)											
114 (1 RCT)	serious [a]	not serious	not serious	serious [b]	none	⨁⨁◯◯ LOW	58	56	-	-	SMD **0.27 lower** (0.64 lower to 0.1 higher)
TUG - 3-month follow up (lower scores indicate improvement)											

Table 2. Aerobic exercise + strength training compared to usual care for knee OA											
Certainty assessment							**Summary of findings**				
103 (1 RCT)	serious [a]	not serious	not serious	not serious	none	⨁⨁⨁◯ MODERATE	55	48	-	-	SMD **0.41 lower** (0.8 lower to 0.02 lower) **Favors exercise**
6-min walk test - 20-24 week intervention (higher scores indicate improvement)											
140 (2 RCTs)	serious [a]	not serious	not serious	serious [b]	none	⨁⨁◯◯ LOW	71	69	-	-	MD **31.63 higher** (4.14 lower to 67.39 higher)
6-min walk test - 18-month intervention (higher scores indicate improvement)											
158 (1 RCT)	serious [a]	not serious	not serious	not serious	none	⨁⨁⨁◯ MODERATE	78	80	-	-	MD **53.3 higher** (17.98 lower to 88.62 higher) **Favors exercise**
6-min walk test - 3-6 month follow up (higher scores indicate improvement)											

Table 2. Aerobic exercise + strength training compared to usual care for knee OA											
Certainty assessment							**Summary of findings**				
129 (2 RCTs)	serious [a]	not serious	not serious	not serious	none	⨁⨁⨁◯ MODERATE	68	61	-	-	MD **43.35 higher** (7.77 higher to 78.93 higher) **Favors exercise**
Chair stand – 8 wk intervention (higher scores indicate improvement)											
51 (1 RCT)	serious [a]	not serious	not serious	serious [b]	none	⨁⨁◯◯ LOW	23	28	-	-	MD **1.4 higher** (2.07 lower to 4.87 higher)
Stair climbing time – 18 month intervention (lower scores indicate improvement)											
158 (1 RCT)	serious [a]	not serious	not serious	serious [b]	none	⨁⨁◯◯ LOW	78	80	-	-	MD **1.41 lower** (3.52 lower to 0.7 higher)
Stair ascent - 20 week intervention (lower scores indicate improvement)											
113 (1 RCT)	serious [a]	not serious	not serious	serious [b]	none	⨁⨁◯◯ LOW	58	55	-	-	MD **1 lower** (2.6 lower to 0.6 higher)
Stair ascent - 3-month follow up (lower scores indicate improvement)											

Table 2. Aerobic exercise + strength training compared to usual care for knee OA											
Certainty assessment							**Summary of findings**				
102 (1 RCT)	serious [a]	not serious	not serious	serious [b]	none	⨁⨁◯◯ LOW	55	47	-	-	MD **2.6 lower** (5.36 lower to 0.16 higher)
Stair descent - 8 week intervention (lower scores indicate improvement)											
113 (1 RCT)	serious [a]	not serious	not serious	serious [b]	none	⨁⨁◯◯ LOW	58	55	-	-	MD **1.5 lower** (3.33 lower to 0.33 higher)
Stair descent - 3-month follow up (lower scores indicate improvement)											
102 (1 RCT)	serious [a]	not serious	not serious	not serious	none	⨁⨁⨁◯ MODERATE	55	47	-	-	MD **2.1 lower** (3.79 lower to 0.41 lower) **Favors exercise**
5-min walk test 12-week intervention											
124 (1 RCT)	serious [a]	not serious	not serious	not serious	none	⨁⨁⨁◯ MODERATE	65	59	-	-	MD **42.19 higher** (14.19 higher to 70.19 higher) **Favors exercise**

Table 2. Aerobic exercise + strength training compared to usual care for knee OA											
Certainty assessment							**Summary of findings**				
Gait speed - preferred - 8 weeks intervention (higher scores indicate improvement)											
51 (1 RCT)	serious [a]	not serious	not serious	serious [b]	none	⨁⨁◯◯ LOW	23	28	-	-	MD **0.2 higher** (0.4 lower to 0.8 higher)

CI: Confidence interval; **SMD:** Standardised mean difference; **MD:** Mean difference

Explanations

a. Participants not blinded. Some studies blinded outcome assessors, others did not report whether assessors were blinded

b. Wide CI that crosses line of no effect

Table 3. RCT data not suitable for effect size calculation or combining with other data

Ref ID, Author, year	Study type	Duration	Population Description	Treatment given to relevant population	Results
4370, Dias, 2003	RCT Moderate quality	12 weeks treatment with 6 months follow up	Knee OA (Altman 1986 criteria): 50 randomized, 47 completed Exercise (n=24 completed, 84% female, age median 74) Control (n=23 completes, 92% female, age median 76)	Both groups - initial education session Exercise (2x/week exercise program including stretching, strengthening, and cool-down, and 3x/week 40 min walking program; all for 12 weeks) Control (to follow advice from education session)	Median [no IQR available] **SF-36 Bodily pain** Exercise: Baseline: 74 Post-treatment (12w): 100 Follow-up (6mo):100 Control: Baseline:74 Post-treatment (12w): 64 Follow-up (6mo): 0 **SF-36 Functional capacity** Exercise: Baseline: 55

					Post-treatment (12w): 72.5 Follow-up (6mo):77.5 <u>Control:</u> Baseline: 45 Post-treatment (12w): 45 Follow-up (6mo): 40

Table 4. Aerobic exercise compared to Usual care for Hip OA

Certainty assessment							Summary of findings				
№ of participants (studies) Follow-up	**Risk of bias**	**Inconsistency**	**Indirectness**	**Imprecision**	**Publication bias**	**Overall certainty of evidence**	**Number of participants**		**Relative effect (95% CI)**	**Anticipated absolute effects**	
							With Usual care for Hip OA	**With Aerobic exercise**		**Risk with Usual care for Hip OA**	**Risk difference with Aerobic exercise**
Pain (lower scores indicate improvement)											
203 (1 RCT)	serious [a]	not serious	not serious	serious [b]	none	⨁⨁◯◯ LOW	102	101	-	-	SMD **0.24 lower** (0.52 lower to 0.04 higher)
Pain - mid-term follow up (lower scores indicate improvement)											

Table 4. Aerobic exercise compared to Usual care for Hip OA											
Certainty assessment							**Summary of findings**				
203 (1 RCT)	serious [a]	not serious	not serious	serious [b]	none	⨁⨁◯◯ LOW	102	101	-	-	SMD **0.15 lower** (0.43 lower to 0.12 higher)
Self-reported function (lower scores indicate improvement)											
203 (1 RCT)	serious [a]	not serious	not serious	not serious	none	⨁⨁⨁◯ MODERATE	102	101	-	-	SMD **0.34 lower** (0.62 lower to 0.06 lower) **Favors aerobic**
Self-reported function – mid-term follow up (lower scores indicate improvement)											
203 (1 RCT)	serious [a]	not serious	not serious	not serious	none	⨁⨁⨁◯ MODERATE	102	101	-	-	SMD **0.35 lower** (0.62 lower to 0.07 lower) **Favors aerobic**
TUG – mid-term follow up (lower scores indicate improvement)											

Table 4. Aerobic exercise compared to Usual care for Hip OA											
Certainty assessment							**Summary of findings**				
203 (1 RCT)	serious [a]	not serious	not serious	not serious	none	⨁⨁⨁◯ MODERATE	102	101	-	-	SMD **0.3 lower** (0.57 lower to 0.02 lower) **Favors aerobic**

CI: Confidence interval; **SMD:** Standardised mean difference

Explanations

a. Participants not blinded; unclear if assessors blinded

b. Wide CI that crosses line of no effect

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PICO 2: Strength training plus usual care compared to usual care for Knee or Hip OA

Summary. The literature searches identified 24 RCTs that compared strength or resistance training to usual care in patients with hip or knee OA (Table 1). Pain: Multiple RCTs compared either strength training[1-5] or resistance training[6-10] with usual care or sham exercise reported lower pain level in the exercise intervention group measured by WOMAC pain subscale. Similar significant and precise results were reported with strength training exercise vs usual care when VAS pain scale was used to measure pain post intervention.[11-14] Similar lower level of pain on NRS pain scale and improvement in pain post intervention was reported in 3 RCTs, one with combined balance plus strength training intervention[15], other with strength plus ultrasound[16] and third with strength training plus flexibility[17] (vs control). Significant improvement was noted in change in pain level from baseline with strength[2,18-21] or resistance[22] training exercises as measured by WOMAC[2,18-20,22] and VAS[21,23] pain scales. One study of strength training did not find significant lowering of pain with strengthening exercise as measured by SF-36.[24]

Function: For self-reported function, multiple RCTs comparing either strength[1-4,15,17] or resistance[6-8] or combined[25] training to usual care/sham exercise, reported significantly lower or improvement in pain level using WOMAC pain subscale with exercise intervention compared to usual care. One study reported better functional level with exercise intervention using Lequesne Functional Index,[11] while another study failed to demonstrate a significant result using the SF36 scale.[24] For performance-based function, significant improvement in Timed Up and Go from baseline post exercise intervention was reported after resistance training by 1 RCT[22] but other RCTs could not demonstrate any benefit for timed Up and Go post treatment,[7,13,26] 6-minute walk time[6,7,26-28] or stride velocity[28] with exercise intervention.

Neuromuscular electrical stimulation (NMES) is the use of electrical stimulation to elicit muscle contractions. It is used to restore muscle activation or to improve strength. Five RCTs assessed pain and function outcomes with NMES compared to usual care(Table 2). The results varied somewhat by study design and scale used to measure outcomes. Two RCTs comparing NMES vs usual care did not find any improvement in pain, one used WOMAC pain scale[6] and the other used Arthritis Impact Measurement Scale post intervention between groups.[29] The same study did not find a significant difference between groups with respect to self-report function (WOMAC function at 14 week follow up) or performance-based (walk time in secs) function.[6] Two RCTs that combined exercise plus NMES intervention (one compared to education,[30] the other compared to exercise alone[31]) found significant improvement in pain, despite using different pain scales (NRS pain scale[30] and VAS pain scale[31] respectively). Neither study found a significant difference in performance-based physical function measured by Timed Up and Go.[30,31] In contrast, another RCT of NMES vs usual care found greater improvement (change) in WOMAC pain and function with NMES compared to controls.[32] None of these studies reported data concerning adverse events.

A literature search update in August 2018 identified two additional RCTs that addressed this comparison.[33,34] Neither study's results altered the findings in the tables below.

Quality of evidence across all critical outcomes: Moderate

Table 1: Strength training compared to usual care for Knee or Hip OA

Certainty assessment							Summary of findings				
№ of participants (studies) Follow-up	**Risk of bias**	**Inconsistency**	**Indirectness**	**Imprecision**	**Publication bias**	**Overall certainty of evidence**	**Number of participants**		**Relative effect (95% CI)**	**Anticipated absolute effects**	
							Controls	**With Exercise interventionPain and function outcomes**		**Risk with placebo**	**Risk difference with Exercise intervention: Pain and function outcomes**
WOMAC pain (mean post) (lower scores indicate improvement)											
753 (11 RCTs)	serious [a]	not serious	not serious	not serious	none	⨁⨁⨁◯ MODERATE	371	382	-	-	SMD **0.47 lower** (0.71 lower to 0.24 lower) **Favors strength training**
WOMAC pain (mean change) (lower scores indicate improvement)											
464 (5 RCTs)	serious [a]	not serious	not serious	not serious	none	⨁⨁⨁◯ MODERATE	210	254	-	-	SMD **1.41 lower** (2.33 lower to 0.49 lower) **Favors strength training**
VAS (0-10, mean) (lower scores indicate improvement)											
409 (4 RCTs)	serious [a]	not serious	not serious	not serious	none	⨁⨁⨁◯ MODERATE	205	204	-	-	MD **2.19 lower** (3.4 lower to 0.97 lower) **Favors strength training**

Table 1: Strength training compared to usual care for Knee or Hip OA											
Certainty assessment							Summary of findings				
VAS pain (0-10, mean change post) (lower scores indicate improvement)											
1601 (2 RCTs)	serious [a]	not serious	not serious	not serious	none	⨁⨁⨁◯ MODERATE	816	785	-	-	MD **0.79 lower** (1.35 lower to 0.23 lower) **Favors strength training**
SF 36 pain (mean, post) (lower scores indicate improvement)											
81 (1 RCT)	serious [a]	not serious	not serious	serious [b]	none	⨁⨁◯◯ LOW	38	43	-	-	MD **2.98 higher** (7.98 lower to 13.94 higher)
NRS pain (mean, post) (lower scores indicate improvement)											
78 (2 RCTs)	serious [a]	not serious	not serious	not serious	none	⨁⨁⨁◯ MODERATE	40	38	-	-	MD **2.56 lower** (3.69 lower to 1.43 lower) **Favors strength training**
NRS pain with activity (mean, post) (lower scores indicate improvement)											
88 (1 RCT)	serious [a]	not serious	not serious	not serious	none	⨁⨁⨁◯ MODERATE	43	45	-	-	MD **1.6 lower** (2.8 lower to 0.4 lower) **Favors strength training**

Table 1: Strength training compared to usual care for Knee or Hip OA											
Certainty assessment							Summary of findings				
Lequesne Functional Index (mean, post) (lower scores indicate improvement)											
55 (1 RCT)	serious [a]	not serious	not serious	not serious	none	⨁⨁⨁◯ MODERATE	27	28	-	-	MD **4.5 lower** (5.32 lower to 3.68 lower) **Favors strength training**
WOMAC function (mean, post) (lower scores indicate improvement)											
653 (11 RCTs)	serious [a]	not serious	not serious	not serious	none	⨁⨁⨁◯ MODERATE	320	333	-	-	SMD **0.53 lower** (0.77 lower to 0.29 lower) **Favors strength training**
WOMAC function (mean change) (lower scores indicate improvement)											
2001 (7 RCTs)	serious [a]	not serious	not serious	not serious	none	⨁⨁⨁◯ MODERATE	991	1010	-	-	SMD **1.43 lower** (2.14 lower to 0.71 lower) **Favors strength training**
SF 36 function (mean, post) (lower scores indicate improvement)											
81 (1 RCT)	serious [a]	not serious	not serious	serious [b]	none	⨁⨁◯◯ LOW	38	43	-	-	MD **7.83 higher** (3.26 lower to 18.92 higher)

Table 1: Strength training compared to usual care for Knee or Hip OA											
Certainty assessment							**Summary of findings**				
6 minute walk test (higher scores indicate improvement)											
89 (5 RCTs)	serious [a]	serious [b]	not serious	serious [b]	none	⨁◯◯◯ VERY LOW	39	50	-	-	MD **16.38 higher** (20.96 lower to 53.71 higher)
Timed up and go (mean, post) (lower scores indicate improvement)											
126 (3 RCTs)	serious [a]	not serious	not serious	serious [b]	none	⨁⨁◯◯ LOW	62	64	-	-	MD **0.35 lower** (1.17 lower to 0.47 higher)
Timed up and go (mean, change) (lower scores indicate improvement)											
41 (1 RCT)	serious [a]	not serious	not serious	not serious	none	⨁⨁⨁◯ MODERATE	17	24	-	-	MD **1.3 lower** (1.98 lower to 0.62 lower) **Favors strength training**
stride velocity m/s (mean post) (higher scores indicate improvement)											
31 (1 RCT)	serious [a]	not serious	not serious	serious [c]	none	⨁⨁◯◯ LOW	16	15	-	-	MD **0.01 lower** (0.13 lower to 0.11 higher)

CI: Confidence interval; **MD:** Mean difference

Explanations

a. Participants were not blinded; some studies did blind outcome assessors

b. Wide CI crosses line of significance

c. Small sample size

Table 2: NMES pain and function outcomes compared to placebo for Knee or Hip

Certainty assessment							Summary of findings				
№ of participants (studies) Follow-up	**Risk of bias**	**Inconsistency**	**Indirectness**	**Imprecision**	**Publication bias**	**Overall certainty of evidence**	**Number of participants**		**Relative effect (95% CI)**	**Anticipated absolute effects**	
							Controls	**With NMES pain and function outcomes**		**Risk with placebo**	**Risk difference with NMES pain and function outcomes**
WOMAC pain (0-20, mean, post) (lower scores indicate improvement)											
53 (2 RCTs)	serious [a]	not serious	not serious	serious [b]	none	⨁⨁◯◯ LOW	25	28	-	-	MD **0.3 lower** (3.48 lower to 2.88 higher)
VAS pain (0-10, mean, post) (lower scores indicate improvement)											
50 (1 RCT)	serious [a]	not serious	not serious	not serious	none	⨁⨁⨁◯ MODERATE	25	25	-	-	MD **1.7 lower** (2.98 lower to 0.42 lower) **Favors NMES**
WOMAC pain (0-20, mean change, post) (lower scores indicate improvement)											

Table 2: NMES pain and function outcomes compared to placebo for Knee or Hip											
Certainty assessment							**Summary of findings**				
30 (1 RCT)	serious [a]	not serious	not serious	not serious	none	⨁⨁⨁◯ MODERATE	14	16	-	-	MD **1.94 lower** (3.86 lower to 0.02 lower) **Favors NMES**
Arthritis Impact Measurement Scale 2–Pain Subscale(lower scores indicate improvement)											
38 (1 RCT)	serious [a]	not serious	not serious	serious [b]	none	⨁⨁◯◯ LOW	18	20	-	-	MD **0.81 lower** (2.25 lower to 0.63 higher)
NRS pain (mean, post) (lower scores indicate improvement)											
100 (1 RCT)	serious [a]	not serious	not serious	not serious	none	⨁⨁⨁◯ MODERATE	50	50	-	-	MD **1.44 lower** (2.65 lower to 0.23 lower) **Favors NMES**
WOMAC function (0-68, mean, post) (lower scores indicate improvement)											

Table 2: NMES pain and function outcomes compared to placebo for Knee or Hip											
Certainty assessment							**Summary of findings**				
53 (2 RCTs)	serious [a]	not serious	not serious	serious [b]	none	⨁⨁◯◯ LOW	25	28	-	-	MD **1.16 higher** (17.81 lower to 20.12 higher)
WOMAC disability (0-68, mean change, post) (lower scores indicate improvement)											
30 (1 RCT)	serious [a]	not serious	not serious	not serious	none	⨁⨁⨁◯ MODERATE	14	16	-	-	MD **9.92 lower** (16.71 lower to 3.13 lower) **Favors NMES**
Timed get up and go (mean, post) (lower scores indicate improvement)											
150 (2 RCTs)	serious [a]	not serious	not serious	serious [b]	none	⨁⨁◯◯ LOW	75	75	-	-	MD **1.24 lower** (3.83 lower to 1.35 higher)
Walk time in secs (mean, post)											

Table 2: NMES pain and function outcomes compared to placebo for Knee or Hip											
Certainty assessment							Summary of findings				
16 (1 RCT)	serious [a]	not serious	not serious	serious [b]	none	⨁⨁◯◯ LOW	6	10	-	-	MD **1.53 higher** (2.61 lower to 5.67 higher)

CI: Confidence interval; **MD:** Mean difference

Explanations

a Participants not blinded; most studies had blind outcome assessors

b. Wide CI crossing line of significance

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PICO 3: Neuromuscular training plus usual care compared to usual care for knee or hip OA

Summary: Neuromuscular training is an exercise regimen designed to improve unconscious control of joints during dynamic activity. The literature search identified four randomized controlled trials [1-4] that addressed this PICO question. The RCTs provided direct evidence by comparing usual care in combination with neuromuscular training to usual care only. The studies by Larsen et al. and Villadsen et al. found greater (improved) mean differences in KOOS pain and function scores (knee) in the neuromuscular training participants compared to usual care.[1,4] It was not possible to blind participants in these studies. This was corroborated with studies by Simao et al. and Trans et al.[2,3] in which mean WOMAC pain scores (knee) were found to be lower in the neuromuscular training group compared to usual care. Villadsen et al.[4] also found a greater mean difference in KOOS pain and function scores favoring neuromuscular training for patients with hip osteoarthritis. The study by Larsen et al.[1] reported an increased odds of musculoskeletal adverse events for participants in the neuromuscular training group compared to usual care; there were fewer gastrointestinal, CNS/psychiatric, and skin/subcutaneous adverse events for neuromuscular participants.

However, none of the adverse event findings showed a statistically significant between group difference, and the imprecision in the findings means the possibility of no difference between groups cannot be ruled out.

A literature search update in August 2018 identified one additional RCT that addressed this comparison.[5] The findings of this study do not alter the findings in the tables below.

Quality of evidence across all critical outcomes: Moderate

Table 1. PICO 3- Neuromuscular Training + Usual Care Compared to Usual Care

Certainty assessment							Summary of findings				
№ of participants (studies) Follow-up	**Risk of bias**	**Inconsistency**	**Indirectness**	**Imprecision**	**Publication bias**	**Overall certainty of evidence**	**Number of patients**		**Relative effect (95% CI)**	**Anticipated absolute effects**	
							With control	**With PICO 3-NM training**		**Risk with control**	**Risk difference with PICO 3-NM training**
KOOS pain (mean change), knee (higher scores indicate reduction in pain)											
258 (2 RCTs)	serious [a]	not serious	not serious	not serious	none	⨁⨁⨁◯ MODERATE	127	131	-	-	MD **2.18 higher** (1.73 higher to 2.64 higher) **Favors NM training**
HOOS pain (mean change), hip (higher scores indicate reduction in pain)											

Table 1. PICO 3- Neuromuscular Training + Usual Care Compared to Usual Care											
Certainty assessment							**Summary of findings**				
165 (1 RCT)	serious [a]	not serious	not serious	not serious	none	⨁⨁⨁◯ MODERATE	81	84	-	-	MD **8.4 higher** (7.91 higher to 8.89 higher) **Favors NM training**
KOOS ADL (knee) (higher scores indicate reduction in pain)											
258 (2 RCTs)	serious [a]	not serious	not serious	not serious	none	⨁⨁⨁◯ MODERATE	127	131	-	-	MD **1.54 higher** (2.37 lower to 5.46 higher)
KOOS ADL (hip) (higher scores indicate reduction in pain)											
165 (1 RCT)	serious [a]	not serious	not serious	not serious	none	⨁⨁⨁◯ MODERATE	81	84	-	-	MD **10.9 higher** (10.35 higher to 11.45 higher) **Favors NM training**
Adverse events (abdominal and intestinal symptoms)											
93 (1 RCT)	serious [a]	not serious	not serious	serious [b]	none	⨁⨁◯◯ LOW	25/47 (53.2%)	20/46 (43.5%)	**OR 0.68** (0.30 to 1.53)	532 per 1,000	**96 fewer per 1,000** (278 fewer to 103 more)

Table 1. PICO 3- Neuromuscular Training + Usual Care Compared to Usual Care											
Certainty assessment							**Summary of findings**				
Adverse events (musculoskeletal symptoms)											
93 (1 RCT)	serious [a]	not serious	not serious	serious [b]	none	⨁⨁◯◯ LOW	16/47 (34.0%)	21/46 (45.7%)	**OR 1.63** (0.70 to 3.76)	340 per 1,000	**116 more per 1,000** (75 fewer to 320 more)
Adverse events (CNS & psychiatric symptoms)											
93 (1 RCT)	serious [a]	not serious	not serious	serious [b]	none	⨁⨁◯◯ LOW	21/47 (44.7%)	19/46 (41.3%)	**OR 0.87** (0.38 to 1.98)	447 per 1,000	**34 fewer per 1,000** (212 fewer to 168 more)
Adverse events (skin & subcutaneous)											
93 (1 RCT)	serious [a]	not serious	not serious	serious [b]	none	⨁⨁◯◯ LOW	12/47 (25.5%)	9/46 (19.6%)	**OR 0.71** (0.27 to 1.89)	255 per 1,000	**60 fewer per 1,000** (171 fewer to 138 more)

CI: Confidence interval; **MD:** Mean difference; **OR:** Odds ratio

Explanations

a. participants not blinded; all studies were single blind (outcome assessors or personnel blinded)

b. Wide 95% CI that overlaps the line of no effect

Table 2. RCT data not suitable for effect size calculation or combining with other data

Ref ID, Author, year	Study type	Duration	Population Description	Treatment given to relevant population	Results
3952_Simao	RCT	12 weeks	Group 1: N=10, mean age 75 (7.4), mean BMI 27.4 (9.7), % women 82 Group 2: N= 10, mean age 69 (3.7), mean BMI 29.8 (2.53), % women 90 Group 3: N=11, mean age 71 (5.3), mean BMI 26.7 (2.74), % women 91	Group 1: squat exercises on a vibratory platform(platform group) Group 2: squat exercises without vibration(squat group) Group 3: the control group.	**Change in WOMAC pain median (IQ range):** **Group 1:** -137.5 (-200 to 0) **Group 2:** -62.5 (-325 to 75) **Group 3:** 0 (-125 to 125) **Change in WOMAC function median (IQ range):** **Group 1:** -175 (-550 to 100) **Group 2:** -100 (-725 to 275) **Group 3:** 75 (-225 to 400)
2555_Tran	RCT	8 weeks	Only women -Clinical and radiographic knee OA, disease duration 2-10 years Group 1: N=18, mean age 58.7 (11.0), mean BMI 29.1 (5.8) Group 2: N=17, mean age 61.5 (9.2), mean BMI 29.2 (6.1) Group 3: N=17, mean age 61.1 (8.5), mean BMI 30.2 (5.4)	3 arms: 1) Balance board with built-in vibration (n=18): vibration frequency increased gradually from 24 Hz to 30 Hz, supervised by physiotherapist, usual care with paracetamol/nsaids, N=18 2) Stable vibration platform (n=17): vibration frequency increased gradually from 24 Hz to 30 Hz, supervised by physiotherapist, usual care with paracetamol/nsaids.N=17 3) Control (n=17): No training session, usual care with paracetamol/nsaids N=17	**WOMAC pain, weighted mean difference (95% CI):** **Group 1 vs 3:** −6.8 (−20.1-6.6) **Group 2 vs 3**: −1.4 (−14.6-11.9)

Ref ID, Author, year	Study type	Duration	Population Description	Treatment given to relevant population	Results
2561_Holsgaard-Larsen	RCT	8 weeks	N=93, men + women (62% in Nemex group, 54% in control group) with Knee OA defined clinically (ACR criteria) -Ages 40-70, mean ae 58years -mean BMI 27	1) Group 1: NEMEX arm: supervised neuromuscular exercises for 8 weeks 2) Group 2: acetaminophen 2000mg/day or equivalent dose of nsaids	**Between group difference in outcomes from baseline (95% CI):** **Koos pain:** -2.07 (-6.45, 2.29) **Koos ADL:** 0.5 (-4.02, 5.01) **Koos sports/recrea:** -2.83 (-10.38, 4.72)

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PICO 4: Aquatic exercises compared to usual care for knee/hip OA

Summary. Twelve RCTs[1-12] compared aquatic exercise to usual care for the treatment of knee and/or hip OA. In adults with knee OA, aquatic exercise did not result in greater improvements in knee pain, self-reported function, or performance based function (Table 1); however, the certainty in these outcomes was low, due to wide confidence intervals for all outcomes.[1-4] Lund et al.[3] also reported no increased risk of pain for those undergoing aquatic exercise; however, the confidence intervals were wide.

Two studies[5,6] evaluated aquatic exercise in adults with hip OA (Table 2). Stener-Victorin et al.[6] observed an improvement in hip pain that lasted up to 6-months after the intervention, however the sample size was small. Arnold et al.[5] did not observe differences in performance-based function (6MWT, 30-sec chair stand, and TUG cognitive). There is reduced confidence in these results as only one study reported each outcome.

Six studies[7-12] evaluated aquatic exercise in mixed samples of knee and/or hip OA. The meta-analysis indicated that those who participated in aquatic exercise reported greater improvements in pain[7-11], self-reported function[7-11], and performance-based function (6MWT[7,8], TUG[7,9,11], stair climbing[9,10]). One smaller study[12] did not report results conducive to meta-analysis, and reported no difference between the aquatic exercise group and a control group.

The participants were not blinded in any studies comparing aquatic exercise to a control.

Quality of evidence across all critical outcomes: Moderate

Table 1. Aquatic exercises compared to usual care for Knee OA

Certainty assessment							Summary of findings				
№ of participants (studies) Follow-up	Risk of bias	Inconsistency	Indirectness	Imprecision	Publication bias	Overall certainty of evidence	Number of Participants/ Study event rates (%)		Relative effect (95% CI)	Anticipated absolute effects	
							With placebo	With Aquatic v. Usual Care for Knee OA		Risk with placebo	Risk difference with Aquatic v. Usual Care for Knee OA
Pain (lower scores indicate improvement)											

Table 1. Aquatic exercises compared to usual care for Knee OA											
Certainty assessment							**Summary of findings**				
199 (3 RCTs)	serious [a]	serious [b]	not serious	serious [c]	none	⨁⨁◯◯ LOW	98	101	-	-	SMD **0.01 lower** (0.78 lower to 0.75 higher)
Self-reported function (lower scores indicate improvement)											
243 (4 RCTs)	serious [a]	not serious	not serious	not serious	none	⨁⨁⨁◯ MODERATE	118	125	-	-	SMD **0.35 lower** (0.67 lower to 0.03 lower) **Favors aquatic**
Pain - Long-term follow-up (>12-months) (lower scores indicate improvement)											
76 (1 RCT)	serious [a]	not serious	not serious	serious [c]	none	⨁⨁◯◯ LOW	36	40	-	-	SMD **0.15 lower** (0.6 lower to 0.3 higher)
Self-reported function - Long-term follow-up (>12-month) (lower scores indicate improvement)											
76 (1 RCT)	serious [a]	not serious	not serious	serious [c]	none	⨁⨁◯◯ LOW	36	40	-	-	SMD **0.07 lower** (0.52 lower to 0.38 higher)
Gait speed (higher scores indicate improvement)											

Table 1. Aquatic exercises compared to usual care for Knee OA											
Certainty assessment							**Summary of findings**				
84 (1 RCT)	serious [a]	not serious	not serious	not serious	none	⨁⨁⨁◯ MODERATE	42	42	-	-	MD **0.05 higher** (0.04 higher to 0.07 higher) **Favors aquatic**
Gait speed - Long-term follow-up (>12 months) (higher scores indicate improvement)											
76 (1 RCT)	serious [a]	not serious	not serious	not serious	none	⨁⨁⨁◯ MODERATE	36	40	-	-	MD **0.05 higher** (0.03 higher to 0.06 higher) **Favors aquatic**
Safety: Increased pain											
50 (1 RCT)	serious [a]	not serious	not serious	serious [c]	none	⨁⨁◯◯ LOW	0/24 (0.0%)	3/26 (11.5%)	**OR 7.30** (0.36 to 149.06)	0 per 1,000	**Not calculable**

CI: Confidence interval; **SMD:** Standardised mean difference; **MD:** Mean difference; **OR:** Odds ratio

Explanations

a. Participants not blinded, most studies blinded outcome assessors

b. I-squared=86%

c. Wide CI

Table 2. Aquatic exercises compared to Usual Care for Hip OA

Certainty assessment							Summary of findings				
№ of participants (studies) Follow-up	**Risk of bias**	**Inconsistency**	**Indirectness**	**Imprecision**	**Publication bias**	**Overall certainty of evidence**	**Number of participants**		**Relative effect (95% CI)**	**Anticipated absolute effects**	
							With Usual Care for Hip OA	**With Aquatic**		**Risk with Usual Care for Hip OA**	**Risk difference with Aquatic**
6-min Walk Test (higher scores indicate improvement)											
51 (1 RCT)	serious [a]	not serious	not serious	serious [b]	none	⨁⨁◯◯ LOW	25	26	-	-	MD **14.2 higher** (24.51 lower to 52.91 higher)
30-sec chair stand (higher scores indicate improvement)											
51 (1 RCT)	serious [a]	not serious	not serious	not serious	none	⨁⨁⨁◯ MODERATE	25	26	-	-	MD **0** (0.93 lower to 0.93 higher)
TUG - cognitive (dual task TUG) (lower scores indicate improvement)											
51 (1 RCT)	serious [a]	not serious	not serious	not serious	none	⨁⨁⨁◯ MODERATE	25	26	-	-	MD **0.9 lower** (2.96 lower to 1.16 higher)

CI: Confidence interval; **MD:** Mean difference

Explanations

a. Participants not blinded; outcome assessors were blinded

b. Wide CI

Table 3. Aquatic exercises compared to Usual Care for Knee or Hip OA

Certainty assessment							Summary of findings				
№ of participants (studies) Follow-up	**Risk of bias**	**Inconsistency**	**Indirectness**	**Imprecision**	**Publication bias**	**Overall certainty of evidence**	**Number of participants**		**Relative effect (95% CI)**	**Anticipated absolute effects**	
							With Usual Care for Knee or Hip OA	**With Aquatic**		**Risk with Usual Care for Knee or Hip OA**	**Risk difference with Aquatic**
Pain (lower scores indicate improvement)											
550 (5 RCTs)	serious [a]	not serious	not serious	not serious	none	⨁⨁⨁◯ MODERATE	267	283	-	-	SMD **0.32 lower** (0.51 lower to 0.12 lower) **Favors aquatic**
Self-reported function (lower scores indicate improvement)											
545 (5 RCTs)	serious [a]	not serious	not serious	not serious	none	⨁⨁⨁◯ MODERATE	265	280	-	-	SMD **0.32 lower** (0.49 lower to 0.15 lower) **Favors aquatic**
TUG (lower scores indicate improvement)											

Table 3. Aquatic exercises compared to Usual Care for Knee or Hip OA											
Certainty assessment							Summary of findings				
202 (3 RCTs)	serious [a]	not serious	not serious	not serious	none	⨁⨁⨁◯ MODERATE	91	111	-	-	MD **0.89 lower** (1.32 lower to 0.47 lower) **Favors aquatic**
6MWT (higher scores indicate improvement)											
109 (2 RCTs)	serious [a]	not serious	not serious	serious [b]	none	⨁⨁◯◯ LOW	53	56	-	-	MD **27.89 higher** (4.25 lower to 60.02 higher)
Stair climbing (lower scores indicate improvement)											
96 (1 RCT)	serious [a]	not serious	not serious	not serious	none	⨁⨁⨁◯ MODERATE	41	55	-	-	MD **1.6 lower** (2.71 lower to 0.49 lower) **Favors aquatic**
Timed stair ascent (lower scores indicate improvement)											

Table 3. Aquatic exercises compared to Usual Care for Knee or Hip OA											
Certainty assessment							Summary of findings				
309 (1 RCT)	serious [a]	not serious	not serious	not serious	none	⨁⨁⨁◯ MODERATE	157	152	-	-	MD **0.54 lower** (1.06 lower to 0.02 lower) **Favors aquatic**
Timed stair descent (lower scores indicate improvement)											
308 (1 RCT)	serious [a]	not serious	not serious	not serious	none	⨁⨁⨁◯ MODERATE	157	151	-	-	MD **0.67 lower** (1.19 lower to 0.15 lower) **Favors aquatic**
8ft walk timed (lower scores indicate improvement)											
312 (1 RCT)	serious [a]	not serious	not serious	serious [b]	none	⨁⨁◯◯ LOW	159	153	-	-	MD **0.33 lower** (0.67 lower to 0.01 higher)

CI: Confidence interval; **SMD:** Standardised mean difference; **MD:** Mean difference

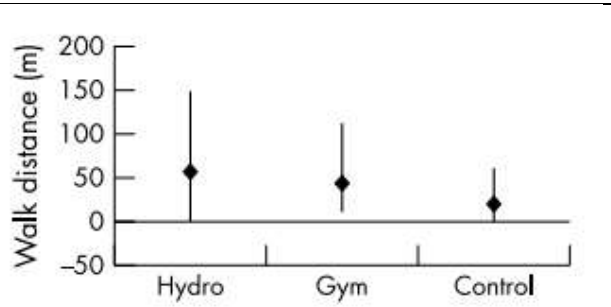
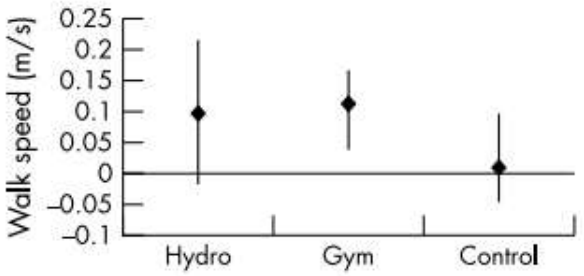
Explanations

a. Participants not blinded; most studies blinded outcome assessors

b. Wide CI

Table 4. RCTs with data not usable in RevMan

Ref ID, Author, year	Study type	Duration	Population Description	Treatment given to relevant population	Results
1211 Stener-Victorin, 2004 Low quality	RCT	5 week intervention	Hip OA (on THR waitlist) Aquatic (n=15, 70.3 years, 8F:7M) Control (n=15, 65.5 years, 9F:6M)	2x/week for 5 weeks, 30 min each Aquatic (warm-up, mobility, strengthening, stretching + patient education) Control (patient education only; 2 meetings, 2 hours each - disease info, home exercise program)	Outcomes available at pre, post, 1m-post, 3m-post, 6m-post Reported here pre, 1-month, 6-month; did not report post because not given for control group VAS pain with motion/load [medians (25^{th}, 75^{th})] Aquatic: - Pre: 55 (32, 64) - 1-month: 30 (18, 59) - 6-months: 28 (18, 70) Control: - Pre: 56 (46, 70) - 1-month: 48.5 (26, 66) - 6-months: 59 (51, 69)
1890, Foley, 2003 Moderate quality – participants not blinded, otherwise ok	RCT	6 week intervention	Hip or knee OA: Group 1 (hydrotherapy: n = 35, mean age 73.0 (8.2), 43% female Group 2 (exercise): n = 35, mean age 69.8 (9.2), 49% female Group 3 (control): n = 35, mean age 69.8	3 arms, 3 exercise sessions/week for 6 weeks: Group 1: hydrotherapy (n = 35) Group 2: exercise (n = 35) Group 3: control (n = 35).	Comparisons for hydrotherapy vs. control: All results presented as median (IQR): WOMAC Pain at post – median change: Hydro: -1.0 (3.0) Control: 1.0 (3.0) WOMAC Function – median change: Hydro: -1.0 (10.0) Control: 0.0 (8.0) 6MWT – median change (IQR)

			(9.0), 57% female		 Walking speed – median change (IQR): 

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PICO 5: Balance training compared to usual care for knee OA

Summary: Four RCTs[1-4] compared balance training compared to usual care for the treatment of knee OA. The meta-analysis of three studies[1,2,4] and the supplemental results of an additional study[3] indicate that balance training may improve pain and performance-based function in adults with knee OA. However, the quality of evidence was low due to lack of blinding, high inconsistency, small sample sizes, and wide confidence intervals.

Quality of evidence across all critical outcomes: Low

Table 1. Balance training compared to usual care for knee OA

Certainty assessment							Summary of findings		
№ of participan	Risk of bias	Inconsistency	Indirectness	Imprecision	Publication bias	Overall certainty	Number of participants	Relative effect	Anticipated absolute effects

Table 1. Balance training compared to usual care for knee OA											
Certainty assessment							Summary of findings				
ts (studies) Follow-up						of evidence	With Usual care for knee OA	With Balance training	(95% CI)	Risk with Usual care for knee OA	Risk difference with Balance training
WOMAC pain (mean, post intervention) (lower scores indicate improvement)											
70 (2 RCTs)	serious [a]	not serious	not serious	serious [c]	none	⨁⨁◯◯ LOW	32	38	-	-	SMD **0.46 lower** (1.39 lower to 0.46 higher)
NRS Pain (mean, post-intervention) (lower scores indicate improvement)											
44 (1 RCT)	serious [a]	not serious	not serious	serious [c,d]	none	⨁⨁◯◯ LOW	22	22	-	-	SMD **0.97 lower** (1.6 lower to 0.34 lower) **Favors balance training**
WOMAC function (mean, post intervention) (lower scores indicate improvement)											
114 (3 RCTs)	serious [a]	not serious	not serious	serious [c]	none	⨁⨁◯◯ LOW	54	60	-	-	SMD **0.51 lower** (1.29 lower to 0.26 higher)

CI: Confidence interval; **SMD:** Standardised mean difference

Explanations

a. Participants and investigators not blinded; no mention of blinding outcome assessors

c. Wide CI

d. Single study, small sample size

Table 2. RCTs with data not suitable for RevMan

Ref ID, Author, year	Study type	Duration	Population Description	Treatment given to relevant population	Results
5485, Sekir, 2005	RCT Low quality	6 weeks	Knee OA (bilateral ACR criteria) Treatment (n=12, 9F:3M, age 59(8.9)) Control (n=10, 7F:3M, age 62(8.1))	Treatment (dynamic balance exercises including walking and stairs in different conditions; frequency progressive from week 1 to week 6, however unclear if increased reps in a session, or increased sessions in a week) Control (no treatment)	Results presented as **mean (IQR)**. VAS pain with walking (15m walk): Training Pre: 3.5 (1.0, 6.9) Post: 1.6 (.0, 2.7) Non-training Pre: 3.4 (1.7, 5.6) Post: 3.9 (1.3, 6.3) 15-m walk time: Training Pre: 10.3 (9.1, 11.8) Post: 9.4 (8.3, 10.8) Non-training Pre: 12.1 (10.6, 13.3) Post: 11.9 (10.5, 13.1) Ambulatory negotiation (Stand-up and 15-m walk) time: Training Pre: 11.3 (10.7, 12.9) Post: 10.0 (8.6, 11.5) Non-training Pre: 13.3 (11.7, 15.5) Post: 12.6 (10.8, 14.6) Chair Rise time: Training Pre: 30.2 (26.8, 34.8) Post: 26.5 (23.2, 31.9) Non-training Pre: 32.8 (28.8, 35.4) Post: 31.8 (28.9, 33.1) Descending stairs time: Training Pre: 8.1 (6.6, 9.9) Post: 6.2 (5.2, 6.9) Non-training Pre: 10.9 (6.6, 13.3) Post: 10.3 (6.6, 10.2) Ascending stairs time: Training pre: 8.2 (7.0, 9.7) Post: 7.0 (6.0, 8.3) Non-training pre: 9.2 (7.2, 9.5) post: 8.9 (7.0, 9.2)

References

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PICO 6. Walking compared to usual care for patients with knee or hip OA

Summary: Studies that addressed this question also addressed PICO 1 and are included in that evidence summary.

PICO 7: Strength training compared to aerobic exercise for knee and/or hip OA

Summary: Two studies[1,2] compared strength training and aerobic exercise for the treatment of knee OA, while one study[3] compared these interventions for the treatment of hip OA. The comparisons between adults with knee OA who underwent strength training compared to aerobic exercise (walking program) were inconclusive with regard to pain, self-reported function, and performance-based function (including a 6-minute walk test, 30-second chair stand test, and the stair climbing test). The findings were imprecise since most outcomes were evaluated in a single study with low sample size and the confidence intervals were wide. In adults with hip OA, Bieler et al.[3] evaluated the effects of a Nordic walking program compared to strength training and home exercises. They observed that the Nordic walking group demonstrated greater improvements in the 6-minute walk test at post-treatment and at 8-month follow up and in the Timed-Up and Go (TUG) at 8-month follow-up. Other pain, self-report function, and performance-based measures were similar between the groups, however some results (TUG at post-treatment, and self-reported function, chair stand test, and stair climbing test at 8-month follow-up) were imprecise with wide confidence intervals.[3]

Quality of Evidence: Very low for knee OA; Low for hip OA

Table 1. Strength training compared to Aerobic exercise for Knee OA

Certainty assessment							Summary of findings				
№ of participants (studies) Follow-up	Risk of bias	Inconsistency	Indirectness	Imprecision	Publication bias	Overall certainty of evidence	Number of participants		Relative effect (95% CI)	Anticipated absolute effects	
							With Aerobic exercise for Knee OA	With Strength training		Risk with Aerobic exercise for Knee OA	Risk difference with Strength training
WOMAC Pain (0-20, lower score indicates pain reduction)											

Table 1. Strength training compared to Aerobic exercise for Knee OA											
Certainty assessment							Summary of findings				
29 (1 RCT)	serious [a]	not serious	not serious	serious [b]	none	⨁⨁◯◯ LOW	14	15	-	-	MD **1.44 lower** (3.74 lower to 0.86 higher)
WOMAC function (0-68, lower score indicates improved function)											
29 (1 RCT)	serious [a]	not serious	not serious	serious [b]	none	⨁⨁◯◯ LOW	14	15	-	-	MD **6.05 lower** (14.05 lower to 1.95 higher)
6-min walk test (higher numbers indicate improvement)											
319 (2 RCTs)	serious [a]	serious [c]	not serious	serious [d]	none	⨁◯◯◯ VERY LOW	158	161	-	-	SMD **0.11 lower** (1.01 lower to 0.8 higher)
30-sec chair stand (higher score indicates improvement)											
29 (1 RCT)	serious [a]	not serious	not serious	serious [b]	none	⨁⨁◯◯ LOW	14	15	-	-	MD **1.06 lower** (3.76 lower to 1.64 higher)
Timed Stair Climbing (lower score indicates improvement)											

Table 1. Strength training compared to Aerobic exercise for Knee OA											
Certainty assessment							**Summary of findings**				
290 (1 RCT)	serious [a]	not serious	not serious	not serious	none	⨁⨁⨁◯ MODERATE	144	146	-	-	MD **0.5 higher** (0.61 lower to 1.61 higher)

CI: Confidence interval; **MD:** Mean difference; **SMD:** Standardized mean difference

Explanations

a. Randomization and blinding not well described

b. Single study with small sample size and wide CI that crosses line of no effect

c. Studies on opposite sides of the no effect line

d. Wide CI

Table 2. Strength training compared to Aerobic exercise for Hip OA											
Certainty assessment							**Summary of findings**				
№ of participants (studies) Follow-up	**Risk of bias**	**Inconsistency**	**Indirectness**	**Imprecision**	**Publication bias**	**Overall certainty of evidence**	**Number of participants**		**Relative effect (95% CI)**	**Anticipated absolute effects**	
							With Aerobic exercise for Hip OA	**With Strength training**		**Risk with Aerobic exercise for Hip OA**	**Risk difference with Strength training**
WOMAC Pain (0-20, lower scores indicate improvement)											

Table 2. Strength training compared to Aerobic exercise for Hip OA											
Certainty assessment							**Summary of findings**				
100 (1 RCT)	serious [a]	not serious	not serious	not serious	none	⨁⨁⨁◯ MODERATE	50	50	-	-	MD **0.2 higher** (1.1 lower to 1.5 higher)
WOMAC function (0-68, lower scores indicate improvement)											
100 (1 RCT)	serious [a]	not serious	not serious	not serious	none	⨁⨁⨁◯ MODERATE	50	50	-	-	MD **1 lower** (6.27 lower to 4.27 higher)
Chair stand test (higher scores indicate improvement)											
100 (1 RCT)	serious [a]	not serious	not serious	not serious	none	⨁⨁⨁◯ MODERATE	50	50	-	-	MD **1.1 lower** (2.38 lower to 0.18 higher)
Stair climbing (higher scores indicate improvement)											
100 (1 RCT)	serious [a]	not serious	not serious	not serious	none	⨁⨁⨁◯ MODERATE	50	50	-	-	MD **1.1 lower** (to 2.24 lower to 0.04 higher)
TUG (lower scores indicate improvement)											

Table 2. Strength training compared to Aerobic exercise for Hip OA											
Certainty assessment							**Summary of findings**				
100 (1 RCT)	serious [a]	not serious	not serious	serious [b]	none	⨁⨁◯◯ LOW	50	50	-	-	MD **0.6 higher** (0.19 lower to 1.39 higher)
6-min Walk Test (higher scores indicate improvement)											
100 (1 RCT)	serious [a]	not serious	not serious	not serious	none	⨁⨁⨁◯ MODERATE	50	50	-	-	MD **39 lower** (15.98 lower to 62.02 lower) **Favors aerobic**
WOMAC Pain - 8-month follow up (0-20, lower scores indicate improvement)											
100 (1 RCT)	serious [a]	not serious	not serious	not serious	none	⨁⨁⨁◯ MODERATE	50	50	-	-	MD **1.15 higher** (0.34 lower to 2.64 higher)
WOMAC function - 8-month follow up (0-68, lower scores indicate improvement)											
100 (1 RCT)	serious [a]	not serious	not serious	serious [b]	none	⨁⨁◯◯ LOW	50	50	-	-	MD **4.5 higher** (1.37 lower to 10.37 higher)

Table 2. Strength training compared to Aerobic exercise for Hip OA											
Certainty assessment							Summary of findings				
Chair stand test - 8-month follow up (higher scores indicate improvement)											
100 (1 RCT)	serious [a]	not serious	not serious	serious [b]	none	⨁⨁◯◯ LOW	50	50	-	-	MD **1.4 lower** (3.13 lower to 0.33 higher)
Stair climbing - 8-month follow up (higher scores indicate improvement)											
100 (1 RCT)	serious [a]	not serious	not serious	serious [b]	none	⨁⨁◯◯ LOW	50	50	-	-	MD **1.5 lower** (3.12 lower to 0.12 higher)
TUG - 8-month follow up (lower scores indicate improvement)											
100 (1 RCT)	serious [a]	not serious	not serious	not serious	none	⨁⨁⨁◯ MODERATE	50	50	-	-	MD **0.7 lower** (0.01 lower to 1.39 lower) **Favors aerobic**
6-min Walk Test - 8-month follow up (higher scores indicate improvement)											

Table 2. Strength training compared to Aerobic exercise for Hip OA											
Certainty assessment							Summary of findings				
100 (1 RCT)	serious [a]	not serious	not serious	not serious	none	⨁⨁⨁◯ MODERATE	50	50	-	-	MD **70 lower** (25.52 lower to 114.48 lower) **Favors aerobic**

CI: Confidence interval; **MD:** Mean difference

Explanations

a. Participants not blinded; outcome assessor was blinded

b. Wide CI

References

1. Samut G, Dincer F, Ozdemir O. The effect of isokinetic and aerobic exercises on serum interleukin-6 and tumor necrosis factor alpha levels, pain, and functional activity in patients with knee osteoarthritis. *Mod Rheumatol.* 2015;25(6):919-924.
2. Ettinger WH, Jr., Burns R, Messier SP, et al. A randomized trial comparing aerobic exercise and resistance exercise with a health education program in older adults with knee osteoarthritis. The Fitness Arthritis and Seniors Trial (FAST). *JAMA.* 1997;277(1):25-31.
3. Bieler T, Siersma V, Magnusson SP, Kjaer M, Christensen HE, Beyer N. In hip osteoarthritis, Nordic Walking is superior to strength training and home-based exercise for improving function. *Scand J Med Sci Sports.* 2017;27(8):873-886.

PICO 8. Neuromuscular training plus usual care compared to aerobic exercise plus usual care

Summary. The literature searches did not identify any studies that addressed this comparison.

Quality of evidence across all critical outcomes: Very low

PICO 9: Aquatic exercise (+usual care) vs. Aerobic (+usual care) for people with knee and/or hip OA.

Summary: Three studies[1-3] compared aquatic exercise to aerobic exercise for adults with predominately knee OA, while one RCT[4] evaluated these exercise programs in adults with knee or hip OA who were preparing for TKA or THA. Generally, the interventions resulted in no difference in pain, self-reported function, and performance-based function; however, the findings were imprecise as the confidence intervals were wide. The quality of evidence was low, due to wide confidence intervals and lack of blinding for the participants.

Quality of evidence across all critical outcomes: Low

Table 1. Aquatic compared to Aerobic (land) for knee OA

Certainty assessment							Summary of findings				
№ of participants (studies) Follow-up	**Risk of bias**	**Inconsistency**	**Indirectness**	**Imprecision**	**Publication bias**	**Overall certainty of evidence**	**Number of subjects**		**Relative effect (95% CI)**	**Anticipated absolute effects**	
							With Aerobic (land) for knee OA	**With Aquatic**		**Risk with Aerobic (land) for knee OA**	**Risk difference with Aquatic**
Pain (lower scores indicate improvement)											
100 (2 RCTs) [c]	serious [a,b]	not serious	not serious	serious [d]	none	⨁⨁◯◯ LOW	50	50	-	-	SMD **0.21 higher** (0.19 lower to 0.6 higher)
Self-reported Function (lower scores indicate improvement)											
146 (3 RCTs) [e]	serious [a,b]	not serious	not serious	serious [d]	none	⨁⨁◯◯ LOW	72	74	-	-	SMD **0.1 higher** (0.3 lower to 0.51 higher)
6-min walk test (higher scores indicate improvement)											

Table 1. Aquatic compared to Aerobic (land) for knee OA											
Certainty assessment							**Summary of findings**				
100 (2 RCTs)	serious [a,b]	not serious	not serious	serious [d]	none	⨁⨁◯◯ LOW	50	50	-	-	SMD **0.08 lower** (0.47 lower to 0.31 higher)

CI: Confidence interval; **SMD:** Standardized mean difference

Explanations

a. Participants and personnel not blinded; outcome assessors were blinded

b. Personnel providing treatment not blinded

c. Alkatan reported WOMAC pain; Wang reported KOOS pain.

d. Wide CI

e. Alkatan reported WOMAC function; Lim reported SF-36 PCS; Wang reported KOOS function.

Table 2. Aquatic compared to Aerobic (land) for knee AND hip OA										
Certainty assessment							**Summary of findings**			
№ of participants (studies) Follow-up	**Risk of bias**	**Inconsistency**	**Indirectness**	**Imprecision**	**Publication bias**	**Overall certainty of evidence**	**Study event rates (%)**		**Relative effect (95% CI)**	**Anticipated absolute effects**	
							With Aerobic (land) for knee AND hip OA	**With Aquatic**		**Risk with Aerobic (land) for knee AND hip OA**	**Risk difference with Aquatic**
Pain (WOMAC) (lower scores indicate improvement)											

Table 2. Aquatic compared to Aerobic (land) for knee AND hip OA											
Certainty assessment							Summary of findings				
66 (1 RCT)	serious [a,b]	not serious	not serious	serious [c]	none	⨁⨁◯◯ LOW	34	32	-	-	SMD **0.1 higher** (0.38 lower to 0.59 higher)
Self-reported function (WOMAC) (lower scores indicate improvement)											
66 (1 RCT)	serious [a,b]	not serious	not serious	serious [c]	none	⨁⨁◯◯ LOW	34	32	-	-	SMD **0.03 higher** (0.45 lower to 0.52 higher)
30-sec Chair Stand											
65 (1 RCT)	serious [a,b]	not serious	not serious	serious [c]	none	⨁⨁◯◯ LOW	34	31	-	-	SMD **0.33 lower** (0.83 lower to 0.16 higher)

CI: Confidence interval; **SMD:** Standardised mean difference

Explanations

a. Participants were not blinded; outcome assessor was blinded

b. Participants were charged for each session.

c. Single study, small sample size

References

1. Alkatan M, Baker JR, Machin DR, et al. Improved Function and Reduced Pain after Swimming and Cycling Training in Patients with Osteoarthritis. *J Rheumatol.* 2016;43(3):666-672.

2. Lim JY, Tchai E, Jang SN. Effectiveness of aquatic exercise for obese patients with knee osteoarthritis: a randomized controlled trial. *PM R.* 2010;2(8):723-731; quiz 793.
3. Wang TJ, Lee SC, Liang SY, Tung HH, Wu SF, Lin YP. Comparing the efficacy of aquatic exercises and land-based exercises for patients with knee osteoarthritis. *J Clin Nurs.* 2011;20(17-18):2609-2622.
4. Gill SD, McBurney H, Schulz DL. Land-based versus pool-based exercise for people awaiting joint replacement surgery of the hip or knee: results of a randomized controlled trial. *Arch Phys Med Rehabil.* 2009;90(3):388-394.

PICO 10. Balance training plus usual care compared to aerobic exercise plus usual care for patients with knee and/or hip OA

Summary. The literature searches did not identify any studies that addressed this comparison.

Quality of evidence across all critical outcomes: Very low

PICO 11. Daily walking plus usual care compared to aerobic exercise plus usual care for patients with knee and/or hip OA

Summary. The literature searches did not identify any studies that addressed this comparison.

Quality of evidence across all critical outcomes: Very low

PICO 12: Neuromuscular training compared to strengthening for knee/hip OA

Summary: The literature search identified three RCTs[1] that compared neuromuscular training to strength training in the treatment of knee OA. There were two types of neuromuscular training that were evaluated. Specifically, Bennell et al.[1] compared neuromuscular training, which included balance and functional strengthening exercises, to quadriceps strengthening for men and women with knee OA and varus alignment. With moderate certainty, they observed no differences in improvement between groups for pain, self-reported function, and performance-based function (stair climbing test, chair stand test, gait speed). They also observed no difference in the odds of reporting increased knee pain, however the certainty of this outcome is low due to a wide confidence interval. Avelar[2] et al. and Bokaeian[3] et al. compared whole body vibration training to strength training for adults with knee OA. They also report no difference in pain, self-reported function and performance-based function between groups; however, the level of evidence is low due to small sample size, wide confidence intervals, and a single study for most outcomes.

Quality of evidence across all critical outcomes: Low

Table 1. Neuromuscular training (balance/functional strength) vs. Quad strengthening for knee OA

Certainty assessment							Summary of findings				
№ of participants (studies) Follow-up	**Risk of bias**	**Inconsistency**	**Indirectness**	**Imprecision**	**Publication bias**	**Overall certainty of evidence**	**Number of participants/Study event rates (%)**		**Relative effect (95% CI)**	**Anticipated absolute effects**	
							With Strengthening	**With Neuromuscular training (balance/functional strength)**		**Risk with Strengthening**	**Risk difference with Neuromuscular training (balance/functional strength)**
WOMAC Pain (0-20, lower scores indicate improvement)											
82 (1 RCT)	serious [a]	not serious	not serious	not serious	none	⨁⨁⨁◯ MODERATE	44	38	-	-	MD **0.7 higher** (0.4 lower to 1.8 higher)
WOMAC function (0-68, lower scores indicate improvement)											
82 (1 RCT)	serious [a]	not serious	not serious	not serious	none	⨁⨁⨁◯ MODERATE	44	38	-	-	MD **0.2 lower** (3.63 lower to 3.23 higher)
Timed Stair Climb (lower scores indicate improvement)											
82 (1 RCT)	serious [a]	not serious	not serious	not serious	none	⨁⨁⨁◯ MODERATE	44	38	-	-	MD **0.02 higher** (0.68 lower to 0.72 higher)

Table 1. Neuromuscular training (balance/functional strength) vs. Quad strengthening for knee OA											
Certainty assessment							**Summary of findings**				
30 sec Chair Stand (higher scores indicate improvement)											
82 (1 RCT)	serious [a]	not serious	not serious	not serious	none	⨁⨁⨁◯ MODERATE	44	38	-	-	MD **0.1 higher** (0.66 lower to 0.86 higher)
Gait speed (higher scores indicate improvement)											
82 (1 RCT)	serious [a]	not serious	not serious	not serious	none	⨁⨁⨁◯ MODERATE	44	38	-	-	MD **0.01 lower** (0.06 lower to 0.04 higher)
Safety (increased knee pain)											
90 (1 RCT)	serious [a]	not serious	not serious	serious [b]	none	⨁⨁◯◯ LOW	10/44 (22.7%)	14/46 (30.4%)	**OR 1.49** (0.58 to 3.82)	227 per 1,000	**77 more per 1,000** (82 fewer to 302 more)

CI: Confidence interval; **MD:** Mean difference; **OR:** Odds ratio

Explanations

a. Participants not blinded; outcome assessor was blinded

b. Wide CI

Table 2. Neuromuscular (whole body vibration) compared to Strength training for knee OA

Certainty assessment							Summary of findings				
№ of participants (studies) Follow-up	**Risk of bias**	**Inconsistency**	**Indirectness**	**Imprecision**	**Publication bias**	**Overall certainty of evidence**	**Number of participants**		**Relative effect (95% CI)**	**Anticipated absolute effects**	
							With Strength training for knee OA	**With Neuromuscular (whole body vibration)**		**Risk with Strength training for knee OA**	**Risk difference with Neuromuscular (whole body vibration)**
Pain (lower scores indicate improvement)											
47 (2 RCTs)	serious [a,b]	not serious	not serious	serious [c]	none	⨁⨁◯◯ LOW	21	26	-	-	SMD **0.33 lower** (0.91 lower to 0.26 higher)
Self-reported Function, WOMAC (0-1700, lower scores indicate improvement)											
21 (1 RCT)	serious [b]	not serious	not serious	serious [d]	none	⨁⨁◯◯ LOW	10	11	-		MD **36 lower** (339.69 lower to 267.69 higher)
TUG (lower scores indicate improvement)											
21 (1 RCT)	serious [b]	not serious	not serious	serious [d]	none	⨁⨁◯◯ LOW	10	11	-	-	MD **0.02 higher** (0.93 lower to 0.97 higher)
30 sec Chair Stand (higher scores indicate improvement)											

Table 2. Neuromuscular (whole body vibration) compared to Strength training for knee OA											
Certainty assessment							Summary of findings				
21 (1 RCT)	serious [b]	not serious	not serious	serious [d]	none	⨁⨁◯◯ LOW	10	11	-	-	MD **0** (2.78 lower to 2.78 higher)
6-meter Walk Test (higher scores indicate improvement)											
21 (1 RCT)	serious [b]	not serious	not serious	serious [d]	none	⨁⨁◯◯ LOW	10	11	-	-	MD **0.47 lower** (53.36 lower to 54.3 higher)

CI: Confidence interval; **SMD:** Standardised mean difference; **MD:** Mean difference

Explanations

a. Participants not blinded; outcome assessor was blinded in at least 1 study

b. Blinding not well described

c. Wide CI

d. Single study, small sample size

References

1. Bennell KL, Kyriakides M, Metcalf B, Egerton T, Wrigley TV, Hodges PW, et al. Neuromuscular versus quadriceps strengthening exercise in patients with medial knee osteoarthritis and varus malalignment: a randomized controlled trial. Arthritis Rheumatol. 2014;66(4):950-959.
2. Avelar NC, Simao AP, Tossige-Gomes R, Neves CD, Rocha-Vieira E, Coimbra CC, et al. The effect of adding whole-body vibration to squat training on the functional performance and self-report of disease status in elderly patients with knee osteoarthritis: a randomized, controlled clinical study. J Altern Complement Med. 2011;17(12):1149-1155.
3. Bokaeian HR, Bakhtiary AH, Mirmohammadkhani M, Moghimi J. The effect of adding whole body vibration training to strengthening training in the treatment of knee osteoarthritis: A randomized clinical trial. J Bodyw Mov Ther. 2016;20(2):334-340.

PICO 13: Aquatic exercise (+usual care) vs. strength training (+usual care) for people with knee and/or hip OA.

Summary: The literature search identified 5 RCTs to evaluate this PICO question. Four RCTs[1-4] were conducted in adults with knee OA and one RCT[5] was conducted in adults with knee or hip OA who were preparing for TKA or THA. All studies compared an aquatic exercise program to a land-based program that included, but was not limited to, strength training. For four studies[1,2,4,5], interventions were conducted in a range of 40-60 minutes, 2-3 time per week for 6-8 weeks. For Silva et al.[3], the intervention duration was 18 weeks. Lund et al.[2] observed that those in the strength training group had greater improvements in pain (KOOS Pain) than the aquatic exercise group in people with knee OA. Conversely, Wyatt et al.[4] and Silva et al.[3] observed that pain improvements may be greater in the aquatic exercise group, but these findings were imprecise with wide confidence intervals in people with knee OA. The comparison of self-reported function, performance-based function, and safety (increased pain) were inconclusive, as the confidence intervals were wide. The quality of evidence to evaluate the PICO question was very low, due primarily to small sample sizes, low study numbers, and wide confidence intervals.

Quality of evidence across all critical outcomes: Very low

Table 1. Aquatic compared to Strength (land) for knee OA

Certainty assessment							Summary of findings				
№ of participants (studies) Follow-up	Risk of bias	Inconsistency	Indirectness	Imprecision	Publication bias	Overall certainty of evidence	Number of patients		Relative effect (95% CI)	Anticipated absolute effects	
							With Strength (land) for knee OA	With Aquatic		Risk with Strength (land) for knee OA	Risk difference with Aquatic
Pain – KOOS (0-100, higher scores indicate improvement)											

Table 1. Aquatic compared to Strength (land) for knee OA											
Certainty assessment							**Summary of findings**				
52 (1 RCT)	serious [a]	not serious	not serious	not serious	none	⨁⨁⨁◯ MODERATE	25	27	-	-	MD **8 lower** (0.45 lower to 15.55 lower) **Favors strength (land)**
Pain – VAS (lower scores indicate improvement)											
110 (2 RCTs)	serious [a,b]	serious [c]	not serious	serious [d]	none	⨁◯◯◯ VERY LOW	55	55	-	-	SMD **0.51 lower** (1.15 lower to 0.13 higher)
Self-reported Function (lower scores indicate improvement)											
98 (2 RCTs)	serious [a]	not serious	not serious	serious [d,f]	none	⨁⨁◯◯ LOW	47	51	-	-	SMD **0.29 lower** (0.69 lower to 0.11 higher)
Safety: Increased pain											

Table 1. Aquatic compared to Strength (land) for knee OA											
Certainty assessment							**Summary of findings**				
52 (1 RCT)	serious [a]	not serious	not serious	serious [f]	none	⨁⨁◯◯ LOW	8/25 (32.0%)	3/27 (11.1%)	**OR 0.27** (0.06 to 1.15)	320 per 1,000	**207 fewer per 1,000** (293 fewer to 31 more)

CI: Confidence interval; **SMD:** Standardised mean difference; **MD:** Mean difference; **OR:** Odds ratio

Explanations

a. Participants not blinded to group assignment; outcome assessors were blinded

b. Randomization method not specified for one study and allocation methods not specified for both studies

c. I squared = 63%; one study does not cross 0, and the other study does cross 0

d. Crosses the no effect line

e. Single study, small sample size

f. Wide CI

Table 2. Aquatic compared to Strength (land) for knee AND hip OA										
Certainty assessment							**Summary of findings**			
№ of participants (studies) Follow-up	**Risk of bias**	**Inconsistency**	**Indirectness**	**Imprecision**	**Publication bias**	**Overall certainty of evidence**	**Number of patients**		**Relative effect (95% CI)**	**Anticipated absolute effects**	
							With Strength (land) for knee AND hip OA	**With Aquatic**		**Risk with Strength (land) for knee AND hip OA**	**Risk difference with Aquatic**
WOMAC Pain (0-20, lower scores indicate improvement)											

Table 2. Aquatic compared to Strength (land) for knee AND hip OA											
Certainty assessment							Summary of findings				
66 (1 RCT)	serious [a,b]	not serious	not serious	serious [c]	none	⨁⨁◯◯ LOW	34	32	-	-	MD **0.3 higher** (1.11 lower to 1.71 higher)
WOMAC function (0-68, lower scores indicate improvement)											
66 (1 RCT)	serious [a,b]	not serious	not serious	serious [c]	none	⨁⨁◯◯ LOW	34	32	-	-	MD **0.4 higher** (5.18 lower to 5.98 higher)
30-sec Chair Stand (higher scores indicate improvement)											
65 (1 RCT)	serious [a,b]	not serious	not serious	serious [c]	none	⨁⨁◯◯ LOW	34	31	-	-	MD **1.5 lower** (3.64 lower to 0.64 higher)

CI: Confidence interval; **MD:** Mean difference

Explanations

a. Participants were not blinded; outcome assessor was blinded.

b. Participants were charged for each session.

c. Single study, small sample size

References

1. Lim JY, Tchai E, Jang SN. Effectiveness of aquatic exercise for obese patients with knee osteoarthritis: a randomized controlled trial. *PM R.* 2010;2(8):723-731; quiz 793.

2. Lund H, Weile U, Christensen R, et al. A randomized controlled trial of aquatic and land-based exercise in patients with knee osteoarthritis. *J Rehabil Med.* 2008;40(2):137-144.
3. Silva LE, Valim V, Pessanha AP, et al. Hydrotherapy versus conventional land-based exercise for the management of patients with osteoarthritis of the knee: a randomized clinical trial. *Phys Ther.* 2008;88(1):12-21.
4. Wyatt FB, Milam S, Manske RC, Deere R. The effects of aquatic and traditional exercise programs on persons with knee osteoarthritis. *J Strength Cond Res.* 2001;15(3):337-340.
5. Gill SD, McBurney H, Schulz DL. Land-based versus pool-based exercise for people awaiting joint replacement surgery of the hip or knee: results of a randomized controlled trial. *Arch Phys Med Rehabil.* 2009;90(3):388-394.

PICO 14: Balance training compared to strength training for knee OA

Summary: Three RCTs[1-3] compared balance/proprioceptive training to strength training for knee OA. No significant differences in pain, self-reported function, and performance based function were observed. However, all findings were inconclusive due to serious imprecision related to wide CIs and small sample size for each outcome.

Quality of evidence across all critical outcomes: Low

Balance training compared to Strength training for knee OA for Knee OA											
Certainty assessment							**Summary of findings**				
№ of participants (studies) Follow-up	**Risk of bias**	**Inconsistency**	**Indirectness**	**Imprecision**	**Publication bias**	**Overall certainty of evidence**	**Number of patients**		**Relative effect (95% CI)**	**Anticipated absolute effects**	
							With Strength training for knee OA	**With Balance training**		**Risk with Strength training for knee OA**	**Risk difference with Balance training**
WOMAC pain (0-20, lower scores indicate improvement)											

Balance training compared to Strength training for knee OA for Knee OA											
Certainty assessment							Summary of findings				
31 (2 RCTs)	serious [a]	not serious	not serious	serious [b]	none	⨁⨁◯◯ LOW	17	14	-	-	MD **0.87 higher** (1.92 lower to 3.66 higher)
KOOS Pain (mean change) (0-100, higher scores indicate improvement)											
42 (1 RCT)	serious [a]	not serious	not serious	serious [b]	none	⨁⨁◯◯ LOW	18	24	-	-	MD **3 lower** (11.48 lower to 5.48 higher)
WOMAC function (0-68, lower scores indicate improvement)											
28 (2 RCTs)	serious [a]	not serious	not serious	serious [b]	none	⨁⨁◯◯ LOW	16	12	-	-	MD **1.25 lower** (11.87 lower to 9.38 higher)
KOOS function (mean change) (0-100, higher scores indicate improvement)											
42 (1 RCT)	serious [a]	not serious	not serious	serious [b]	none	⨁⨁◯◯ LOW	18	24	-	-	MD **6 lower** (13.88 lower to 1.88 higher)
Walking time (seconds) (lower scores indicate improvement)											
42 (1 RCT)	serious [a]	not serious	not serious	serious [b]	none	⨁⨁◯◯ LOW	18	24	-	-	MD **1 lower** (2.6 lower to 0.6 higher)
TUG (timed get up and go) (lower scores indicate improvement)											
56 (2 RCTs)	serious [a]	not serious	not serious	serious [b]	none	⨁⨁◯◯ LOW	27	29	-	-	MD **0.07 lower** (1.02 lower to 0.88 higher)

Balance training compared to Strength training for knee OA for Knee OA											
Certainty assessment							Summary of findings				
Time going up stairs (lower scores indicate improvement)											
56 (2 RCTs)	serious [a]	not serious	not serious	serious [b]	none	⨁⨁◯◯ LOW	27	29	-	-	MD **0.1 lower** (1.05 lower to 0.85 higher)
Time going down stairs (lower scores indicate improvement)											
56 (2 RCTs)	serious [a]	not serious	not serious	serious [b]	none	⨁⨁◯◯ LOW	27	29	-	-	MD **0.7 higher** (0.89 lower to 2.29 higher)

CI: Confidence interval; **MD:** Mean difference

Explanations

a. Participants and/or investigators not blinded; at least 1 study blinded the outcome assessor

b. Small sample size

References

1. Rogers MW, Tamulevicius N, Coetsee MF, Curry BF, Semple SJ. Knee Osteoarthritis and the Efficacy of Kinesthesia, Balance & Agility Exercise Training: A Pilot Study. Int J Exerc Sci. 2011;4(2):124-132.
2. Rogers MW, Tamulevicius N, Semple SJ, Krkeljas Z. Efficacy of home-based kinesthesia, balance & agility exercise training among persons with symptomatic knee osteoarthritis. J Sports Sci Med. 2012;11(4):751-758.
3. Chaipinyo K, Karoonsupcharoen O. No difference between home-based strength training and home-based balance training on pain in patients with knee osteoarthritis: a randomised trial. Aust J Physiother. 2009;55(1):25-30.

PICO 15. Daily walking plus usual care compared to strength training plus usual care

Summary. The literature searches did not identify any studies that addressed this comparison.

Quality of evidence across all critical outcomes: Very low

PICO 16. Aquatic exercise plus usual care compared to neuromuscular training plus usual care

Summary. The literature searches did not identify any studies that addressed this comparison.

Quality of evidence across all critical outcomes: Very low

PICO 17. Balance training plus usual care compared to neuromuscular training plus usual care

Summary. The literature searches did not identify any studies that addressed this comparison.

Quality of evidence across all critical outcomes: Very low

PICO 18. Daily walking plus usual care compared to neuromuscular training plus usual care

Summary. The literature searches did not identify any studies that addressed this comparison.

Quality of evidence across all critical outcomes: Very low

PICO 19: Aquatic exercise (+usual care) compared to balance exercise (+ usual care) for knee OA

Summary: One study[1] compared aquatic exercises with a land-based exercise program that included balance exercises for treating knee OA. Lund et al.[1] observed that participants in the land-based exercise group reported greater pain improvement than those in the aquatic exercise group. Although there was no difference for self-reported function, the finding was imprecise due to wide 95% CI that includes the possibility of a difference between groups. Those in the aquatic exercise group had lower odds of reported increased pain compared to the land-based exercise group; however the confidence interval was too wide to rule out the possibility of no difference between groups.

Quality of evidence across all critical outcomes: Low

Aquatic compared to Balance (Land) for knee OA

Certainty assessment							Summary of findings				
№ of participants (studies) Follow-up	**Risk of bias**	**Inconsistency**	**Indirectness**	**Imprecision**	**Publication bias**	**Overall certainty of evidence**	**Number of subjects/Study event rates (%)**		**Relative effect (95% CI)**	**Anticipated absolute effects**	
							With Balance (Land) for knee OA	**With Aquatic**		**Risk with Balance (Land) for knee OA**	**Risk difference with Aquatic**
KOOS Pain (0-100, higher scores indicate improvement)											
52 (1 RCT)	serious [a]	not serious	not serious	not serious	none	⨁⨁⨁◯ MODERATE	25	27	-	-	MD **8 higher** (0.45 higher to 15.55 higher) **Favors balance (land)**
KOOS Function (0-100, higher scores indicate improvement)											
52 (1 RCT)	serious [a]	not serious	not serious	serious [b,c]	none	⨁⨁◯◯ LOW	25	27	-	-	MD **5.5 higher** (2.3 lower to 13.3 higher)
Safety (increased knee pain)											

Aquatic compared to Balance (Land) for knee OA											
Certainty assessment							**Summary of findings**				
52 (1 RCT)	serious [a]	not serious	not serious	serious [b]	none	⨁⨁◯◯ LOW	8/25 (32.0%)	3/27 (11.1%)	**OR 0.27** (0.06 to 1.15)	320 per 1,000	**207 fewer per 1,000** (293 fewer to 31 more)

CI: Confidence interval; **MD:** Mean difference; **OR:** Odds ratio

Explanations

a. Participants not blinded, outcome assessor was blinded

b. Wide confidence interval

c. Crossed no effect line

1. Lund H, Weile U, Christensen R, et al. A randomized controlled trial of aquatic and land-based exercise in patients with knee osteoarthritis. *J Rehabil Med.* 2008;40(2):137-144.

PICO 20. Daily walking plus usual care compared to aquatic exercise plus usual care for patients with knee and/or hip OA

Summary. The literature searches did not identify any studies that addressed this comparison.

Quality of evidence across all critical outcomes: Very low

PICO 21. Daily walking plus usual care compared to balance training plus usual care for patients with knee and/or hip OA

Summary. The literature searches did not identify any studies that addressed this comparison.

Quality of evidence across all critical outcomes: Very low

PICO 22. Unsupervised exercise vs. supervised exercise for knee/hip OA

Summary. The literature searches did not identify any studies that addressed this comparison.

Quality of evidence across all critical outcomes: Very low

PICO 23: Unsupervised prescribed exercise vs. supervised exercise for knee/hip OA

Summary: Seven RCTs[1-6][Callaghan 1995] compared unsupervised prescribed exercise to supervised exercises for the treatment of knee OA. The pain results of four studies[1-4] were appropriate to combine in a meta-analysis, and indicated that supervised exercise reduces pain to a significantly greater extent than unsupervised exercise (Table 1). McCarthy et al.[2] observed that pain improvements were maintained at 6- and 12-month follow up. McCarthy et al.[2] also observed greater short-term improvements in self-reported function with supervised exercise compared to unsupervised exercise; however, these differences were not maintained at 6- and 12-months. Tunay et al.[3] reported greater improvement in TUG with supervised execise. Colak et al.[4] reported no differences in the 6MWT, however the confidence intervals were wide. Three studies[5,6][Callaghan 1995] reported mixed results that could not be used in the meta-analysis (Table 2).

Bieler et al.[7] compared unsupervised prescribed exercise to supervised aerobic exercise and to supervised strength training for the treatment of hip OA. Generally, they observed no differences in pain, self-reported function, and performance-based function (chair stand test, stair climbing, TUG) between unsupervised and supervised exercise after intervention and after an 8-month follow-up. An exception was the performance on 6MWT (Tables 3 and 4). Those in the supervised aerobic exercise group demonstrated greater improvements on the 6MWT compared to the unsupervised group, and these differences were maintained at the 8-month follow-up.

Quality of evidence across all critical outcomes: Low for knee, Moderate for hip

Table 1. Unsupervised prescribed compared to supervised exercise for knee OA

Certainty assessment							Summary of findings				
№ of participants (studies) Follow-up	Risk of bias	Inconsistency	Indirectness	Imprecision	Publication bias	Overall certainty of evidence	Number of participants		Relative effect (95% CI)	Anticipated absolute effects	
							With Supervised exercise for knee OA	With Unsupervised prescribed		Risk with Supervised exercise for knee OA	Risk difference with Unsupervised prescribed

Table 1. Unsupervised prescribed compared to supervised exercise for knee OA											
Certainty assessment							Summary of findings				
Pain (lower scores indicate improvement)											
465 (4 RCTs)	serious [a]	not serious	not serious	not serious	none	⨁⨁⨁◯ MODERATE	254	211	-	-	SMD **0.44 higher** (0.26 higher to 0.63 higher) **Favors supervised exercise**
Pain - mid term follow up (lower scores indicate improvement)											
214 (1 RCT)	serious [a]	not serious	not serious	not serious	none	⨁⨁⨁◯ MODERATE	111	103	-	-	SMD **0.29 higher** (0.02 higher to 0.56 higher) **Favors supervised exercise**
Pain - long term follow up (lower scores indicate improvement)											
214 (1 RCT)	serious [a]	not serious	not serious	not serious	none	⨁⨁⨁◯ MODERATE	111	103	-	-	SMD **0.42 higher** (0.15 higher to 0.69 higher) **Favors supervised exercise**
Self-reported function (lower scores indicate improvement)											

Table 1. Unsupervised prescribed compared to supervised exercise for knee OA											
Certainty assessment							Summary of findings				
214 (1 RCT)	serious [a]	not serious	not serious	not serious	none	⨁⨁⨁◯ MODERATE	111	103	-	-	SMD **0.31 higher** (0.04 higher to 0.58 higher) **Favors supervised exercise**
Self-reported function - mid term follow up (lower scores indicate improvement)											
214 (1 RCT)	serious [a]	not serious	not serious	serious [b]	none	⨁⨁◯◯ LOW	111	103	-	-	SMD **0.22 higher** (0.05 lower to 0.49 higher)
Self-reported function - long term follow up (lower scores indicate improvement)											
214 (1 RCT)	serious [a]	not serious	not serious	serious [b]	none	⨁⨁◯◯ LOW	111	103	-	-	SMD **0.25 higher** (0.02 lower to 0.52 higher)
6-min walk test (higher scores indicate improvement)											
56 (1 RCT)	serious [a]	not serious	not serious	serious [b]	none	⨁⨁◯◯ LOW	33	23	-	-	SMD **0.02 lower** (0.55 lower to 0.51 higher)
TUG (lower scores indicate improvement)											

Table 1. Unsupervised prescribed compared to supervised exercise for knee OA											
Certainty assessment							**Summary of findings**				
60 (1 RCT)	serious [a]	not serious	not serious	not serious	none	⨁⨁⨁◯ MODERATE	30	30	-	-	SMD **0.54 lower** (1.06 lower to 0.02 lower) **Favors unsupervised exercise**

CI: Confidence interval; **SMD:** Standardised mean difference

Explanations

a. Participants and/or assessors not blinded

b. Wide CI

Table 2. RCT data not suitable for effect size calculation or combining with other data

Ref ID, Author, year	Study type	Duration	Population Description	Treatment given to relevant population	Results
3621, Callaghan, 1995	RCT Moderate quality	4 weeks	Knee OA	Supervised (Group 2; 20 min supervised PT session, 2x/week; all open-chain exercises) Unsupervised (Group 3; advice; instruction on how to perform weight bearing exercises at home to be performed 10x daily)	Median % change in VAS pain score (range); negative number indicates reduction in pain Supervised: 18% (-500 to +14) Unsupervised: -21% (-100 to +17)
6208, Chamberlain, 1982	RCT Moderate quality	Using data up to 4 weeks, as another randomization was	Knee OA	Supervised (Group A; diarthermy + supervised exercises + home exercises 2x/day; only 2 exercises given)	Comparison of VAS pain score: Supervised: T= 13.5;N=9; not significant Unsupervised: T= 10.5;N= 11; significant at P < 0.05

		introducing after that		Unsupervised (Group B; 3 instruction sessions in 1 week, then to be completed at home; only 2 exercises given)	* Wilcoxon Matched Pair Signed Ranks Test used.
293, Kudo, 2013	RCT Low quality	3 months	Knee OA	Supervised: (group exercise class, 90 min, 2x/week, 3 months Unsupervised: (workshop to introduce home exercise program, then to perform 2x/week for 3 months) "The subjects did not have any other conservative treatments such as medication during the participating period of the program."	Estimated from BAR Chart: WOMAC index (total) scores normalized to 100%: Supervised: Pre: 82 (11) Post: 92 (7) Unsupervised: Pre: 81 (12) Post: 85 (12.5)

Table 3. Unsupervised prescribed compared to supervised aerobic for Hip OA

Certainty assessment							Summary of findings				
№ of participants (studies) Follow-up	**Risk of bias**	**Inconsistency**	**Indirectness**	**Imprecision**	**Publication bias**	**Overall certainty of evidence**	**Number of participants**		**Relative effect (95% CI)**	**Anticipated absolute effects**	
							With Supervised aerobic for Hip OA	**With Unsupervised prescribed**		**Risk with Supervised aerobic for Hip OA**	**Risk difference with Unsupervised prescribed**
WOMAC Pain (0-20, lower scores indicate improvement)											
102 (1 RCT)	serious [a]	not serious	not serious	not serious	none	⨁⨁⨁◯ MODERATE	50	52	-	-	MD **0.75 higher** (0.64 lower to 2.14 higher)

Table 3. Unsupervised prescribed compared to supervised aerobic for Hip OA											
Certainty assessment							Summary of findings				
WOMAC function (0-68, lower scores indicate improvement)											
102 (1 RCT)	serious [a]	not serious	not serious	not serious	none	⨁⨁⨁◯ MODERATE	50	52	-	-	MD **1.25 higher** (3.04 lower to 5.54 higher)
Chair stand test (higher scores indicate improvement)											
102 (1 RCT)	serious [a]	not serious	not serious	not serious	none	⨁⨁⨁◯ MODERATE	50	52	-	-	MD **1.1 lower** (2.49 lower to 0.29 higher)
Stair climbing (lower scores indicate improvement)											
102 (1 RCT)	serious [a]	not serious	not serious	not serious	none	⨁⨁⨁◯ MODERATE	50	52	-	-	MD **1 higher** (0.19 lower to 2.19 higher)
TUG (lower scores indicate improvement)											
102 (1 RCT)	serious [a]	not serious	not serious	not serious	none	⨁⨁⨁◯ MODERATE	50	52	-	-	MD **0.7 higher** (0.14 lower to 1.54 higher)
6-min Walk Test (higher scores indicate improvement)											

Table 3. Unsupervised prescribed compared to supervised aerobic for Hip OA											
Certainty assessment							Summary of findings				
102 (1 RCT)	serious [a]	not serious	not serious	not serious	none	⨁⨁⨁◯ MODERATE	50	52	-	-	MD **32 lower** (7.12 lower to 56.88 lower) **Favors supervised aerobic**
WOMAC Pain - 8-month follow up (0-20, lower scores indicate improvement)											
102 (1 RCT)	serious [a]	not serious	not serious	not serious	none	⨁⨁⨁◯ MODERATE	50	52	-	-	MD **0.5 higher** (1.06 lower to 2.06 higher)
WOMAC function - 8-month follow up (0-68, lower scores indicate improvement)											
102 (1 RCT)	serious [a]	not serious	not serious	not serious	none	⨁⨁⨁◯ MODERATE	50	52	-	-	MD **2 higher** (2.67 lower to 6.67 higher)
Chair stand test - 8-month follow up (higher scores indicate improvement)											
102 (1 RCT)	serious [a]	not serious	not serious	not serious	none	⨁⨁⨁◯ MODERATE	50	52	-	-	MD **0.3 lower** (2.03 lower to 1.43 higher)
Stair climbing - 8-month follow up (lower scores indicate improvement)											
102 (1 RCT)	serious [a]	not serious	not serious	not serious	none	⨁⨁⨁◯ MODERATE	50	52	-	-	MD **0.3 lower** (1.52 lower to 0.92 higher)
TUG - 8-month follow up (lower scores indicate improvement)											

Table 3. Unsupervised prescribed compared to supervised aerobic for Hip OA											
Certainty assessment							**Summary of findings**				
102 (1 RCT)	serious [a]	not serious	not serious	not serious	none	⨁⨁⨁◯ MODERATE	50	52	-	-	MD **0.1 higher** (0.74 lower to 0.94 higher)
6-min Walk Test - 8-month follow up (higher scores indicate improvement)											
102 (1 RCT)	serious [a]	not serious	not serious	not serious	none	⨁⨁⨁◯ MODERATE	50	52	-	-	MD **52 lower** (5.65 lower to 98.35 lower) **Favors supervised exercise**

CI: Confidence interval; **MD:** Mean difference

Explanations

a. Participants not blinded; outcome assessor was blinded

Table 4. Unsupervised prescribed compared to supervised strength for Hip OA											
Certainty assessment							**Summary of findings**				
№ of participants (studies) Follow-up	**Risk of bias**	**Inconsistency**	**Indirectness**	**Imprecision**	**Publication bias**	**Overall certainty of evidence**	**Number of participants**		**Relative effect (95% CI)**	**Anticipated absolute effects**	
							With Supervised strength for Hip OA	**With Unsupervised prescribed**		**Risk with Supervised strength for Hip OA**	**Risk difference with Unsupervised prescribed**
WOMAC Pain (0-20, lower scores indicate improvement)											

Table 4. Unsupervised prescribed compared to supervised strength for Hip OA											
Certainty assessment							Summary of findings				
102 (1 RCT)	serious [a]	not serious	not serious	not serious	none	⨁⨁⨁◯ MODERATE	50	52	-	-	MD **0.55 higher** (0.68 lower to 1.78 higher)
WOMAC function (0-68, lower scores indicate improvement)											
102 (1 RCT)	serious [a]	not serious	not serious	not serious	none	⨁⨁⨁◯ MODERATE	50	52	-	-	MD **2.25 higher** (1.79 lower to 6.29 higher)
Chair stand test (higher scores indicate improvement)											
102 (1 RCT)	serious [a]	not serious	not serious	not serious	none	⨁⨁⨁◯ MODERATE	50	52	-	-	MD **0** (1.12 lower to 1.12 higher)
Stair climbing (lower scores indicate improvement)											
102 (1 RCT)	serious [a]	not serious	not serious	not serious	none	⨁⨁⨁◯ MODERATE	50	52	-	-	MD **0.1 lower** (1 lower to 0.8 higher)
TUG (lower scores indicate improvement)											
102 (1 RCT)	serious [a]	not serious	not serious	not serious	none	⨁⨁⨁◯ MODERATE	50	52	-	-	MD **0.1 higher** (0.52 lower to 0.72 higher)
6-min Walk Test (higher scores indicate improvement)											

Table 4. Unsupervised prescribed compared to supervised strength for Hip OA											
Certainty assessment							Summary of findings				
102 (1 RCT)	serious [a]	not serious	not serious	not serious	none	⨁⨁⨁◯ MODERATE	50	52	-	-	MD **7 lower** (28.49 lower to 14.49 higher)
WOMAC Pain - 8-month follow up (0-20, lower scores indicate improvement)											
102 (1 RCT)	serious [a]	not serious	not serious	not serious	none	⨁⨁⨁◯ MODERATE	50	52	-	-	MD **0.65 lower** (2.14 lower to 0.84 higher)
Self-report function - 8-month follow up (0-68, lower scores indicate improvement)											
102 (1 RCT)	serious [a]	not serious	not serious	not serious	none	⨁⨁⨁◯ MODERATE	50	52	-	-	MD **2.5 lower** (7.08 lower to 2.08 higher)
Chair stand test - 8-month follow up (higher scores indicate improvement)											
102 (1 RCT)	serious [a]	not serious	not serious	not serious	none	⨁⨁⨁◯ MODERATE	50	52	-	-	MD **1.1 higher** (0.69 lower to 2.89 higher)
Stair climbing - 8-month follow up (lower scores indicate improvement)											
102 (1 RCT)	serious [a]	not serious	not serious	not serious	none	⨁⨁⨁◯ MODERATE	50	52	-	-	MD **0.8 higher** (0.65 lower to 2.25 higher)
TUG - 8-month follow up (lower scores indicate improvement)											

Table 4. Unsupervised prescribed compared to supervised strength for Hip OA											
Certainty assessment							Summary of findings				
102 (1 RCT)	serious [a]	not serious	not serious	not serious	none	⨁⨁⨁◯ MODERATE	50	52	-	-	MD **0.8 higher** (0.04 lower to 1.64 higher)
6-min Walk Test - 8-month follow up (higher scores indicate improvement)											
102 (1 RCT)	serious [a]	not serious	not serious	not serious	none	⨁⨁⨁◯ MODERATE	50	52	-	-	MD **18 lower** (58.76 lower to 22.76 higher)

CI: Confidence interval; **MD:** Mean difference

Explanations

a. Participants not blinded; outcome assessor was blinded

References

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PICO 24: Self-efficacy/self-management vs UC for knee or hip OA

Summary. There were 23 non-blinded RCTs directly evaluating the effect of self-efficacy/self-management vs usual care for knee or hip OA. Subjects with hip OA were included in eleven RCTs, but only one of these trials exclusively studied subjects with hip OA (Poulsen et al). Twelve studies included knee OA only. The methodology for self-efficacy/self-management programs varied widely across studies. Most included some form of supervised instruction by a nurse or physical therapist, although the number of sessions varied widely (between one and eighteen), as did the focus of the sessions (exercise instruction vs OA pathophysiology education vs pain coping skills training vs goal setting). One study evaluated online modules without in-person instruction (Rini et al); one study included NSAID use reduction in the intervention (Mazucca et al, 2004); and two studies used activity trackers (Murphy et al, Li et al). Control groups were also rather different, and included no-attention, an educational pamphlet or video, instruction to exercise at home, and waitlist for intervention. A variety of pain and function outcomes were reported between different studies, hence data pooling was limited for each outcome.

Among studies that included subjects with hip OA, three studies reported no difference in WOMAC pain between intervention and control groups (Moe et al, Murphy et al, Buszewicz et al), one study reported no difference in HOOS pain (Poulsen et al), three studies reported no difference in AIMS2 pain scores (Hopman-Rock et al, Rini et al, Wetzels et al), and one study favored intervention (Allen et al). The same study also favored intervention for pain assessment by VAS, while others found no difference (Hopman- Rock et al, Moe et al, Poulsen et al). One study used a composite pain outcome and favored intervention (Broderick et al), and one study used the EuroQol-5D pain assessment tool, and also favored intervention (Hansson et al). Hence, of the ten studies that reported any pain outcomes, seven found no difference between intervention and control , and three favored intervention. For function outcomes, three studies found no difference in WOMAC function (Moe et al, Murphy et al, Buszewicz et al), one study found no difference in HOOS function (Poulsen et al), four studies found no difference in AIMS2 function (Allen et al, Hopman-Rock et al, Rini et al, Wetzels et al). There was also no difference in SF-36 function assessment (Heuts et al, Moe et al), or up-and-go tests (Hansson et al, Hopman-Rock et al). A single study that used a composite function outcome favored intervention (Broderick et al).

Among studies that evaluated subjects with knee OA only, three reported no difference in WOMAC pain between intervention and control groups (De Rizende et al 2016, Mazzuca et al 2004, Sommers et al), and one favored intervention (Coleman et al). One study reported no difference in KOOS pain (Li et al). One study reporting AIMS2 pain favored intervention (Keefe et al). On pain assessment by VAS, five studies reported no difference (De Rizende et al 2016, Mazzuca et al 1997, Ravaud et al, Yip et al 2007, Yip et al 2008), and one study favored intervention (Heuts et al). One study found no difference in pain by SF-36 (Kao et al). For all pain outcomes, nine studies found no difference between intervention and control, and three favored intervention. For function outcomes, three studies found no difference in WOMAC function scores between intervention and control (Mazzuca et al 2004, Ravaud et al, Somers et al), and one study favored intervention (Coleman et al). One study found no difference in KOOS function (Li et al), one study found no difference in SF-36 function (Kao et al), two studies found no difference in HAQ disability scores (Mazzuca et al 1997, Yip et al 2008), and one study found no difference in the timed up-and-go test (De Rizende et al 2017). Overall, eight studies found no difference in function outcomes between intervention and control, and one favored intervention.

A literature search update in August 2018 identified five additional relevant RCTs (Ganji et al., Isaramalai et al., da Silva et al., Omidi et al., Saffari et al.). The findings of these studies did not alter the overall findings in the tables below.

Quality of evidence across all critical outcomes: Moderate

Table 1. Self-management + UC compared to UC for knee and hip OA

Certainty assessment							Summary of findings				
№ of participants (studies) Follow-up	Risk of bias	Inconsistency	Indirectness	Imprecision	Publication bias	Overall certainty of evidence	Number of events		Relative effect (95% CI)	Anticipated absolute effects	
							With UC	With self-management + UC		Risk with UC	Risk difference with self-management + UC
WOMAC pain (0-20, lower scores indicate improvement)											

Table 1. Self-management + UC compared to UC for knee and hip OA											
Certainty assessment							Summary of findings				
448 (2 RCTs)	serious [a]	not serious	not serious	not serious	none	⨁⨁⨁◯ MODERATE	223	225	-	-	MD **0.32 lower** (0.75 lower to 0.11 higher)
HOOS pain (0-100, higher scores indicate improvement)											
66 (1 RCT)	serious [a]	not serious	not serious	not serious	none	⨁⨁⨁◯ MODERATE	32	34	-	-	MD **4 lower** (9.83 lower to 1.83 higher)
AIMS2 Pain (lower scores indicate improvement)											
634 (4 RCTs)	serious [a]	not serious	not serious	not serious	none	⨁⨁⨁◯ MODERATE	314	320	-	-	MD **0.58 lower** (0.91 lower to 0.25 lower) **Favors self-management**
Pain by VAS (0-10, lower scores indicate improvement)											
791 (4 RCTs)	serious [a]	not serious	not serious	not serious	none	⨁⨁⨁◯ MODERATE	399	392	-	-	MD **0.24 lower** (0.86 lower to 0.38 higher)
WOMAC function (0-68, lower scores indicate improvement)											

Table 1. Self-management + UC compared to UC for knee and hip OA											
Certainty assessment							Summary of findings				
448 (2 RCTs)	serious [a]	not serious	not serious	not serious	none	⨁⨁⨁◯ MODERATE	223	225	-	-	MD **0.02 higher** (0.39 lower to 0.42 higher)
HOOS function (0-100, higher scores indicate improvement)											
66 (1 RCT)	serious [a]	not serious	not serious	not serious	none	⨁⨁⨁◯ MODERATE	32	34	-	-	MD **4 lower** (9.62 lower to 1.62 higher)
AIMS2 function (lower scores indicate improvement)											
638 (4 RCTs)	serious [a]	not serious	not serious	not serious	none	⨁⨁⨁◯ MODERATE	318	320	-	-	MD **0.15 lower** (0.4 lower to 0.09 higher)
SF-36 function (higher scores indicate improvement)											
510 (2 RCTs)	serious [a]	not serious	not serious	serious [b]	none	⨁⨁◯◯ LOW	260	250	-	-	MD **0.66 higher** (0.34 lower to 1.67 higher)
Timed up-and-go test (lower scores indicate improvement)											

Table 1. Self-management + UC compared to UC for knee and hip OA											
Certainty assessment							Summary of findings				
96 (1 RCT)	serious [a]	not serious	not serious	serious [b]	none	⨁⨁◯◯ LOW	46	50	-	-	MD **0.9 lower** (2.24 lower to 0.44 higher)

CI: Confidence interval; **MD:** Mean difference

Explanations

a. Subjects not blinded; unclear if any studies blinded outcome assessors, but blinding could not be done for self-reported outcomes

b. Wide confidence intervals

Table 2. RCT data not suitable for effect size calculation or combining with other data

Ref ID, Author, year	Study type	Duration	Population Description	Treatment given to relevant population	Results
Broderick, 2014	single-blinded RCT	10-20 weeks	256 patients with knee or hip OA	10 weekly 40 min sessions of pain coping skills training with nurse practitioner vs non-intervention; both groups received information on OA resourses in the community	Composite pain and function scores comprised of AIMS2 pain and function, WOMAC, Beck depression, and coping questionnaires' pain questions: Composite pain: Treatment group: -0.38 (SE 0.07); control group – 0.17 (SE 0.07) Composite function: Treatment group: -0.28 (SE 0.06); control group – 0.1 (SE 0.06)
Buszewicz, 2006	single-blind RCT	4 months	812 subjects with OA of the hip or knee by medical records (no clear radiographic criteria)	"Challenging arthritis" programme, which appears to be an in-person 6 session x 2.5 hr course + OA education booklet vs OA education booklet	WOMAC pain mean difference (treatment vs control): -0.15 (-0.57-0.28) WOMAC function mean difference (treatment vs control): -1.22 (-2.59-0.16)

Hansson, 2010	single-blind RCT	5 weeks, outcomes assessed at 6 months	114 patients (mean age 63) with knee, hip, or hand OA.	Patient education (5 group sessions, 3 hours each, once a week for 5 weeks focusing on self-efficacy) vs usual care (described as "living as usual")	EuroQol-5D instrument for assessment f global health/pain/function/anxiety: Fewer patients with "extreme problems" due to pain in the intervention group at 6 months (13% vs 21% among controls, p<0.001) Timed sit to stand test (number of times) at 6 months: mean difference intervention vs control 5.19 (-5.3 to 10.92), p=0.1

Table 3. Knee only Self-management + UC compared to UC for knee OA

Certainty assessment							Summary of findings				
№ of participants (studies) Follow-up	**Risk of bias**	**Inconsistency**	**Indirectness**	**Imprecision**	**Publication bias**	**Overall certainty of evidence**	**Number of patients**		**Relative effect (95% CI)**	**Anticipated absolute effects**	
							With UC	**With Knee only Self-management + UC**		**Risk with UC**	**Risk difference with Knee only Self-management + UC**
WOMAC pain (0-20, lower scores indicate improvement)											
493 (4 RCTs)	serious [a]	serious [b]	not serious	not serious	none	⨁⨁◯◯ LOW	225	268	-	-	MD **0.76 lower** (1.81 lower to 0.29 higher)
KOOS pain (0-100, higher scores indicate improvement)											

Table 3. Knee only Self-management + UC compared to UC for knee OA											
Certainty assessment							Summary of findings				
34 (1 RCT)	serious [a]	not serious	not serious	not serious	none	⨁⨁⨁◯ MODERATE	17	17	-	-	MD **3.9 higher** (4.9 lower to 12.7 higher)
AIMS2 Pain (lower scores indicate improvement)											
174 (2 RCTs)	serious [a]	not serious	not serious	not serious	none	⨁⨁⨁◯ MODERATE	82	92	-	-	MD **0.61 lower** (1.35 lower to 0.13 higher)
Pain by VAS (0-10, lower scores indicate improvement)											
974 (6 RCTs)	serious [a]	not serious	not serious	not serious	none	⨁⨁⨁◯ MODERATE	505	469	-	-	MD **0.65 lower** (0.92 lower to 0.37 lower) **Favors self-management**
SF-36 pain (higher scores indicate improvement)											
205 (1 RCT)	serious [a]	not serious	not serious	serious [c]	none	⨁⨁◯◯ LOW	91	114	-	-	MD **2.91 higher** (1.47 lower to 7.29 higher)
HAQ pain (lower scores indicate improvement)											

Table 3. Knee only Self-management + UC compared to UC for knee OA											
Certainty assessment							**Summary of findings**				
165 (1 RCT)	serious [a]	not serious	not serious	not serious	none	⨁⨁⨁◯ MODERATE	83	82	-	-	MD **0.13 lower** (1 lower to 0.74 higher)
WOMAC function (0-68, lower scores indicate improvement)											
763 (4 RCTs)	serious [a]	serious [b]	not serious	not serious	none	⨁⨁◯◯ LOW	377	386	-	-	MD **2.23 lower** (5.3 lower to 0.84 higher)
KOOS function (0-100, higher scores indicate improvement)											
34 (1 RCT)	serious [a]	not serious	not serious	serious [c]	none	⨁⨁◯◯ LOW	17	17	-	-	MD **7.2 higher** (1.4 lower to 15.8 higher)
SF-36 Function (higher scores indicate improvement)											
205 (1 RCT)	serious [a]	not serious	not serious	serious [c]	none	⨁⨁◯◯ LOW	91	114	-	-	MD **3.72 lower** (8.02 lower to 0.58 higher)
HAQ disability (lower scores indicate improvement)											

Table 3. Knee only Self-management + UC compared to UC for knee OA											
Certainty assessment							Summary of findings				
239 (2 RCTs)	serious [a]	not serious	not serious	not serious	none	⨁⨁⨁◯ MODERATE	118	121	-	-	MD **0.05 lower** (0.67 lower to 0.57 higher)
Timed up-and-go test (lower scores indicate improvement)											
45 (1 RCT)	serious [a]	not serious	not serious	serious [c]	none	⨁⨁◯◯ LOW	21	24	-	-	MD **0.7 higher** (2.61 lower to 4.01 higher)

CI: Confidence interval; **MD:** Mean difference

Explanations

a. Subjects not blinded; most studies did not report blinding outcome assessors

b. One study favoring intervention, other with null result

c. Wide confidence intervals

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PICO 25: CBT compared to usual care for knee OA

Summary: Two RCTs[1-2] compared cognitive-behavioral therapy to usual care for adults with knee OA. No significant difference was observed between groups post-treatment for pain and self-reported function. At 3-6 month follow-up, there was again no difference in pain between groups, however there is low certainty with this outcome as there was imprecision in the effect estimate.

Quality of evidence for all critical outcomes: Low

CBT compared to usual care for knee OA											
Certainty assessment							Summary of findings				
Nº of participants (studies) Follow-up	Risk of bias	Inconsistency	Indirectness	Imprecision	Publication bias	Overall certainty of evidence	Number of subjects		Relative effect (95% CI)	Anticipated absolute effects	
							With usual care for knee OA	With CBT		Risk with usual care for knee OA	Risk difference with CBT
WOMAC Pain (lower scores indicate improvement)											
203 (2 RCTs)	serious [a]	not serious	not serious	serious [b]	none	⨁⨁◯◯ LOW	103	100	-	-	SMD **0.11 lower** (0.39 lower to 0.16 higher)
WOMAC function (0-68, lower scores indicate improvement)											
110 (1 RCT)	serious [a]	not serious	not serious	serious [b]	none	⨁⨁◯◯ LOW	55	55	-	-	MD **0.20 lower** (8.22 lower to 7.82 higher)
WOMAC Pain - mid term follow up (0-20, lower scores indicate improvement)											

CBT compared to usual care for knee OA											
Certainty assessment							Summary of findings				
76 (1 RCT)	serious [a]	not serious	not serious	serious [b]	none	⨁⨁◯◯ LOW	40	36	-	-	MD **0.49 higher** (0.66 lower to 1.64 higher)

CI: Confidence interval; **SMD:** Standardised mean difference; **MD:** Mean difference

Explanations

a. Participants not blinded for Helminen; both studies blinded outcome assessors

b. Wide 95% CI that includes possibility of a clinically significant difference between groups

References

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PICO 26: Weight loss compared to usual care for knee or hip OA

Summary: The literature search identified six clinical trials that directly evaluated the effects of weight loss on pain and function in knee OA, but none in hip OA. All studies included long-term weight loss programs (6-18 months), except the study by Christensen et al (8 weeks). Weight loss was achieved either by calorie restriction (Bliddal et al, Gudbergsen et al, Christensen et al), or with diet and exercise regimens (Messier et al, Miller et al, Sommers et al). Participants were not blinded in any of the trials, attrition rates were high in two studies (Bliddal et al, Somers et al). Five of the studies directly reported WOMAC pain scores (Bliddal et al, Christensen et al, Messier et al, Miller et al, Somers et al), and one study reported percent of subjects achieving WOMAC pain score reduction of 50% or more (Gudbergsen et al). Three of the studies favored intervention for pain outcomes (Bliddal et al, Miller et al, Gudbergsen et al), and three reported no significant difference between intervention and control (Christensen et al, Messier et al, Somers et al). Similarly, all six studies reported function outcomes, three favored intervention

(Christensen et al, Gudbergsen et al, Miller et al), and the rest reported null results (Bliddal et al, Messier et al, Somers et al). Five out of six studies reported adverse events. Of these, none reported serious adverse events, one study (Bliddal et al) reported minor adverse events in the calorie restriction group (constipation, flatulence, dizziness, and heightened sensitivity to cold). Two available systematic reviews of RCTs and observational studies (Groen et al, Gill et al) did not include adverse events data.

Quality of evidence across all critical outcomes: Moderate

Table 1. Weight loss compared to usual care for knee and Hip OA

Certainty assessment							Summary of findings				
№ of participants (studies) Follow-up	**Risk of bias**	**Inconsistency**	**Indirectness**	**Imprecision**	**Publication bias**	**Overall certainty of evidence**	**Number of patients**		**Relative effect (95% CI)**	**Anticipated absolute effects**	
							With placebo	**With Weight loss**		**Risk with placebo**	**Risk difference with Weight loss**
WOMAC Pain subscale (lower scores indicate improvement)											
448 (5 RCTs)	serious [a]	not serious	not serious	not serious	none	⨁⨁⨁◯ MODERATE	222	226	-	-	SMD **0.32 lower** (0.59 lower to 0.04 lower) **Favors weight loss**
Achieved pain reduction of >50% on WOMAC pain scale											

Table 1. Weight loss compared to usual care for knee and Hip OA											
Certainty assessment							**Summary of findings**				
30 (1 RCT)	serious [a]	not serious	not serious	serious [b]	none	⨁⨁◯◯ LOW	2/15 (13.3%)	6/15 (40.0%)	**OR 4.33** (0.71 to 26.53)	133 per 1,000	**266 more per 1,000** (35 fewer to 670 more)
WOMAC function score (lower scores indicate improvement)											
448 (5 RCTs)	serious [a]	not serious	not serious	not serious	none	⨁⨁⨁◯ MODERATE	222	226	-	-	SMD **0.30 lower** (0.52 lower to 0.09 lower) **Favors weight loss**
6 min walk distance (higher scores indicate improvement)											
201 (2 RCTs)	serious [a]	not serious	not serious	serious [b]	none	⨁⨁◯◯ LOW	99	102	-	-	MD **40.16 higher** (6.68 lower to 86.99 higher)

CI: Confidence interval; **MD:** Mean difference; **OR:** Odds ratio

Explanations

a. Participants not blinded; outcome assessors were blinded

b. Wide confidence interval

Table 2. RCT and systematic review data not suitable for RevMan

Ref ID, Author, year	Study type	Duration	Population Description	Treatment given to relevant population	Results
RefID 6617 Gudbergsen 2011	single-blind RCT	32 weeks	30 overweight women with knee OA	32 weeks of low-calorie formulated diet given to 15 pts vs advice to restrict calorie intake to 15 pts	The WOMAC disability index showed improvement in the LED group when compared with the control group, MD of - 266 mm (95%CI: -468.9 to -63.1; p < 0.01) There were no adverse events
RefID 2808 Groen, 2015	Systematic review of RCTs and observational studies (any study design)	Inception - 2014	13 studies, 11 of them single arm or surgical technique (intervention vs intervention) studies	Bariatric surgery for pain and function in OA (unspecified site)	All 13 studies reported pain outcomes. Ten out of 13 studies (77%) reported a significant improvement in at least one pain assessment tool. Five out of 13 studies analysed the effect of bariatric surgery on knee physical function. All five studies (100%) reported significant improvements Adverse event data were not reported Low quality of evidence
RefID 565 Gill 2011	Systematic review of RCTs and observational studies (any study design)	Not reported	6 studies, five case series and one case-control study	Bariatric surgery for pain, radiographic severity, and quality of life in OA of the hip and knee	All studies reported pain outcomes, but one of them also involved arthroplasty. All reported significant improvement in at least one pain assessment tool. One of the studies specifically reported function, and showed improvement. Adverse event data were not reported Low quality of evidence; surprisingly young patients included

References:

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PICO 27. Acupuncture/UC compared to UC for knee and/or hip OA

Summary. The literature searches identified 12 RCTs that compared acupuncture (or electroacupuncture) plus usual care to sham acupuncture and/or usual care in patients with knee OA.[1-12] Eight of the RCTs included a control group with a sham needle (penetrating or non-penetrating)[1-8], and 10 included a usual care control group.[1,3-7,9-12] In a meta-analysis of 7 RCTs, acupuncture showed a small, statistically significant benefit over sham acupuncture for WOMAC pain and function at 6 to 12 weeks, but there was very high heterogeneity among study effect sizes . Five RCTs found no significant between-group difference in WOMAC pain at 26 weeks, and 3 RCTs showed no significant between-group difference in WOMAC pain at 1 year. Similarly, 5 RCTs found no significant between-group difference in WOMAC function at 26 weeks, and one RCT found no significant difference at 1 year. Two RCTs found no significant between-group difference in the six-minute walk test and one RCT found no difference in the TUG test. Meta-analysis of 2 RCTs found a significant elevation in serious adverse events in the acupuncture group relative to the sham control group (Table 1).

For acupuncture plus usual care versus usual care,[1,3-7,9-12] a meta-analysis of 7 RCTs found large between-group differences in WOMAC pain and function favoring acupuncture at 6 to 12 weeks. Although there was high heterogeneity in the effect sizes, the lower confidence limit around the summary effect still included a small-to-moderate size effect favoring acupuncture. Three RCTs collectively showed a small between-group difference in WOMAC pain that did not reach statistical significance at 26 weeks, and 3 RCTs showed no difference at 1 year. Similarly, 3 RCTs found a small between-group difference in WOMAC function favoring acupuncture at 26 weeks, and 3 RCTs showed no difference at 1 year. One

RCT found no significant between-group difference in six minute walk distance. Serious adverse events, increased knee pain, and injury did not differ significantly between acupuncture and usual care groups, but the findings were imprecise and therefore inconclusive (Table 2).

Three RCTs compared acupuncture to sham acupuncture in patients with hip OA.[12-14] For acupuncture versus sham, 2 RCTs found no significant between-group difference in pain or function at 4 to 6 weeks (Table 3).[13,14] For acupuncture plus usual care versus usual care, one RCT[12] found a large between-group difference in WOMAC pain and function favoring acupuncture at 3 months (Table 4). The data ponts for these studies were obtained from a systematic review by Manheimer et al., who had received unpublished data from the study authors.

Quality of evidence across all critical outcomes: Knee OA: Low for short-term and long-term outcomes. Hip OA: Low (short-term data only).

Table 1. Acupuncture compared to Sham Acupuncture for Knee OA

Certainty assessment							Summary of findings				
№ of participants (studies) Follow-up	**Risk of bias**	**Inconsistency**	**Indirectness**	**Imprecision**	**Publication bias**	**Overall certainty of evidence**	**Study event rates (%)**		**Relative effect (95% CI)**	**Anticipated absolute effects**	
							With Sham Acupuncture	**With Acupuncture**		**Risk with Sham Acupuncture**	**Risk difference with Acupuncture**
WOMAC Pain (6-12 weeks)											
1617 (7 RCTs)	not serious	serious [a]	not serious	serious [c]	none	⨁⨁◯◯ LOW	843	774	-	-	SMD **0.44 lower** (0.81 lower to 0.07 lower) **Favors acupuncture**
WOMAC Pain (26 weeks)											
1612 (5 RCTs)	not serious	not serious	not serious	not serious	none	⨁⨁⨁⨁ HIGH	250	246	-	-	SMD **0.06 lower** (0.18 lower to 0.07 higher)

Table 1. Acupuncture compared to Sham Acupuncture for Knee OA											
Certainty assessment							Summary of findings				
WOMAC Pain (1 year)											
204 (1 RCT)	not serious	not serious	not serious	serious [b]	none	⨁⨁⨁◯ MODERATE	105	99	-	-	SMD **0.14 higher** (0.13 lower to 0.42 higher)
WOMAC Function / SF-12 PCS (6-12 weeks)											
2308 (8 RCTs)	not serious	serious [a]	not serious	serious [c]	none	⨁⨁◯◯ LOW	1208	1100	-	-	SMD **0.42 lower** (0.71 lower to 0.12 lower) **Favors acupuncture**
WOMAC Function / SF-12 PCS (26 weeks)											
1623 (5 RCTs)	not serious	not serious	not serious	not serious	none	⨁⨁⨁⨁ HIGH	615	572	-	-	SMD **0.07 lower** (0.21 lower to 0.08 higher)
WOMAC Function (1 year)											
205 (1 RCT)	not serious	not serious	not serious	serious [b]	none	⨁⨁⨁◯ MODERATE	105	100	-	-	SMD **0.08 higher** (0.19 lower to 0.36 higher)
6 minute walk distance (feet)											

Table 1. Acupuncture compared to Sham Acupuncture for Knee OA											
Certainty assessment							**Summary of findings**				
496 (2 RCTs)	not serious	not serious	not serious	serious [b,c]	none	⨁⨁⨁◯ MODERATE	250	246	-	-	MD **30.03 lower** (79.2 lower to 19.13 higher)
TUG (seconds)											
455 (1 RCT)	not serious	not serious	not serious	serious [b]	none	⨁⨁⨁◯ MODERATE	302	153	-	-	MD **0** (0.88 lower to 0.88 higher)
SAE											
1072 (2 RCTs)	not serious	not serious	not serious	serious [d]	none	⨁⨁⨁◯ MODERATE	14/556 (2.5%)	34/516 (6.6%)	**OR 2.72** (1.44 to 5.14)	25 per 1,000	**40 more per 1,000** (11 more to 92 more) **Favors sham**

CI: Confidence interval; **SMD:** Standardised mean difference; **MD:** Mean difference; **OR:** Odds ratio

Explanations

a. High I^2
b. Crosses no effect line
c. Wide CI
d. Wide CI and small percentage of studies reported the outcome.

Table 2. Acupuncture/UC compared to UC for Knee OA										
Certainty assessment							**Summary of findings**			
№ of participants (studies) Follow-up	**Risk of bias**	**Inconsistency**	**Indirectness**	**Imprecision**	**Publication bias**	**Overall certainty of evidence**	**Study event rates (%)**		**Relative effect (95% CI)**	**Anticipated absolute effects**	
							With UC	**With acupuncture/UC**		**Risk with UC**	**Risk difference with acupuncture/UC**

Table 2. Acupuncture/UC compared to UC for Knee OA

Certainty assessment							Summary of findings				
WOMAC pain at 6 to 12 weeks											
1568 (7 RCTs)	serious [a]	serious [b]	not serious	not serious	none	⨁⨁◯◯ LOW	710	858	-	-	SMD **0.81 lower** (1.22 lower to 0.4 lower) **Favors acupuncture**
WOMAC pain at 26 wks											
1088 (3 RCTs)	serious [a]	not serious	not serious	serious [c]	none	⨁⨁◯◯ LOW	108	142	-	-	SMD **0.35 lower** (0.71 lower to 0.01 higher)
WOMAC pain at 1 yr followup, post scores											
348 (3 RCTs)	serious [a]	not serious	not serious	serious [c]	none	⨁⨁◯◯ LOW	175	173	-	-	SMD **0.01 lower** (0.22 lower to 0.2 higher)
WOMAC function / SF-12 PCS at 6 to 12 wks											
2210 (8 RCTs)	serious [a]	serious [b]	not serious	not serious	none	⨁⨁◯◯ LOW	1026	1184	-	-	SMD **0.73 lower** (1.13 lower to 0.33 lower) **Favors acupuncture**
WOMAC function / SF-12 PCS at 26 wks											

Table 2. Acupuncture/UC compared to UC for Knee OA											
Certainty assessment							Summary of findings				
1093 (3 RCTs)	serious [a]	not serious	not serious	serious [c]	none	⨁⨁◯◯ LOW	424	468	-	-	SMD **0.27 lower** (0.51 lower to 0.04 lower) **Favors acupuncture**
WOMAC function at 1 yr followup											
348 (3 RCTs)	serious [a]	not serious	not serious	serious [c]	none	⨁⨁◯◯ LOW	174	174	-	-	SMD **0.01 lower** (0.22 lower to 0.2 higher)
6 minute walk distance (change from baseline - feet)											
250 (1 RCT)	serious [a]	not serious	not serious	serious [c]	none	⨁⨁◯◯ LOW	108	142	-	-	MD **77.8 higher** (11.43 lower to 167.03 higher)
50m walk time (seconds)											
104 (1 RCT)	serious [a]	not serious	not serious	serious [c]	none	⨁⨁◯◯ LOW	52	52	-	-	MD **3.5 lower** (11.76 lower to 4.76 higher)
Increased knee pain											
813 (3 RCTs)	serious [a]	serious [c]	not serious	serious [c]	none	⨁◯◯◯ VERY LOW	10/402 (2.5%)	13/411 (3.2%)	**OR 2.37** (0.26 to 21.26)	25 per 1,000	**32 more per 1,000** (18 fewer to 327 more)
SAEs											

Table 2. Acupuncture/UC compared to UC for Knee OA											
Certainty assessment							**Summary of findings**				
1245 (3 RCTs)	not serious	not serious	not serious	serious [c]	none	⨁⨁⨁◯ MODERATE	27/579 (4.7%)	37/666 (5.6%)	**OR 1.17** (0.54 to 2.52)	47 per 1,000	**7 more per 1,000** (21 fewer to 63 more)
Injury											
672 (2 RCTs)	not serious	not serious	not serious	serious [c]	none	⨁⨁⨁◯ MODERATE	1/331 (0.3%)	1/341 (0.3%)	**OR 0.99** (0.10 to 9.79)	3 per 1,000	**0 fewer per 1,000** (3 fewer to 26 more)

CI: Confidence interval; **SMD:** Standardised mean difference; **MD:** Mean difference; **OR:** Odds ratio

Explanations

a. Comparison cannot be blinded

b. High I^2

c. Wide CI that crosses no effect line

Table 3. Acupuncture compared to sham for hip OA											
Certainty assessment							**Summary of findings**				
№ of participants (studies) Follow-up	**Risk of bias**	**Inconsistency**	**Indirectness**	**Imprecision**	**Publication bias**	**Overall certainty of evidence**	**Study event rates (%)**		**Relative effect (95% CI)**	**Anticipated absolute effects**	
							With sham (hip)	**With Acupuncture**		**Risk with sham (hip)**	**Risk difference with Acupuncture**
VAS Pain (4 to 6 weeks)											
120 (2 studies)	serious [a]	not serious	not serious	serious [b]	none	⨁⨁◯◯ LOW	58	62	-	-	SMD **0.13 lower** (0.49 lower to 0.22 higher)
Function (4 to 6 weeks)											

Table 3. Acupuncture compared to sham for hip OA

Certainty assessment							Summary of findings				
120 (2 studies)	serious [a]	not serious	not serious	serious [b]	none	⨁⨁◯◯ LOW	58	62	-	-	SMD **0.15 lower** (0.51 lower to 0.21 higher)

CI: Confidence interval; **SMD:** Standardized mean difference

Explanations

a. Investigators not blinded to treatment (performance bias)

b. Wide 95% CI overlaps with line of no effect

Table 4. Acupuncture/UC compared to UC for hip OA

Certainty assessment							Summary of findings				
№ of participants (studies) Follow-up	**Risk of bias**	**Inconsistency**	**Indirectness**	**Imprecision**	**Publication bias**	**Overall certainty of evidence**	**Study event rates (%)**		**Relative effect (95% CI)**	**Anticipated absolute effects**	
							With UC (hip)	**With Acupuncture/UC**		**Risk with UC (hip)**	**Risk difference with Acupuncture/UC**
WOMAC pain (3 months)											
137 (1 study)	serious [a]	not serious	not serious	serious [b]	none	⨁⨁◯◯ LOW	64	73	-	-	SMD **1.21 lower** (1.58 lower to 0.84 lower) **Favors acupuncture**
WOMAC function (3 months)											

Table 4. Acupuncture/UC compared to UC for hip OA											
Certainty assessment							**Summary of findings**				
137 (1 study)	serious [a]	not serious	not serious	serious [b]	none	⨁⨁◯◯ LOW	64	73	-	-	SMD **1.17 lower** (1.54 lower to 0.81 lower) **Favors acupuncture**

CI: Confidence interval; S**MD:** Standardized mean difference

Explanations

a. No blinding

b. Single study with large effect size

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PICO 28. Mind body practices plus UC compared to UC for hip and knee OA

Summary. The literature searches identified 10 RCTs and one systematic review that compared various mind-body practices plus usual care to usual care alone in patients with hip and/or knee OA. Each mind-body practice was evaluated in a separate analysis (Tables 1-8).

Table 1 presents evidence from 7 RCTs that compared the efficacy of Tai chi and usual care to usual care alone in patients with knee and/or hip OA.[1-7] Fransen et al.[2] was the only study that included some patients with hip OA, all others exclusively enrolled patients with knee OA. Meta-analyses of the 7 RCTs found a significant between-group difference favoring tai chi over usual care alone for improvement in WOMAC pain and function at 8 to 24 weeks follow-up. Only one small RCT evaluated WOMAC pain and function at 1-year follow-up,[6] and the finding was inconclusive due to a wide 95% CI that included the possibility of no difference between groups. A few RCTs also found evidence for a significant benefit favoring tai chi in improvement in objective function measures (chair stand, timed up and go, and 6 meter walk test). The overall quality of evidence was moderate due to serious risk of bias in some studies.

Table 2 presents evidence from two RCTs that compared Yoga plus usual care to usual care in 91 patients with knee OA.[8,9] Collectively these studies found significant improvement in WOMAC pain and function, chair stands, and timed fast walking at 8 weeks favoring Yoga over usual

care. The quality of evidence was moderate due to serious risk of bias (patients not blinded). A systematic review of Yoga in patients with knee OA did not alter these findings (Table 9).[10] Similarly, an additional RCT identified in a literature search update in August 2018 did not alter these findings.[13]

Table 3 presents evidence from one RCT that compared hypnosis plus usual care to usual care in 21 patients with knee and/or hip OA. [11] At 6 months following treatment, the study found no significant between-group difference in VAS pain scores. The quality of evidence was low due to serious risk of bias (patients not blinded) and serious imprecision in the effect estimate (wide 95% CI that included the possibility of a between-group difference) that rendered the results inconclusive. Table 4 found the same results from a comparison of relaxation and usual care in the same trial.

Tables 5-7 present evidence from one RCT comparing external qigong therapy (EQT) plus usual care to sham therapy plus usual care in 112 patients with knee OA.[12] The study used two healers, one of whom was considered more effective than the other. Results were reported together for increased pain and separately for each healer for time to walk 50 feet at 3 months. The number of patients with increased pain did not differ significantly between groups (Table 6), but the finding was inconclusive due to a wide 95% CI that includes the possibility of a between-group difference. Walking time over 50 feet significantly favored EQT when administered by the more effective healer (Table 7), but showed no significant between-group difference when administered by the less effective healer (Table 8). Similarly, WOMAC pain and function were substantially decreased by the more effective healer compared to the less effective healer (Table 9) The quality of evidence was low due to serious risk of bias (no allocation concealment) and serious imprecision for increased pain.

Quality of evidence across all critical outcomes: Moderate for Tai Chi and Yoga; Low for hypnosis, relaxation, and EQT

Table 1. Tai chi/UC compared to UC for hip and knee OA

Certainty assessment							Summary of findings				
№ of participants (studies) Follow-up	Risk of bias	Inconsistency	Indirectness	Imprecision	Publication bias	Overall certainty of evidence	Number of patients		Relative effect (95% CI)	Anticipated absolute effects	
							With UC for knee OA	With tai chi/UC		Risk with UC for knee OA	Risk difference with tai chi/UC
WOMAC pain, at 8 to 24 weeks											

Table 1. Tai chi/UC compared to UC for hip and knee OA											
Certainty assessment							**Summary of findings**				
350 (7 RCTs)	serious [a]	not serious	not serious	not serious	none	⨁⨁⨁◯ MODERATE	137	173	-	-	SMD **0.59 lower** (0.89 lower to 0.29 lower) **Favors Tai Chi**
WOMAC pain at 1 yr, change score (lower scores indicate improvement)											
40 (1 RCT)	not serious	not serious	not serious	serious [b]	none	⨁⨁⨁◯ MODERATE	20	20	-	-	SMD **0.46 lower** (1.09 lower to 0.17 higher)
WOMAC function at 8 to 24 weeks (lower scores indicate improvement)											
350 (7 RCTs)	serious [a]	not serious	not serious	not serious	none	⨁⨁⨁◯ MODERATE	137	173	-	-	SMD **0.67 lower** (0.89 lower to 0.46 lower) **Favors Tai Chi**
WOMAC function at 1 yr, change scores (lower scores indicate improvement)											

Table 1. Tai chi/UC compared to UC for hip and knee OA											
Certainty assessment							**Summary of findings**				
40 (1 RCT)	not serious	not serious	not serious	serious [b]	none	⨁⨁⨁◯ MODERATE	20	20	-	-	SMD **0.36 lower** (0.99 lower to 0.26 higher)
chair stand test (seconds) at 12 to 21 wks, change score (lower scores indicate improvement)											
95 (2 RCTs)	not serious	not serious	not serious	serious [b]	none	⨁⨁⨁◯ MODERATE	47	48	-	-	SMD **0.88 lower** (1.84 lower to 0.08 higher)
chair stand at 1 yr, change score, time in seconds (lower scores indicate improvement)											
40 (1 RCT)	not serious	not serious	not serious	serious [c]	none	⨁⨁⨁◯ MODERATE	20	20	-	-	MD **5.98 lower** (10.73 lower to 1.23 lower) **Favors Tai Chi**
Timed up and go test, change scores at 12-21 weeks (lower scores indicate improvement)											

Table 1. Tai chi/UC compared to UC for hip and knee OA											
Certainty assessment							Summary of findings				
198 (3 RCTs)	serious [d]	not serious	not serious	not serious	none	⨁⨁⨁◯ MODERATE	68	84	-	-	MD **0.56 lower** (0.93 lower to 0.18 lower) **Favors Tai Chi**
6 meter (seconds) walk test at wk 8, change score (lower scores indicate improvement)											
44 (1 RCT)	serious [d]	not serious	not serious	serious [c]	none	⨁⨁◯◯ LOW	15	29	-	-	MD **1.4 lower** (2.14 lower to 0.66 lower) **Favors Tai Chi**
gait velocity at 24 weeks (higher scores indicate improvement)											
40 (1 RCT)	serious [a]	not serious	not serious	serious [b]	none	⨁⨁◯◯ LOW	19	21	-	-	MD **8.4 higher** (1.33 higher to 15.47 higher) **Favors Tai Chi**

CI: Confidence interval; **MD:** Mean difference; **SMD:** Standardised mean difference

Explanations

a. Patients not blinded in 3 studies

b. Wide 95% CI that overlaps line of no effect

c. Small study with wide 95% CI

d. Patients not blinded

Table 2. Yoga/UC compared to UC for hip and knee OA

Certainty assessment							Summary of findings				
№ of participants (studies) Follow-up	**Risk of bias**	**Inconsistency**	**Indirectness**	**Imprecision**	**Publication bias**	**Overall certainty of evidence**	**Study event rates (%)**		**Relative effect (95% CI)**	**Anticipated absolute effects**	
							With UC	**With yoga/UC**		**Risk with UC**	**Risk difference with yoga/UC**
WOMAC pain at 8 weeks, post scores (0-20, lower scores indicate improvement)											
91 (2 RCTs)	serious [a]	not serious	not serious	not serious	none	⨁⨁⨁◯ MODERATE	41	50	-	-	MD **1.8 lower** (2.93 lower to 0.68 lower) **Favors yoga**
WOMAC function at 8 weeks, post scores (0-68, lower scores indicate improvement)											
91 (2 RCTs)	serious [a]	not serious	not serious	not serious	none	⨁⨁⨁◯ MODERATE	41	50	-	-	MD **6.14 lower** (9.68 lower to 2.6 lower) **Favors yoga**
repeated chair stands at 8 weeks, post score (from the SPPB test) (higher scores indicate improvement)											

Table 2. Yoga/UC compared to UC for hip and knee OA											
Certainty assessment							Summary of findings				
91 (2 RCTs)	serious [a]	not serious	not serious	not serious	none	⨁⨁⨁◯ MODERATE	41	50	-	-	MD **0.6 higher** (0.23 higher to 0.98 higher) **Favors yoga**
timed 8 foot walk at 8 weeks, post score (from the SPPB test) (higher scores indicate improvement)											
91 (2 RCTs)	serious [a]	not serious	not serious	not serious	none	⨁⨁⨁◯ MODERATE	41	50	-	-	MD **0.4 higher** (0.21 higher to 0.59 higher) **Favors yoga**

CI: Confidence interval; **MD:** Mean difference

Explanations

a. Patients not blinded; outcome assessor blinded in at least 1 study

Table 3. Hypnosis/UC compared to wait list control/UC for hip and knee OA for hip and knee OA									
Certainty assessment							Summary of findings		
№ of participant		**Inconsistency**	**Indirectness**	**Imprecision**	**Publication bias**	**Overall certaint**	**Number of patients**	**Relative effect**	**Anticipated absolute effects**

Table 3. Hypnosis/UC compared to wait list control/UC for hip and knee OA for hip and knee OA											
Certainty assessment							Summary of findings				
s (studies) Follow-up	**Risk of bias**					**y of evidence**	**With wait list control/UC for hip and knee OA**	**With hypnosis/UC**	**(95% CI)**	**Risk with wait list control/UC for hip and knee OA**	**Risk difference with hypnosis/UC**
pain VAS at 6 months post scores (0-10, lower scores indicate improvement)											
21 (1 RCT)	serious [a]	not serious	not serious	serious [b]	none	⨁⨁◯◯ LOW	10	11	-	-	MD **1.93 lower** (4.01 lower to 0.15 higher)

CI: Confidence interval; **MD:** Mean difference

Explanations

a. Patients not blinded, allocation concealment and outcome assessment not reported

b. Wide 95% CI that overlaps line of no effect

Table 4. Relaxation/UC compared to wait list/UC for hip and knee OA											
Certainty assessment							Summary of findings				
№ of participants (studies) Follow-up	**Risk of bias**	**Inconsistency**	**Indirectness**	**Imprecision**	**Publication bias**	**Overall certainty of evidence**	**Number of patients**		**Relative effect (95% CI)**	**Anticipated absolute effects**	
							With wait list/UC	**With relaxation/UC**		**Risk with wait list/UC**	**Risk difference with relaxation/UC**

Table 4. Relaxation/UC compared to wait list/UC for hip and knee OA											
Certainty assessment							**Summary of findings**				
pain VAS at 6 months, post scores (0-10, lower scores indicate improvement)											
21 (1 RCT)	serious [a]	not serious	not serious	serious [b]	none	⨁⨁◯◯ LOW	10	11	-	-	MD **1.51 lower** (3.27 lower to 0.25 higher)

CI: Confidence interval; **MD:** Mean difference

Explanations

a. Patients not blinded, allocation concealment and blinded outcome assessment not reported

b. Wide 95% CI that overlaps line of no effect

Table 5. EQT/UC compared to UC (both effective and noneffective healers combined) for hip and knee OA											
Certainty assessment							**Summary of findings**				
№ of participants (studies) Follow-up	**Risk of bias**	**Inconsistency**	**Indirectness**	**Imprecision**	**Publication bias**	**Overall certainty of evidence**	**Number of patients**		**Relative effect (95% CI)**	**Anticipated absolute effects**	
							With UC (both effective and noneffective healers combined)	**With EQT/UC**		**Risk with UC (both effective and noneffective healers combined)**	**Risk difference with EQT/UC**
increased pain											

Table 5. EQT/UC compared to UC (both effective and noneffective healers combined) for hip and knee OA											
Certainty assessment							**Summary of findings**				
112 (1 RCT)	serious [a]	not serious	not serious	serious [b]	none	⨁⨁◯◯ LOW	2/52 (3.8%)	5/60 (8.3%)	**OR 2.27** (0.42 to 12.24)	38 per 1,000	45 more per 1,000 (22 fewer to 290 more)

CI: Confidence interval; **OR:** Odds ratio

Explanations

a. No allocation concealment

b. Wide 95% CI that overlaps line of no effect

Table 6. EQT (more effective healer)/UC compared to UC for hip and knee OA										
Certainty assessment							**Summary of findings**			
№ of participants (studies) Follow-up	**Risk of bias**	**Inconsistency**	**Indirectness**	**Imprecision**	**Publication bias**	**Overall certainty of evidence**	**Number of patients**		**Relative effect (95% CI)**	**Anticipated absolute effects**	
							With UC	**With EQT (more effective healer)/UC**		**Risk with UC**	**Risk difference with EQT (more effective healer)/UC**
time (seconds) to walk 50 feet at 3 months, post scores (lower scores indicate improvement)											

Table 6. EQT (more effective healer)/UC compared to UC for hip and knee OA											
Certainty assessment							**Summary of findings**				
61 (1 RCT)	serious [a]	not serious	not serious	not serious	none	⨁⨁⨁◯ MODERATE	49	12	-	-	MD **1.8 lower** (2.84 lower to 0.76 lower) **Favors EQT**

CI: Confidence interval; **MD:** Mean difference

Explanations

a. No allocation concealment

Table 7. EQT/UC (less effective healer) compared to UC for hip and knee OA											
Certainty assessment							**Summary of findings**				
№ of participants (studies) Follow-up	**Risk of bias**	**Inconsistency**	**Indirectness**	**Imprecision**	**Publication bias**	**Overall certainty of evidence**	**Number of patients**		**Relative effect (95% CI)**	**Anticipated absolute effects**	
							With UC	**With EQT/UC (less effective healer)**		**Risk with UC**	**Risk difference with EQT/UC (less effective healer)**
time (seconds) to walk 50 feet, 3 month post scores (lower scores indicate improvement)											
94 (1 RCT)	serious [a]	not serious	not serious	not serious	none	⨁⨁⨁◯ MODERATE	49	45	-	-	MD **0.3 lower** (1.34 lower to 0.74 higher)

CI: Confidence interval; **MD:** Mean difference

Explanations

a. No allocation concealment

Table 8. Systematic review and RCT data not suitable for effect size calculation or combining with other data

Ref ID, Author, year	Study type	Duration	Population Description	Treatment given to relevant population	Results
3115 Kan, 2016	Systematic review	"A total of 9 articles (6 studies) were included (Six articles (three RCTs), one quasi-RCT], and two single group pre-post studies) were included. The most common yoga protocol is 40~90 minutes/session, lasting for at least 8 weeks."	372 patients with knee OA. The mean age of subjects varied from 51 to 71 years.	Comparators: three had a control group which did conventional exercise during the experimental time, in another study both groups were treated with EMG biofeedback, knee muscle strengthening exercises, and Transcutaneous Electrical Nerve Stimulation (TENS), and the yoga group received additionally Iyengar Yoga, and the remaining two studies did not have control group. Yoga: 8 weeks in four studies and 12-weeks in two studies. Almost every study had 3-4 sessions per week with each session varying from 60 to 90 minutes. The type of yoga practice in three studies all consisted of asana movement), pranayama (breathing), and meditation	"Relevant articles were identified using the following databases: Medline (1966 to Jul 2015; via Ovid), EMBASE (1980 to Jul 2015; via Ovid), the Cochrane Central Register of Controlled Trials (CENTRAL) (The Cochrane Library, Issue 7 of 12 Jul 2015), Pubmed (1966 to Jul 2015), and Physiotherapy Evidence Database (PEDro) (1929 to Jul 2015; via website)." The methodological quality was assessed using the Downs and Black's Quality Index, which consists of 27 items. A score of 23 or higher indicates good-quality, a score between 22 and 13 indicates medium-quality, and a score of 12 or lower represents a poor-quality article with high risk of bias. The results of the quality assessment were: one good-quality, seven medium-quality articles and one trial was poor-quality article. **WOMAC pain** Both studies (one single group pre-post study and a two group comparison) reporting this outcome found significant improvements compared to baseline and between groups, respectively. **VAS pain** Four studies reported VAS pain. Three out of four studies found positive results for yoga. In one study there was a significant difference in pain both within (p < 0.001) and between groups (p < 0.001) after the 3-month yoga intervention combined with physiotherapy with higher effect size in the yoga group than in the control group (therapeutic exercise with physiotherapy). In another study, the yoga group showed a more reduced VAS (56.83%) than control group (38.15%) after 8 weeks of intervention and the pre- and postintervention ratings of VAS score showed a statistically significant reduction of pain intensity in yoga group compared with control group (p < 0.05). In a third study, pre- and postintervention scores had a significant improvement in pain after

				(relaxation), the type of yoga practiced in other two studies was asana (movement), and the last study did not mention the yoga type studied.	12 weeks of yoga based exercise, and in the fourth study no significant differences were detected in pain between the 8-week yoga group and the control group (home-based activities); however, the pre-post scores showed a significant difference in the yoga group but not in the control group. **Mobility** Three studies assessed mobility, with mixed results. In one trial, there was a significant difference in walking time within and between groups after 12 weeks of intervention with higher effect size in the yoga than in the control group. In a second study, the 50-foot walk time was unchanged after 8 weeks of yoga exercise. In the third study. a Six-Minute Walk Test (6MWT), a 30-second chair stand test (30 s CST), and a stair-climbing protocol were used to assess mobility. The pre- to postintervention scores showed a significant improvement when measured with 6MWT and 30s CST after 12 weeks of yoga intervention, but no significant change could be detected in stair-climbing.
2883 Chen, 2008	RCT	3 months	112 patients with knee OA	External Qigong Therapy (administered by 2 different healers and reported separately by healer) vs sham	WOMAC pain and function results were presented in a graph without SD/measure of variance for the followup visits **WOMAC pain** Sham Baseline (n=52) 49.9 (SD=20.2) 3 month followup (n=42) 35 (SD=NR) Healer 1 (less effective healer) Baseline (n=47) 51.6 (SD=21.4) 3 month followup (n=39) 37 (SD=NR) Healer 2 (more effective healer) Baseline (n=13) 45 (SD= 18.6) 3 month followup (n=11) 19 (SD=NR) **WOMAC function** Sham Baseline (n=52) 55.3 (SD=19.1) 3 month followup (n=42) 41 (SD=NR) Healer 1 (less effective healer) Baseline (n=47) 50.5 (SD=21.5) 3 month followup (n=39) 38 (SD=NR) Healer 2 (more effective healer) Baseline (n=13) 46.5 (SD = 20.7) 3 month followup (n=11) 21 (SD=NR)

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PICO 29: Cane and usual care compared to usual care alone for knee OA.

Evidence Summary: One RCT by Jones et al.[1] evaluated the effect of cane use in addition to usual care for knee OA in a RCT. Compared to the control group, those who used a cane for two months reported significantly greater improvement in pain and self-reported function. Performance on the 6-minute walk test did not differ significantly between groups, but the estimate is imprecise with wide confidence intervals.

Quality of evidence: Moderate

Cane compared to Usual Care for Knee OA											
Certainty assessment							**Summary of findings**				
№ of participants (studies) Follow-up	**Risk of bias**	**Inconsistency**	**Indirectness**	**Imprecision**	**Publication bias**	**Overall certainty of evidence**	**Number of patients**		**Relative effect (95% CI)**	**Anticipated absolute effects**	
							With Usual Care for Knee OA	**With Cane**		**Risk with Usual Care for Knee OA**	**Risk difference with Cane**
VAS Pain (0-10, lower scores indicate improvement)											
64 (1 RCT)	serious [a]	not serious	not serious	not serious	none	⨁⨁⨁◯ MODERATE	32	32	-	-	MD **2.11 lower** (2.81 lower to 1.41 lower) **Favors cane**
SF-36 Physical Function (0-100, higher scores indicate improvement)											

Cane compared to Usual Care for Knee OA											
Certainty assessment							**Summary of findings**				
64 (1 RCT)	serious [a]	not serious	not serious	not serious	none	⨁⨁⨁◯ MODERATE	32	32	-	-	MD **9.06 higher** (0.67 higher to 17.45 higher) **Favors cane**
6-minute Walk Test (higher scores indicate improvement)											
64 (1 RCT)	serious [a]	not serious	not serious	serious [b]	none	⨁⨁◯◯ LOW	32	32	-	-	MD **6.5 lower** (24.06 lower to 11.06 higher)

CI: Confidence interval; **MD:** Mean difference

Explanations

a. Participants and PTs not blinded, outcome assessor was blinded

b. Wide confidence interval

References

1. Jones A, Silva PG, Silva AC, et al. Impact of cane use on pain, function, general health and energy expenditure during gait in patients with knee osteoarthritis: a randomised controlled trial. *Ann Rheum Dis.* 2012;71(2):172-179.

PICO 30: Heat application, including ultrasound, for knee OA

Summary: There were 18 original RCTs evaluating the effectiveness of heat in the management of knee OA, 11 of them included assessment of therapeutic ultrasound. All RCTs provided direct evidence for therapeutic heat effects compared with various control scenarios.

Eight studies reported the effects of heat application (hot water or hot packs) or diathermy on knee OA pain (Yildirim et al, Atamaz et al, Aciksoz et al, Giombini et al, Branko et al, Rattanachaiyanont et al, Lim et al, Cetin et al). All diathermy studies were double-blind (Atamaz et al, Giombini et al, Rattanachaiyanont et al), and hot water/hot pack application studies were not blinded. Study duration varied between 3 weeks and 10 weeks. Pain outcomes in most studies included WOMAC pain, one study assessed pain by visual analog scale only (Cetin et al). Most studies found no significant improvement in OA pain with heat application or diathermy. One diathermy study (Giombini et al) and one hot water application study (Branko et al) favored intervention. One additional study of hot pack applications showed no difference in WOMAC pain, but a small difference in VAS favoring intervention (Aciksoz et al). Six studies reported WOMAC function outcomes (Yildirim et al, Atamaz et al, Aciksoz et al, Giombini et al, Branko et al, Rattanachaiyanont et al). Of these, three studies favored intervention, and three reported null results. There was one systematic review of RCTs (Loefler et al) that assessed adverse events of thermal diathermy. This review found no significant adverse events of diathermy, although reporting of adverse events was limited to one study.

All but two of the eleven ultrasound RCTs (Kulcu et al, Cetin et al) were double-blinded. There were variations in ultrasound protocols (continuous vs pulsed, duration of application, intensity, application field). Study duration varied from 1 week to 8 weeks. Five studies reported WOMAC pain, of these two favored intervention (Ozgonenel et al, Kulsu et al), and three reported null results (Loyola-Sanchez et al, Cakir et al, Ulus et al). Ten studies reported pain by VAS, of these six favored intervention (Ozgonenel et al, Yildiiz et al, Jia et al, Tascioglu et al, Yang et al, Kulcu et al), and four reported null results (Cetin et al, Cakir et al, Ulus et al, Falconer et al). Four studies reported WOMAC function scores. Of these, two reported no significant difference between ultrasound and sham (Loyola-Sanchez et al, Ulus et al), and the other two (Ozgonenel et al, Kulcu et al) favored intervention. Of note, the study by Kulcu et al that favored intervention for all pain and function outcomes was non-blinded. Seven studies included reporting of adverse events (Ulus et al, Ozgonenel et al, Tascioglu et al, Falconer et al, Jia et al, Loyola-Sanchez et al, Yang et al). All but one study reported no adverse events. The study by Yang et al reported “mental stress, dizziness, or palpitations” in three patients, these resolved quickly after treatment was stopped.

Quality of evidence across all critical outcomes: Low

Table 1. Hot packs, Diathermy compared to UC for Knee OA

Certainty assessment							Summary of findings		
№ of participants		**Inconsistency**	**Indirectness**	**Imprecision**	**Publication bias**	**Overall certainty**	**Number of patients**		**Anticipated absolute effects**

Table 1. Hot packs, Diathermy compared to UC for Knee OA											
Certainty assessment							Summary of findings				
(studies) Follow-up	Risk of bias					of evidence	With UC	With hot packs, Diathermy	Relative effect (95% CI)	Risk with UC	Risk difference with hot packs, Diathermy
WOMAC pain (0-20, lower scores indicate improvement)											
422 (6 RCTs)	serious [a]	serious [b]	not serious	not serious	none	⨁⨁◯◯ LOW	209	213	-	-	MD **3.22 lower** (7.01 lower to 0.58 higher)
Pain by VAS (0-10, lower scores indicate improvement)											
159 (3 RCTs)	serious [a]	not serious	not serious	not serious	none	⨁⨁⨁◯ MODERATE	79	80	-	-	MD **0.63 lower** (1.18 lower to 0.08 lower) **Favors heat**
WOMAC Function (0-68, lower scores indicate improvement)											
422 (6 RCTs)	serious [a]	serious [c]	not serious	not serious	none	⨁⨁◯◯ LOW	209	213	-	-	MD **11.39 lower** (23.29 lower to 0.52 higher)

CI: Confidence interval; **MD:** Mean difference

Explanations

a. Patinets not blinded in most trials, outcome assessors blinded in some

b. two studies favoring intervention and four studies with null result

c. Two studies with markedly higher effect size favoring intervention

Table 2. Ultrasound compared to UC for Knee OA

Certainty assessment							Summary of findings				
№ of participants (studies) Follow-up	**Risk of bias**	**Inconsistency**	**Indirectness**	**Imprecision**	**Publication bias**	**Overall certainty of evidence**	**Number of patients**		**Relative effect (95% CI)**	**Anticipated absolute effects**	
							With UC	**With Ultrasound**		**Risk with UC**	**Risk difference with Ultrasound**
WOMAC pain (0-20, lower scores indicate improvement)											
171 (4 RCTs)	not serious	not serious	not serious	serious [a]	none	⨁⨁⨁◯ MODERATE	85	86	-	-	MD **2.2 lower** (3.28 lower to 1.12 lower) **Favors ultrasound**
Pain by VAS (0-10, lower scores indicate improvement)											

Table 2. Ultrasound compared to UC for Knee OA											
Certainty assessment							Summary of findings				
391 (7 RCTs)	not serious	not serious	not serious	not serious	none	⨁⨁⨁⨁ HIGH	193	198	-	-	MD **0.89 lower** (1.29 lower to 0.49 lower) **Favors ultrasound**
WOMAC function (0-68, lower scores indicate improvement)											
132 (3 RCTs)	not serious	not serious	not serious	serious [a]	none	⨁⨁⨁◯ MODERATE	66	66	-	-	MD **3.92 lower** (7.49 lower to 0.35 lower) **Favors ultrasound**

CI: Confidence interval; **MD:** Mean difference

Explanations

a. Wide confidence intervals

Table 3. RCT data not suitable for effect size calculation or combining with other data

Ref ID, Author, year	Study type	Duration	Population Description	Treatment given to relevant population	Results

2774 Lim, 2013	Non-blinded RCT	8 weeks	44 patients with chronic stroke + knee OA	Leg immersion into warm whirlpool for 30 min 5 times a week for 8 weeks vs usual activities; 30 min of physical therapy with every session in both groups	WOMAC pain: Intervention group: Pre-intervention 15 (SD 3.74); post-intervention 11.1 (4.64) Control group: Pre-intervention 13.37 (SD 2.12); post-intervention 9.75 (1.35)
2527 Falconer, 1992	Double blind RCT	4-6 weeks	74 Knee OA patients	Ultrasound 1MHz 12 treatments 2-3 times a week over 4-6 weeks vs identical sham protocol. Both groups received 30 min of stretching and strengthening exercises	Results for VAS reported in a graph and approximated from graph here: Pain by VAS in the US group (cm): Pre-intervention 4.4 (SE 0.5); post-intervention 2.8 (0.5) Control group: Pre-intervention 6.2 (SE 0.5); post-intervention 3.9 (0.5)
3495 Yang, 2011	RCT with sham, but blinding not described	5 days?	87 patients with knee OA (100 knees randomized)	ultrasound treatment 35 min vs sham, for 5 sessions (seems daily from the figures, but not clearly stated)	Pain reported as "VAS efficacy index", described as (VAS score pre-treatment – VAS after treatment)/VAS pre-treatment*100: Treatment group VAS efficacy index: mean = 0.3640, SD = 0.28062 Control group VAS efficacy index: mean = 0.1000, SD = 0.18729 P for between-group rank sum test <0.001
7271 Kulcu, 2009	non-blinded RCT	3 weeks	45 patients with knee OA, who did not respond to NSAIDs	Continuous ultrasound 10 min vs no treatment vs electromagnetic field therapy 35 min; 15 sessions in 3 weeks	Pain by VAS and WOMAC, median (range): VAS: US group (N = 15) pre-treatment 7 (5-10); post-treatment 2 (0-6). Control group (N = 15) pre-treatment 7 (4-9); post-treatment 5 (2-10). WOMAC Pain US group (N = 15) pre-treatment 9.5 (1-17); post-treatment 4.5 (0-11). Control group (N = 15) pre-treatment 7 (5-9); post-treatment 8 (5-9). WOMAC Function US group (N = 15) pre-treatment 31 (6-41); post-treatment 11.5 (0-26). Control group (N = 15) pre-treatment 25 (17-35); post-treatment 24 (18-30).

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PICO 31. Therapeutic cooling plus usual care compare to usual care for patients with hip or knee OA

Summary: There were 3 original RCTs evaluating the effectiveness of therapeutic cooling in the management of knee OA. All RCTs provided direct evidence for therapeutic cooling effects on knee OA pain and function.

All studies were single-blind RCTs, and used slightly different cold application protocols. Aciksoz et al[1] applied cold compresses for 20 min twice a day for 3 weeks, Elsaman et al[2] applied cold compresses for 10 min daily for 2 weeks, and Pietrosimone at al[3] studied a single 20 min ice bag application with same day outcome assessment. Control conditions also varied between studies: pill placebo (Elsaman et al[2]), and no intervention (Aciksoz et al[1], Pietrosimone et al[3]). Aciksoz et al[1] allowed standard OA care including NSAIDs in all groups.

All studies reported pain with movement by VAS. Combined analysis of the three studies found a significant improvement in this outcome favoring cooling. Only one study reported WOMAC pain and function (Aciksoz et al), and found no significant difference between control and intervention for both outcomes. None of the studies reported on adverse events related to cold application.

Quality of evidence across all critical outcomes: Low

Cold application compared to control for Knee OA

Certainty assessment							Summary of findings				
№ of participants (studies) Follow-up	**Risk of bias**	**Inconsistency**	**Indirectness**	**Imprecision**	**Publication bias**	**Overall certainty of evidence**	**Study event rates (%)**		**Relative effect (95% CI)**	**Anticipated absolute effects**	
							With control	**With Cold application**		**Risk with control**	**Risk difference with Cold application**
Pain with movement, VAS (0-10, lower scores indicate improvement)											
187 (3 RCTs)	serious [a]	not serious	not serious	not serious	none	⨁⨁⨁◯ MODERATE	94	93	-	-	MD **1.02 lower** (1.65 lower to 0.38 lower) **Favors cold application**
WOMAC Pain (0-10, lower scores indicate improvement)											
64 (1 RCT)	serious [a]	not serious	not serious	serious [b]	none	⨁⨁◯◯ LOW	32	32	-	-	MD **0.11 higher** (1 lower to 1.22 higher)
WOMAC Function (0-10, lower scores indicate improvement)											
64 (1 RCT)	serious [a]	not serious	not serious	serious [b]	none	⨁⨁◯◯ LOW	32	32	-	-	MD **0.06 higher** (0.89 lower to 1.01 higher)

CI: Confidence interval; **MD:** Mean difference

Explanations

a. Participants not blinded

b. Single small study

References:

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PICO 32: TENS plus usual care vs usual care in Knee OA.

Summary. The literature search identified 12 trials that addressed this comparison. Three studies[1-3] examined VAS pain at 4-8 week TENS therapy intervals. While heterogeneity was low overall, the results did not show significant benefit from TENS. Similarly, WOMAC pain and physical function did not show significant improvements with TENS in 2 studies [1, 4]. In 2 other studies[5, 6], TENS therapy was given and VAS pain was assessed immediately afterward without significant heterogeneity or benefit. Another study [7] compared the same group of patients using sequential phases in therapy, but there was no true control. In Law, et al[8], 3 different TENS groups were compared to placebo, but the goal of the study was to compare relative effectiveness of different TENS frequencies. A non-randomized continuous trial[9], the same pts were studied in 2 sequential phases with high dropout, not ITT, and the pain outcome was a non PICO scale. Five studies[8-12] were charted in a Word table, as the data was not suitable for RevMan.

Overall, no significant benefit was noted with TENS for VAS pain, WOMAC pain, or WOMAC function in patients with knee OA. The quality of the data was low, with small groups and variable control (sham TENS, exercise, varying TENS currents and different duration of sessions with TENS), making data difficult to compare across studies.

Quality of evidence across all critical outcomes: Low

Table 1. TENS+Usual Care compared to Usual Care for Hip and Knee OA

Certainty assessment							Summary of findings				
№ of participants (studies) Follow-up	**Risk of bias**	**Inconsistency**	**Indirectness**	**Imprecision**	**Publication bias**	**Overall certainty of evidence**	**Number of patients**		**Relative effect (95% CI)**	**Anticipated absolute effects**	
							With Usual Care	**With TENS+ Usual Care**		**Risk with Usual Care**	**Risk difference with TENS+Usual Care**
VAS pain at 4-8 weeks (0-100 scale) (lower scores indicate improvement)											
146 (3 studies)	serious [a]	not serious	not serious	not serious	none	⨁⨁⨁◯ MODERATE	73	73	-	-	MD **2.08 lower** (7.72 lower to 3.56 higher)
VAS pain at 6 months (0-100 scale) (lower scores indicate improvement)											
74 (1 study)	not serious	not serious	not serious	serious [b]	none	⨁⨁⨁◯ MODERATE	37	37	-	-	MD **1.5 lower** (11.48 lower to 8.48 higher)
WOMAC pain at 4 weeks (0-20, lower scores indicate improvement)											
98 (2 studies)	serious [a]	not serious	not serious	not serious	none	⨁⨁⨁◯ MODERATE	49	49	-	-	MD **0.94 lower** (2.08 lower to 0.19 higher)
WOMAC Function at 4 weeks (0-68, lower scores indicate improvement)											
98 (2 studies)	serious [a]	not serious	not serious	not serious	none	⨁⨁⨁◯ MODERATE	49	49	-	-	MD **1.35 lower** (4.28 lower to 1.59 higher)
VAS pain right after treatment (0-10 scale) (lower scores indicate improvement)											

Table 1. TENS+Usual Care compared to Usual Care for Hip and Knee OA											
Certainty assessment							Summary of findings				
72 (2 studies)	serious [a]	not serious	not serious	serious [b]	none	⨁⨁◯◯ LOW	37	35	-	-	MD **0.93 lower** (2.39 lower to 0.54 higher)
WOMAC pain at 6 months (0-20, lower scores indicate improvement)											
74 (1 study)	not serious	not serious	not serious	not serious	none	⨁⨁⨁⨁ HIGH	37	37	-	-	MD **0.7 lower** (2.2 lower to 0.8 higher)
WOMAC function at 6 months (0-68, lower scores indicate improvement)											
74 (1 study)	not serious	not serious	not serious	not serious	none	⨁⨁⨁⨁ HIGH	37	37	-	-	MD **0.4 lower** (5.31 lower to 4.51 higher)

CI: Confidence interval; **MD:** Mean difference

Explanations

a. Participants not blinded in some studies; unclear in some studies if outcome assessors were blinded

b. Wide confidence interval that crosses line of no effect

Table 2. RCT data not suitable for effect size calculation or combining with other data

Ref ID, Author, year	Study type	Duration	Population Description	Treatment given to relevant population	Results
8046 Cherian 2015	Prospective randomized single blind trial	3 months	25 pts with K+L grade 1 and 2	TENS vs usual care	VAS pain was primary outcome, reported means and ranges but no SD Change in VAS pain for TENS group (N=13) was -2.6 and for control group (N+=10) was -1.3 with p=0.18

Ref ID, Author, year	Study type	Duration	Population Description	Treatment given to relevant population	Results
5820 Law 2004	Double blind RCT	14 days	36 pts with grade II knee OA and pain	1)2 Hz TENS, 2)100 Hz TENS, 3)alternating 2 and 100 Hz, and 4)placebo TENS 5 days a week for 2 weeks	The 3 active TENS groups had significantly reduced knee pain by VAS across treatment sessions but no significant between group differences were found.
5819 Cheing 2003	RCT	14 days	38 patients aged 50-80 years with K+L grade 2 or higher radiographic knee OA and pain on VAS. Mean age 65.5, 34 female and 4 male	1) TENS 20 minutes, 2) TENS 40 min, 3)TENS 60 min, 4)placebo 5 days per week for 20 weeks	By day 10, a significantly greater cumulative reduction in VAS pain was found in the TENS 40 min (83.4%) and TENS 60 (68.37%) groups than the other 2 groups ($p<0.003$) and maintained at 2 week follow up. TENS group 40 min (256 min) and TENS group 60 min (258) min produced the more prolonged pain relief at day 10, but TENS 40 min group produced the longest pain relief period by the follow up session.
1861 Cherian 2016	Prospective randomized single blind trial	1 year	70 pts with K+L grade 2-4	TENS vs usual care (1 year follow up of Refid 8046, Cherian 2015)	VAS pain was primary outcome, reported means but no SD Change in VAS pain for TENS group (N=33) was -0.4 and for control group (N+=37) was +0.62 but no p value reported. Final pain VAS for TENS cohort was 4.55 and for control group was 5.1 with p=0.55
283 Lone 2002	Controlled single blind trial	3 phases of 2 weeks each with 1 week washout	60 patients with clinical and x-ray knee OA for >6 months age 40-70 yrs and 40-70 kg weight	Phase I placebo drug+placebo TENS Phase II Diclofenac 50 mg TID+placebo TENS Phase III placebo drug+active TENS	Pain assessed on 6 point descriptive scale 9Downie 1978) $P<0.5$ favoring diclofenac over placebo, analysis of phases 2 and 3, 2 and 1 and 3 and 1 revealed significant pain relief ($p<0.0001$) and improved walking ($p<0.0001$) after TENS in the group with mild to moderate pain, but not effective in patients with severe pain

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PICO 33: Pulsed vibration therapy (+ usual care) compared to usual care for knee OA

Summary: One RCT[1] compared muscle vibration therapy to sham vibration therapy for adults with knee OA. Rabini et al.[1] evaluated three applications per day (total 30 minutes per day) for 3 consecutive days applied bilaterally to the distal quadriceps muscle. The treatment group reported greater improvement in the WOMAC composite score from baseline to 24-week follow up. The pain and function subscales of the WOMAC were not reported independently.

Quality of evidence: Low

Focal muscle vibration compared to Sham for Knee OA											
Certainty assessment							**Summary of findings**				
№ of participants (studies) Follow-up	**Risk of bias**	**Inconsistency**	**Indirectness**	**Imprecision**	**Publication bias**	**Overall certainty of evidence**	**Number of subjects**		**Relative effect (95% CI)**	**Anticipated absolute effects**	
							With Sham	**With Focal muscle vibration**		**Risk with Sham**	**Risk difference with Focal muscle vibration**
Pain and Self-reported Function (0-96, WOMAC composite score) (lower scores indicate improvement)											
50 (1 RCT)	serious [a]	not serious	not serious	serious [b]	none	⨁⨁◯◯ LOW	25	25	-	-	MD **27.2 lower** (32.71 lower to 21.69 lower) **Favors pulsed vibration**

CI: Confidence interval; **MD:** Mean difference

Explanations

a. Physical therapists who delivered treatment not blinded; patients and outcome assessor were blind
b. Single small study with large effect

References

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PICO 34: Massage therapy+ usual care compared to usual care for knee OA

Summary. Six RCTs addressed this comparison. The studies differed in the methods of massage therapy, with 2 studies with aromatherapy oils, 1 study with Thai massage, another study with self-massage and 2 studies by the same authors looking at massage therapy with PT. Two studies used aromatherapy oils with their massage. In one study(1), massage with orange and ginger oil (active aromatherapy) was compared to olive oil (aromatherapy control) massage and to control of usual care, without significant difference from control for massage with either oil with Pain VAS. Another study(2) used aromatherapy with lavender oil, without significant benefit. Thai massage was studied (3) and compared to an herbal compress and usual care, but the 2 interventions groups were not allowed usual care, which differs from the PICO comparison. A study of self-massage (4) did not show benefit for WOMAC pain. The 2 studies by the same group (5, 6) did show benefit for WOMAC pain at 8 weeks, however the primary goal of Perlman 2012 (5) was to identify optimal dosage of massage. Overall, only the 2 studies performed by the same authors (5, 6) showed any benefit of massage. The addition of aromatherapy did not show improvement in pain by VAS and WOMAC in knee OA. There was variability in the massage techniques and regimen making generalization of findings difficult. A literature search update in August 2018 identified one additional relevant RCT (7), but it did not alter the findings observed in the tables below.

Quality of evidence across all critical outcomes: Low

Table 1. Massage compared to usual care for Knee OA

Certainty assessment							Summary of findings				
№ of participants (studies) Follow-up	**Risk of bias**	**Inconsistency**	**Indirectness**	**Imprecision**	**Publication bias**	**Overall certainty of evidence**	**Number of patients**		**Relative effect (95% CI)**	**Anticipated absolute effects**	
							With usual care	**With Massage**		**Risk with usual care**	**Risk difference with Massage**
VAS Pain during walking at 3 weeks (0-100, lower scores indicate improvement)											
40 (1 study)	serious [a]	not serious	not serious	serious [b]	none	⨁⨁◯◯ LOW	20	20	-	-	MD **2.15 lower** (12.41 lower to 8.11 higher)

Table 1. Massage compared to usual care for Knee OA

Certainty assessment							Summary of findings				
VAS pain 1 week post massage (0-10, lower scores indicate improvement)											
53 (1 study)	serious [a]	not serious	not serious	serious [b]	none	⨁⨁◯◯ LOW	26	27	-	-	MD **0.34 lower** (1.02 lower to 0.34 higher)
VAS pain 4 weeks post massage (0-10, lower scores indicate improvement)											
53 (1 study)	serious [a]	not serious	not serious	serious [b]	none	⨁⨁◯◯ LOW	26	27	-	-	MD **0.07 higher** (0.61 lower to 0.75 higher)
WOMAC pain 4 weeks post massage (0-20, lower scores indicate improvement)											
34 (1 study)	not serious	not serious	not serious	serious [b]	none	⨁⨁⨁◯ MODERATE	17	17	-	-	MD **0.94 lower** (2.82 lower to 0.94 higher)
WOMAC pain at 8 weeks (0-100, lower scores indicate improvement)											
117 (2 studies)	serious [c]	not serious	not serious	serious [d]	none	⨁⨁◯◯ LOW	58	59	-	-	MD **21.74 lower** (26.05 lower to 17.43 lower) **Favors massage**
WOMAC pain at 12 weeks (0-20, lower scores indicate improvement)											

Table 1. Massage compared to usual care for Knee OA											
Certainty assessment							**Summary of findings**				
36 (1 study)	serious [a]	not serious	not serious	serious [b]	none	⨁⨁◯◯ LOW	18	18	-	-	MD **0.61 lower** (1.85 lower to 0.62 higher)
Time to climbing ten steps (sec) at 3 weeks (lower scores indicate improvement)											
40 (1 study)	serious [a]	not serious	not serious	serious [b]	none	⨁⨁◯◯ LOW	20	20	-	-	MD **1 lower** (3.08 lower to 1.08 higher)

CI: Confidence interval; **MD:** Mean difference

Explanations

a. Patients not blinded in most trials; most have blinded outcome assessors

b. Wide CI that crosses line of no effect

c. Patients and personnel not blinded

d. Two small studies by same research group with large effect

Table 2. Massage with aromatherapy oils compared to usual care for Knee OA									
Certainty assessment							**Summary of findings**		
№ of participants		**Inconsistency**	**Indirectness**	**Imprecision**	**Publication bias**	**Overall certainty**	**Number of patients**	**Relative effect**	**Anticipated absolute effects**

Table 2. Massage with aromatherapy oils compared to usual care for Knee OA											
Certainty assessment							Summary of findings				
(studies) Follow-up	Risk of bias					of evidence	With usual care	With Massage with aromatherapy oils	(95% CI)	Risk with usual care	Risk difference with Massage with aromatherapy oils
VAS pain 1 week post massage (0-10, lower scores indicate improvement)											
53 (1 study)	serious [a]	not serious	not serious	not serious	none	⨁⨁⨁◯ MODERATE	26	27	-	-	MD **1.01 lower** (1.59 lower to 0.43 lower) **Favors massage**
VAS pain 4 weeks post massage (0-10, lower scores indicate improvement)											
53 (1 study)	serious [a]	not serious	not serious	not serious	none	⨁⨁⨁◯ MODERATE	26	27	-	-	MD **0.29 higher** (0.35 lower to 0.93 higher)
WOMAC pain 4 weeks post massage (0-20, lower scores indicate improvement)											
36 (1 study)	serious [a]	not serious	not serious	serious [b]	none	⨁⨁◯◯ LOW	17	19	-	-	MD **1.08 lower** (2.98 lower to 0.82 higher)

CI: Confidence interval; **MD:** Mean difference

Explanations

a. Patients not blinded to massage vs usual care; outcome assessor was blinded

b. Small study with CI that crosses line of no effect

References

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7. Tanaka R, Umehara T, Kawabata Y, Sakuda T. Effect of Continuous Compression Stimulation on Pressure-Pain Threshold and Muscle Spasms in Older Adults With Knee Osteoarthritis: A Randomized Trial. J Manipulative Physiol Ther. 2018 May;41(4):315-322.

PICO 35: Manual Therapy plus Exercise plus Usual Care compared to Usual Care for Knee and Hip OA

Summary. Five RCTs addressed this comparison. Two studies[1, 2] evaluated the utility of manual therapy plus exercise vs usual care in hip OA, while the other 3 studies examined the effect in knee OA.[3-5] A study of hip OA[1] differed from the other studies as the control group didn't get usual care alone, but received sham PT and inert gel ultrasound. In the other hip study[2], manual therapy was given weekly for 8 weeks. In a knee OA study[5], manual therapy was used for knee OA without an exercise component in a small group of patients, with a treatment given 3 times per week over 2 weeks. In another small study[4], 30 knee OA patients received either osteopathic manual therapy without exercise vs osteopathic usual care, and they received only one treatment, with primary outcome measures of Doppler flow. The intervention and outcomes generally did not fit the PICO outline. Deyle et al[3] used sub-therapeutic ultrasound and PT for the control group.

For hip OA, manual therapy did not appear to provide significant improvement in function, but in one study[2], may have helped with pain during activity, although the 2 studies were different as noted above. For knee OA, manual therapy provided a small improvement in pain, and in one study showed significant improvement in 6 minute walk distance compared to usual care.[3]
A literature search update in August 2018 identified two additional relevant RCTs.[6,7] They did not alter the findings observed in the tables below.

Quality of evidence across all critical outcomes: Low

Manual Therapy+Exercise+Usual Care compared to Usual Care for Hip or Knee OA											
Certainty assessment							**Summary of findings**				
№ of participants (studies) Follow-up	**Risk of bias**	**Inconsistency**	**Indirectness**	**Imprecision**	**Publication bias**	**Overall certainty of evidence**	**Study event rates (%)**		**Relative effect (95% CI)**	**Anticipated absolute effects**	
							With Usual Care	**With Manual Therapy+ Exercise+ Usual Care**		**Risk with Usual Care**	**Risk difference with Manual Therapy+ Exercise+ Usual Care**
Hip pain VAS at 13 weeks (0-100, lower scores indicate improvement)											
96 (1 study)	not serious	not serious	serious [a]	serious [e]	none	⨁⨁◯◯ LOW	50	46	-	-	MD **4.9 higher** (4.36 lower to 14.16 higher)
Hip pain VAS during activity at 9 wks (0-10, lower scores indicate improvement)											
86 (1 study)	not serious	not serious	not serious	not serious	none	⨁⨁⨁⨁ HIGH	43	43	-	-	MD **1.42 lower** (2.75 lower to 0.09 lower) **Favors manual therapy + exercise**
Knee pain VAS at 2 weeks (0-10, lower scores indicate improvement)											

Manual Therapy+Exercise+Usual Care compared to Usual Care for Hip or Knee OA											
Certainty assessment							**Summary of findings**				
43 (1 study)	serious [f]	not serious	serious [b]	not serious	none	⨁⨁◯◯ LOW	17	26	-	-	MD **1.2 lower** (2.34 lower to 0.06 lower) **Favors manual therapy + exercise**
Knee pain VAS right after manual therapy (lower scores indicate improvement)											
30 (1 study)	not serious	not serious	serious [c]	not serious	none	⨁⨁⨁◯ MODERATE	15	15	-	-	MD **0.1 lower** (1.21 lower to 1.01 higher)
WOMAC PF hip OA 9 wks (0-68, lower scores indicate improvement)											
86 (1 study)	not serious	not serious	not serious	not serious	none	⨁⨁⨁⨁ HIGH	43	43	-	-	MD **6.78 lower** (13.86 lower to 0.3 higher)
WOMAC PF hip OA at 13 wks (0-68, lower scores indicate improvement)											
96 (1 study)	not serious	not serious	serious [a]	not serious	none	⨁⨁⨁◯ MODERATE	50	46	-	-	MD **1.1 higher** (3.77 lower to 5.97 higher)
6 min walk test knee OA at 8 wks (higher scores indicate improvement)											
69 (1 study)	serious [g]	not serious	serious [d]	not serious	none	⨁⨁◯◯ LOW	36	33	-	-	MD **77.7 higher** (58 higher to 97.4 higher) **Favors manual therapy + exercise**

CI: Confidence interval; **MD:** Mean difference

Explanations

a.Control group had sham PT and ultrasound with inert gel which differs from other studies

b. Differs from PICO 35 as no exercise involved, only manual therapy

c. Patients received only one treatment, no exercise, and primary outcome measure was Doppler flow. The intervention and outcomes generally did not fit the PICO outline.

d. Control group received subtherapeutic ultrasound with PT, no pain assessment

e. Wide 95% CI that crosses line of no effect

f. Unclear if outcome assessors were blinded. Personnel delivering treatment could not be blinded.

g. >10% dropout, no ITT analysis

References

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5. Pollard H, Ward G, Hoskins W, Hardy K. The effect of a manual therapy knee protocol on osteoarthritic knee pain: a randomised controlled trial. J Can Chiropr Assoc. 2008;52:229-42.
6 Allen KD1, Arbeeva L2, Callahan LF3, Golightly YM4, Goode AP5, Heiderscheit BC6, et al. Physical therapy vs internet-based exercise training for patients with knee osteoarthritis: results of a randomized controlled trial. Osteoarthritis Cartilage. 2018 Mar;26(3):383-396.
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PICO 36. Weight Loss plus exercise compared to exercise alone for Knee OA

Summary. Three RCTs addressed this comparison in patients with knee OA. Two studies did not have PICO outcomes as primary outcomes, with compressive force the main outcomes in one study[(1)] and mobility related self-efficacy in the other[(2)]. The third study[(3)] was very small with only 24 participants with high attrition and outcomes measured using a 6 point Likert scales, including for pain, which was not a PICO measure scale. In the Focht study[(2)], applicable outcome measures were 6 minute walk distance and stair-climb time, while in the Messier 2013 study[(1)], the applicable outcomes measures were WOMAC pain and 6 minute walk distance at 18 months. For 6-minute walk distance and stair climb time, weight loss plus exercise intervention were superior to exercise alone. WOMAC Pain showed a significant small between-group difference at 18 months favored weight loss plus exercise over exercise; however, pain on a 6 point Likert scale at 24 weeks showed no significant between-group difference with serious imprecision due to small sample size. 6-minute walk distance and stair climb time generally favored exercise plus diet vs exercise alone, although the difference was not significant at all time points.

Quality of evidence across all critical outcomes: Moderate

Weight Loss plus exercise compared to exercise alone for Knee OA											
Certainty assessment							**Summary of findings**				
№ of participants (studies) Follow-up	**Risk of bias**	**Inconsistency**	**Indirectness**	**Imprecision**	**Publication bias**	**Overall certainty of evidence**	**Number of patients**		**Relative effect (95% CI)**	**Anticipated absolute effects**	
							With exercise alone	**With Weight Loss+exercise**		**Risk with exercise along**	**Risk difference with Weight Loss+exercise**
WOMAC Pain at 18 months (0-20, lower scores indicate improvement)											
302 (1 RCT)	serious [a]	not serious	not serious	not serious	none	⨁⨁⨁◯ MODERATE	150	152	-	-	MD **1.1 lower** (1.74 lower to 0.46 lower) **Favors weight loss**

Weight Loss plus exercise compared to exercise alone for Knee OA											
Certainty assessment							Summary of findings				
Pain (Likert) at 24 weeks (1-5, lower scores indicate improvement)											
24 (1 RCT)	serious [a]	not serious	not serious	serious [b]	none	⨁⨁◯◯ LOW	11	13	-	-	MD **0.64 higher** (0.43 lower to 1.71 higher)
6 minute walk distance at 24 weeks (higher scores indicate improvement)											
24 (1 RCT)	serious [a]	not serious	not serious	serious [b]	none	⨁⨁◯◯ LOW	11	13	-	-	MD **103 higher** (3.94 lower to 209.94 higher)
6 minute walk distance at 18 months (higher scores indicate improvement)											
458 (2 RCTs)	serious [a]	not serious	not serious	not serious	none	⨁⨁⨁◯ MODERATE	230	228	-	-	MD **20 higher** (6.12 higher to 33.89 higher) **Favors weight loss**
Stair-climb time at 24 weeks (lower scores indicate improvement)											
24 (1 RCT)	serious [a]	not serious	not serious	serious [c]	none	⨁⨁◯◯ LOW	11	13	-	-	MD **1.28 lower** (2.22 lower to 0.34 lower) **Favors weight loss**

Weight Loss plus exercise compared to exercise alone for Knee OA											
Certainty assessment							Summary of findings				
Stair-climb time at 18 months (lower scores indicate improvement)											
156 (1 RCT)	serious [a]	not serious	not serious	not serious	none	⨁⨁⨁◯ MODERATE	80	76	-	-	MD **0.3 lower** (1.88 lower to 1.28 higher)

CI: Confidence interval; **MD:** Mean difference

Explanations

a. Patients not blinded; blinding of outcome assessors not reported

b. Small sample size and wide CI that crosses line of no effect

c. Small sample size

References

1. Messier SP, Mihalko SL, Legault C, Miller GD, Nicklas BJ, DeVita P, et al. Effects of intensive diet and exercise on knee joint loads, inflammation, and clinical outcomes among overweight and obese adults with knee osteoarthritis: the IDEA randomized clinical trial. JAMA. 2013;310:1263-73.
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3. Messier SP, Loeser RF, Mitchell MN, Valle G, Morgan TP, Rejeski WJ, et al. Exercise and weight loss in obese older adults with knee osteoarthritis: a preliminary study. J Am Geriatr Soc. 2000;48:1062-72.

PICO 37. Self-efficacy plus exercise compared to exercise alone for patients with hip or knee OA

Summary. The literature searches did not identify any studies that addressed this comparison.

Quality of evidence across all critical outcomes: Very low

PICO 38: Manual Therapy plus Exercise compared to Exercise for Knee and Hip OA

Summary: The literature searches identified 5 RCTs that addressed this comparison. Three studies(1-3) compared exercise plus manual therapy vs exercise in adults with knee OA; however, the primary purpose of one of the studies(3) was to assess design integrity and sample size estimation for a confirmatory study. One study was a randomized trial for hip OA patients(4) however, in this study, the comparison groups were manual therapy alone vs exercise and the primary outcome was "general perceived improvement" on a 6 point Likert scale. Another study included patients with hip and/or knee OA(5). Outcome measures were diverse, with pain scores as outcomes in only 2 studies(1, 3), but in those 2 studies, there was decreased pain with the addition of manual therapy to exercise seen at 5 weeks(3) and at 1 year(1). The findings were imprecise for WOMAC scores due to wide CIs around the effect estimates. Most outcomes were evaluated in a single study with low sample size and wide confidence intervals. Although the overall trend appeared to favor the addition of manual therapy, most findings were inconclusive due to serious imprecision.

Quality of Evidence across all critical outcomes: Low

Manual Therapy plus Exercise compared to Exercise for Knee and Hip OA											
Certainty assessment							**Summary of findings**				
№ of participants (studies) Follow-up	**Risk of bias**	**Inconsistency**	**Indirectness**	**Imprecision**	**Publication bias**	**Overall certainty of evidence**	**Study event rates (%)**		**Relative effect (95% CI)**	**Anticipated absolute effects**	
							With Exercise	**With Manual Therapy+ Exercise**		**Risk with Exercise**	**Risk difference with Manual Therapy+Exercise**
WOMAC Pain score at 5 weeks (0-500, lower scores indicate improvement)											
56 (1 RCT)	serious [a]	not serious	not serious	serious [b]	none	⨁⨁◯◯ LOW	28	28	-	-	MD **31.5 lower** (72.4 lower to 9.4 higher)

Manual Therapy plus Exercise compared to Exercise for Knee and Hip OA											
Certainty assessment							**Summary of findings**				
WOMAC Physical Function at 5 weeks (0-1700, lower scores indicate improvement)											
56 (1 RCT)	serious [a]	not serious	not serious	not serious	none	⨁⨁⨁◯ MODERATE	28	28	-	-	MD **32.8 lower** (191.4 lower to 125.8 higher)
WOMAC Total score at 4-5 weeks (0-2400, lower scores indicate improvement)											
176 (2 RCTs)	serious [a]	not serious	not serious	serious [b]	none	⨁⨁◯◯ LOW	88	88	-	-	MD **173.95 lower** (368.26 lower to 20.36 higher)
WOMAC Total score difference at 1 year (0-2400, lower scores indicate improvement)											
139 (2 RCTs)	serious [a]	serious [c]	not serious	not serious	none	⨁⨁◯◯ LOW	70	69	-	-	MD **18.98 lower** (59.25 lower to 21.29 higher)
6 minute walk at 4 weeks (higher scores indicate improvement)											
120 (1 RCT)	serious [a]	not serious	not serious	serious [b]	none	⨁⨁◯◯ LOW	60	60	-	-	MD **28.7 higher** (12.54 lower to 69.94 higher)

CI: Confidence interval; **MD:** Mean difference

Explanations

a. Patients not blinded; outcome assessors blinded

b. Wide 95% CI that overlaps line of no effect

c. High inconsistency with I^2=92%

d. Small sample size

References

1. Abbott JH, Chapple CM, Fitzgerald GK, Fritz JM, Childs JD, Harcombe H, et al. The Incremental Effects of Manual Therapy or Booster Sessions in Addition to Exercise Therapy for Knee Osteoarthritis: A Randomized Clinical Trial. J Orthop Sports Phys Ther. 2015;45:975-83.
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PICO 39: Intra-articular corticosteroids compared to oral NSAIDS for knee or hip OA

Summary: One study[(1)] compared intra-articular corticosteroids with oral NSAIDS The comparison included 2 different NSAIDs and 2 different corticosteroids, but one of the NSAIDS (aceclofenac) and one of the IA drugs (Cortivazol) are not available in US and were not on the list of drugs to be evaluated. Data charted represents data comparing Diclofenac 150 mg BID to betamethasone 2 mg intra-articularly x 3. This was a low quality study as the patients were randomized alternately with poor allocation concealment and assessors did not appear to be blinded. While 83 patients were treated, 13 were excluded, and the reported data was only on 70 patients, and not an ITT analysis. Both groups had decrease in pain levels and there was no significant difference between groups. The finding was imprecise as the confidence interval was wide.

Quality of evidence across critical outcome: Low

IA steroid compared to NSAIDs for Knee OA									
Certainty assessment							Summary of findings		
№ of participants		Inconsistency	Indirectness	Imprecision	Publication bias	Overall certainty	Number of patients	Relative effect	Anticipated absolute effects

IA steroid compared to NSAIDs for Knee OA											
Certainty assessment							Summary of findings				
(studies) Follow-up	Risk of bias					of evidence	With NSAIDs	With IA steroid	(95% CI)	Risk with NSAIDs	Risk difference with IA steroid
VAS pain walking (0-100, lower scores indicate improvement)											
70 (1 RCT)	serious [a]	not serious	not serious	serious [b]	none	⨁⨁◯◯ LOW	35	35	-	-	MD **2.38 lower** (14.97 lower to 10.21 higher)

CI: Confidence interval; **MD:** Mean difference

Explanations

a. Poor allocation concealment and patients not blinded to therapy. Patients randomized alternately and not by a specific method. No ITT analysis.

b. Wide 95% CI that crosses the line of no effect

References

1. Dieu-Donne O, Theodore O, Joelle ZT, Pierre D, Smaila O, Christian C, et al. An Open Randomized Trial Comparing the Effects of Oral NSAIDs Versus Steroid Intra-Articular Infiltration in Congestive Osteoarthritis of the Knee. Open Rheumatol J. 2016;10:8-12.

PICO 40. Long-acting intra-articular corticosteroids compared to oral NSAIDs for patients with knee or hip OA

Summary. The literature searches did not identify any studies that addressed this comparison.

Quality of evidence across all critical outcomes: Very low

PICO 41: Intra-articular hyaluronic acid compared to oral NSAIDs for knee or hip OA

Summary (hip): The literature search identified three RCTs [1-3] that indirectly addressed this PICO question for patients with hip OA (Table 1). The RCTs provided indirect evidence by comparing a single intra-articular hyaluronic acid injection to an intra-articular saline control. Participants who received an intra-articular hyaluronic acid injection versus saline had slightly lower mean differences in WOMAC pain and function scores, but the difference was not statistically significant. Studies by Atachia et al.[3] and Qvistgaard et al.[2], not included in RevMan (Table 3), corroborated these results. There was a trend for increased adverse events for those receiving hyaluronic acid, but this finding was inconclusive due to too few events.

Summary (knee): The literature search identified 35 randomized control trials[1,4-31,33-38] and two systematic reviews[32,39] that addressed this PICO question. The RCTs compared intra-articular hyaluronic acid injections to an intra-articular saline control with oral NSAID use permitted. However, a published SR[39] found that studies that were double-blind with sham (saline) controls reported much smaller effects of HA on pain and function compared to sham treatment. The SR also identified unpublished data from 5 RCTs that found no between-group difference in pain and function for HA versus sham treatment. Since there was evidence of bias in small and unblinded RCTs, we only analyzed data from double-blind, sham-controlled RCTs with at least 30 patients/arm and 4 or more weeks of follow-up (Table 2). The results from 15 RCTs[4,5,11,13,17-21,23,25,36-38] that met these criteria suggest that HA injection led to a very small, not clinically significant improvement in pain and function compared to sham treatment.

Quality of evidence across all critical outcomes: Low

Table 1. Intra-Articular Hyaluronic Acid compared to Saline [Hip]

Certainty assessment							Summary of findings				
№ of participants (studies) Follow-up	Risk of bias	Inconsistency	Indirectness	Imprecision	Publication bias	Overall certainty of evidence	Number of patients		Relative effect (95% CI)	Anticipated absolute effects	
							With saline	With IA Hyaluronic Acid		Risk with saline	Risk difference with IA Hyaluronic Acid

Table 1. Intra-Articular Hyaluronic Acid compared to Saline [Hip]											
Certainty assessment							Summary of findings				
WOMAC pain (hip)- single injection (0-100, lower scores indicate improvement)											
85 (1 RCT)	not serious	not serious	not serious	serious[a]	Publication bias suspected	⨁⨁◯◯ LOW	43	42	-	-	MD **1.1 lower** (11.08 lower to 8.88 higher)
WOMAC function (hip)- single injection (0-100, lower scores indicate improvement)											
85 (1 RCT)	not serious	not serious	not serious	serious[a]	Publication bias suspected	⨁⨁◯◯ LOW	43	42	-	-	MD **1 higher** (8.08 lower to 10.08 higher)

Explanations

a. Single small study

Table 2. Intra-Articular Hyaluronic Acid compared to Sham Control [Knee]									
Certainty assessment							Summary of findings		
№ of participants		**Inconsistency**	**Indirectness**	**Imprecision**	**Publication bias**	**Overall certainty**	**Number of patients**		**Anticipated absolute effects**

Table 2. Intra-Articular Hyaluronic Acid compared to Sham Control [Knee]

Certainty assessment							Summary of findings				
(studies) Follow-up	**Risk of bias**					**of evidence**	**With sham control**	**With IA Hyaluronic acid**	**Relative effect (95% CI)**	**Risk with sham control**	**Risk difference with IA Hyaluronic acid**
Pain (WOMAC or VAS combined)											
3387 (15 RCTs)	serious [a]	not serious	not serious	not serious	publication bias strongly suspected	⨁⨁◯◯ LOW	1620	1767	-	-	SMD **0.13 lower** (0.21 lower to 0.06 lower) **Favors HA, not clinically significant**
Function (WOMAC)											
1827 (7 RCTs)	serious [a]	not serious	not serious	not serious	publication bias strongly suspected	⨁⨁◯◯ LOW	866	961	-	-	SMD **0.16 lower** (0.26 lower to 0.05 lower) **Favors HA, not clinically significant**

CI: Confidence interval; **SMD:** Standardized mean difference

Explanations

a. Several studies lacked information on randomization method and allocation concealment, some studies did not blind treating physicians.

Table 3. RCT data not suitable for effect size calculation or combining with other data

Ref ID, Author, year	Study type	Duration	Population Description	Treatment given to relevant population	Results
KNEE					
5498, Strand, 2012	RCT	13 weeks	Pts with knee OA (KL grade 1-3). HA group (n=247, 40.5% males), 60.9 yrs +/- 10.24; control group (n=128, 39.8% males) 60.3 yrs +/- 9.97.	A single IA injection of Gel-200 (30 mg cross-linked HA in 3.0 mL) or PBS (3.0 mL) at week 0	Mean changes from baseline in WOMAC pain subscores demonstrated a statistically significant advantage of 6.39 mm for Gel-200 treatment over PBS at week 13 (P = 0.037; Fig. 2 and Table IIa). Group data provided on graph (SD not provided at group level). WOMAC physical function subscores showed a difference of 5.42 (0.47, 11.31) at week 13.
HIP					
3320, Atchia, 2010	RCT	16 weeks	Patients with primary hip osteoarthritis. HA group (n=18, 7 males) 69 yrs ± 9; placebo (saline) (n=18, 7 males) 70 yrs ± 10	standard care (non-injection group); normal saline (3 ml); non-animal stabilised hyaluronic acid (durolane, 3 ml/60 mg licensed for single injection) or methylprednisolone acetate (depomedrone, 3 ml/120 mg).	<u>Estimated from graph:</u> WOMAC function at 56 days Control (saline)= 7 Steroid= 5 HA=6 No-injection= 6.5 (p=0.04) WOMAC pain at 56 days Control (saline)= 6.5 Steroid=5 HA=5.5 No-injection= 6.0 P=0.06 The effect size (calculated as the mean change from baseline divided by the baseline SD) of the benefit from corticosteroid was large, becoming moderate by week 8: 1.5, 1.0 and 0.5 for NRS pain; 1.9, 1.1 and 0.6 for WOMAC pain; and 1.3, 0.9 and 0.4 for WOMAC function, at weeks 1, 4 and 8, respectively. There was a non-significant trend for improvement with

					saline injection at week 1 (effect size of 0.44 and 0.41 for NRS pain and WOMAC pain, respectively), which was not apparent at later assessments. Adverse: There was one confirmed case of post-arthroplasty infection (durolane group). Four patients in the durolane group had significant flare of symptoms within a few days of the injection. In one case septic arthritis had to be excluded and a diagnostic aspiration was performed at week 1, which excluded infection. The symptoms settled within a few days of the aspiration
4774, Qvistgaard, 2006	RCT	90 days	Hip OA as defined by the ACR criteria29, radiographic changes of hip OA30, age above 18 years, stable medication for at least 3 weeks before inclusion. HA group (n=33, 61% females) 65 yrs (14), Control (n=36, 61% females) 64 yrs (11).	Patients were randomized to (1) one injection with 1 mL (40 mg Depo-medrol) methylprednisolone corticosteroid followed by two sham injections, (2) three injections of 2 mL HA (Hyalgan), or (3) three intra-articular injections of 2 mL saline water. Secondary outcome measures were WOMAC total scale and PGA VAS.	Estimated from graph: Pain on walking (VAS) at 90 days HA group: 37 mm Saline (control): 41 mm “there was a significant treatment effect across all time-points (P Z 0.044), due to a significant improvement following corticosteroid compared to saline, SMD Steroid Z 0.6 (95% CI: 0.1e1.1, P Z 0.021) whereas HA compared to saline was SMDHA Z 0.4 (0.1 to 0.9; P Z 0.13). The difference between placebo (saline) and corticosteroid was significant at 14 and 28 days but vanished after 3 months (P14 days Z 0.006; P28 days Z 0.006; P3 months Z 0.58).”

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PICO 42: Intra-articular platelet rich plasma compared to oral NSAIDs for knee or hip OA

Summary: The literature search identified two RCTs[1,2] and three systematic reviews (two with meta-analyses)[3-5] that indirectly addressed this PICO question. The RCTs provided indirect evidence by comparing intra-articular platelet rich plasma to an intra-articular injection of phosphate buffered saline[1] or acetaminophen[2]. The systematic review[3] compared intra-articular PRP to intra-articular hyaluronic acid and the two systematic review and meta-analyses[4,5] compared to placebo injections (saline, local anesthetic). The two RCTs[1,2] reported lower WOMAC function and pain scores at 6 weeks, 3 months, 6 months, and 12 months (Table 1). The systematic review and meta-analyses[3-5] found improvements in pain and WOMAC scores across all time-points up to 12 months. One systematic review[5] reported an increased odds of adverse events for intra-articular PRP injections versus hyaluronic acid injections (Table 2). However, the lack of a standardized preparation and injection protocol makes it difficult to implement PRP in general practice and raises safety concerns that outweigh the small benefits identified in the literature.

Quality of evidence across all critical outcomes: Low

Table 1. Intra-articular platelet rich plasma compared to saline or acetaminophen for Osteoarthritis

Certainty assessment							Summary of findings				
№ of participants (studies) Follow-up	**Risk of bias**	**Inconsistency**	**Indirectness**	**Imprecision**	**Publication bias**	**Overall certainty of evidence**	**Number of patients**		**Relative effect (95% CI)**	**Anticipated absolute effects**	
							With control	**With intra-articular platelet rich plasma**		**Risk with control**	**Risk difference with intra-articular platelet rich plasma**
WOMAC function - 6 weeks (0-68, lower scores indicate improvement)											
65 (1 RCT) 5071	serious [a]	not serious	serious [c]	serious [d]	none	⨁◯◯◯ VERY LOW	32	33	-	-	MD **9.5 lower** (14.47 lower to 4.53 lower) **Favors plasma**
WOMAC function - 3 months (0-68, lower scores indicate improvement)											
95 (2 RCTs) 4649, 5071	serious [a]	not serious [b]	serious [c]	not serious	none	⨁⨁◯◯ LOW	47	48	-	-	MD **14.79 lower** (24.58 lower to 5 lower) **Favors plasma**
WOMAC function - 6 months (0-68, lower scores indicate improvement)											

Table 1. Intra-articular platelet rich plasma compared to saline or acetaminophen for Osteoarthritis

Certainty assessment							Summary of findings				
95 (2 RCTs) 4649, 5071	serious [a]	not serious [b]	serious [c]	not serious	none	⨁⨁◯◯ LOW	47	48	-	-	MD **15.61 lower** (29.51 lower to 1.7 lower) **Favors plasma**
WOMAC function - 12 months (0-68, lower scores indicate improvement)											
30 (1 RCT) 4649	not serious	not serious	serious [c,e]	serious [d]	none	⨁⨁◯◯ LOW	15	15	-	-	MD **23 lower** (30.37 lower to 15.63 lower) **Favors plasma**
WOMAC pain - 6 weeks (0-20, lower scores indicate improvement)											
65 (1 RCT) 5071	serious [a]	not serious	serious [c]	serious [d]	none	⨁◯◯◯ VERY LOW	32	33	-	-	MD **2.7 lower** (4.04 lower to 1.36 lower) **Favors plasma**
WOMAC pain - 3 months (0-20, lower scores indicate improvement)											

Table 1. Intra-articular platelet rich plasma compared to saline or acetaminophen for Osteoarthritis											
Certainty assessment							Summary of findings				
95 (2 RCTs) 4649, 5071	serious [a]	not serious [b]	serious [c]	not serious	none	⨁⨁◯◯ LOW	47	48	-	-	MD **4.43 lower** (7.36 lower to 1.49 lower) **Favors plasma**
WOMAC pain - 6 months (0-20, lower scores indicate improvement)											
30 (1 RCT) 4649	not serious	not serious	serious [c]	serious [d]	none	⨁⨁◯◯ LOW	15	15	-	-	MD **6 lower** (8.04 lower to 3.96 lower) **Favors plasma**
WOMAC pain - 12 months (0-20, lower scores indicate improvement)											
30 (1 RCT) 4649	not serious	not serious	serious [c]	serious [d]	none	⨁⨁◯◯ LOW	15	15	-	-	MD **7 lower** (9.58 lower to 4.42 lower) **Favors plasma**

CI: Confidence interval; **MD:** Mean difference

Explanations

a. 5071_Mendia: Not blinded

b. Although statistical heterogeneity was moderate to high, the direction of effect is consistent and the difference in effect sizes are unlikely to change clinical decisions.

c. Both studies compared to acetaminophen and not NSAIDs

d. Single small study

Table 2. Systematic review data

Ref ID, Author, year	Study type	Duration	Population Description	Treatment given to relevant population	Results
2999, Tietze, 2014	Systematic review	Up to 12 months	13 articles met the inclusion criteria: 12 focused on knee OA, and 1 on hip OA.	intraarticular PRP injections for the treatment of large-joint OA	All studies showed statistically significant improvement in patient outcome scores with PRP. Platelet-rich plasma has a statistically significant benefit in knee OA when compared with hyaluronic acid. The benefit from PRP appears to last between 6 and 12 months. Pain was primary focus measured by (VAS, KOOS, WOMAC, Lesquene).
1120, Chang, 2014	Systematic review with meta-analysis	Up to 12 months	Eight single-arm studies, 3 quasi-experimental studies, and 5 randomized controlled trials were identified, comprising 1543 participants.	PRP to treat knee chondral degenerative lesions	Compared with the preinjection condition, the authors found a pooled effect size of 2.31 (95% CI, 1.53e3.09) at 2 months, 2.52 (95% CI, 1.94e3.09) at 6 months, and 2.88 (95% CI, .97e4.79) at 12 months, which all favored the status after PRP treatment. **NOTE- I^2 statistic was 97.3%, 96.3%, and 98.6% Function (effect) was measured by IKDC, KOOS, and WOMAC.
2375, Riboh, 2015	Systematic review with meta-analysis	?unclear	6 randomized controlled trials (evidence level 1) and 3 prospective comparative studies (evidence level 2) with a total of 1055 patients	Review focused on leukocyte rich vs leukocyte poor PRP injections compared to placebo injections, including normal saline and/or local anesthetic	Injection of LP-PRP resulted in significantly better WOMAC scores than did injection of hyaluronic acid (mean difference, –21.14; 95% CI, –39.63 to –2.65) or placebo (mean difference, –17.84; 95% CI, –34.95 to –0.73). No such difference was observed with LR-PRP (mean difference, –14.28; 95% CI, –44.80 to 16.25). PRP injections resulted in a higher incidence of adverse reactions than hyaluronic acid (odds ratio, 5.63; 95% CI, 1.38-22.90), but there was no difference between LR-PRP and LP-PRP (odds ratio, 0.78; 95% CI, 0.05-11.93) [17/1055 total patients].

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PICO 43: Intra-articular stem cells compared to oral NSAIDs for knee or hip OA

Summary: The literature search identified one RCT[1] that addressed this PICO question. The RCT provided indirect evidence by comparing intra-articular stem cell injection to placebo injection (plasmalyte); NSAID use was permitted but not part of the allocated intervention. None of the between-group differences in VAS pain scores were statistically significant. Lower concentrations of stem cells (25 million cells) tended to have larger mean differences in pain VAS scores, especially at 12 months, compared to placebo. However, this RCT[1] was a small RCT with 15 participants (10 active, 5 placebo) per stem cell concentration, so all of the findings are imprecise; further large scales studies are warranted. There was not an increased risk of adverse events for participants receiving intra-articular stem cells compared to placebo, but there were too few events to identify differences in adverse event rates (Table 1).
A literature search update in August 2018 identified an additional relevant double-blind RCT[2] that compared intra-articular TissueGene chondrocytes (TG-C) to placebo saline injection in patients with knee OA. Although the TG-C group showed significantly greater improvement in VAS pain (26 and 39 weeks), KOOS pain (26, 39, and 52 weeks), and KOOS ADL (only at 26 weeks), serious adverse events were significantly more frequent in the TG-C group (11 vs. 0) (Table 2).

Quality of evidence across all critical outcomes: Low

Table 1. Stem cells compared to control injection for Osteoarthritis

Certainty assessment							Summary of findings		
№ of participants		**Inconsistency**	**Indirectness**	**Imprecision**	**Publication bias**	**Overall certainty**	**Number of patients**		**Anticipated absolute effects**

Table 1. Stem cells compared to control injection for Osteoarthritis											
Certainty assessment							Summary of findings				
(studies) Follow-up	Risk of bias					of evidence	With control	With stem cells	Relative effect (95% CI)	Risk with control	Risk difference with stem cells
Pain VAS-25 million cells - 1 month (0-100, lower scores indicate improvement)											
15 (1 RCT)	not serious	not serious	serious [a]	serious [b]	none	⨁⨁◯◯ LOW	10	10	-	-	MD **9.3 lower** (35.63 lower to 17.03 higher)
Pain VAS-25 million cells - 3 month (0-100, lower scores indicate improvement)											
20 (1 RCT)	not serious	not serious	serious [a]	serious [b]	none	⨁⨁◯◯ LOW	10	10	-	-	MD **13.1 lower** (36.87 lower to 10.67 higher)
Pain VAS-25 million cells - 6 month (0-100, lower scores indicate improvement)											
20 (1 RCT)	not serious	not serious	serious [a]	serious [b]	none	⨁⨁◯◯ LOW	10	10	-	-	MD **20.9 lower** (42.08 lower to 0.28 higher)
Pain VAS-25 million cells - 12 month (0-100, lower scores indicate improvement)											

Table 1. Stem cells compared to control injection for Osteoarthritis											
Certainty assessment							**Summary of findings**				
20 (1 RCT)	not serious	not serious	serious [a]	serious [b]	none	⨁⨁◯◯ LOW	10	10	-	-	MD **19 lower** (39.56 lower to 1.56 higher)
Pain VAS-50 million cells - 1 month (0-100, lower scores indicate improvement)											
20 (1 RCT)	not serious	not serious	serious [a]	serious [b]	none	⨁⨁◯◯ LOW	10	10	-	-	MD **9.6 lower** (37.5 lower to 18.3 higher)
Pain VAS-50 million cells - 3 month (0-100, lower scores indicate improvement)											
20 (1 RCT)	not serious	not serious	serious [a]	serious [b]	none	⨁⨁◯◯ LOW	10	10	-	-	MD **7.1 higher** (19.14 lower to 33.34 higher)
Pain VAS-50 million cells - 6 month (0-100, lower scores indicate improvement)											
20 (1 RCT)	not serious	not serious	serious [a]	serious [b]	none	⨁⨁◯◯ LOW	10	10	-	-	MD **0.3 higher** (29.22 lower to 29.82 higher)
Pain VAS-50 million cells - 12 month (0-100, lower scores indicate improvement)											

Table 1. Stem cells compared to control injection for Osteoarthritis											
Certainty assessment							**Summary of findings**				
20 (1 RCT)	not serious	not serious	serious [a]	serious [b]	none	⨁⨁◯◯ LOW	10	10	-	-	MD **3.7 higher** (28.19 lower to 35.59 higher)
Pain VAS-75 million cells - 1 month (0-100, lower scores indicate improvement)											
20 (1 RCT)	not serious	not serious	serious [a]	serious [b]	none	⨁⨁◯◯ LOW	10	10	-	-	MD **14.1 higher** (9.33 lower to 37.53 higher)
Pain VAS-75 million cells - 3 month (0-100, lower scores indicate improvement)											
20 (1 RCT)	not serious	not serious	serious [a]	serious [b]	none	⨁⨁◯◯ LOW	10	10	-	-	MD **3.4 higher** (28.79 lower to 35.59 higher)
Pain VAS-75 million cells - 6 month 0-100, (lower scores indicate improvement)											
20 (1 RCT)	not serious	not serious	serious [a]	serious [b]	none	⨁⨁◯◯ LOW	10	10	-	-	MD **6.3 lower** (34.75 lower to 22.15 higher)

Table 1. Stem cells compared to control injection for Osteoarthritis											
Certainty assessment							**Summary of findings**				
Pain VAS-75 million cells - 12 month (0-100, lower scores indicate improvement)											
20 (1 RCT)	not serious	not serious	serious [a]	serious [b]	none	⨁⨁◯◯ LOW	10	10	-	-	MD **2.2 lower** (32.13 lower to 27.73 higher)
Pain VAS-150 million cells - 1 month (0-100, lower scores indicate improvement)											
20 (1 RCT)	not serious	not serious	serious [a]	serious [b]	none	⨁⨁◯◯ LOW	10	10	-	-	MD **7.2 lower** (32.87 lower to 18.47 higher)
Pain VAS-150 million cells - 3 month (0-100, lower scores indicate improvement)											
20 (1 RCT)	not serious	not serious	serious [a]	serious [b]	none	⨁⨁◯◯ LOW	10	10	-	-	MD **15.2 lower** (44.49 lower to 14.09 higher)
Pain VAS-150 million cells - 6 month (0-100, lower scores indicate improvement)											

Table 1. Stem cells compared to control injection for Osteoarthritis											
Certainty assessment							**Summary of findings**				
20 (1 RCT)	not serious	not serious	serious [a]	serious [b]	none	⨁⨁◯◯ LOW	10	10	-	-	MD **0.2 higher** (31.82 lower to 32.22 higher)
Pain VAS-150 million cells - 12 month (0-100, lower scores indicate improvement)											
20 (1 RCT)	not serious	not serious	serious [a]	serious [b]	none	⨁⨁◯◯ LOW	10	10	-	-	MD **6.1 higher** (24.73 lower to 36.93 higher)
Severe Adverse Events - 25 million cells											
20 (1 RCT)	not serious	not serious	serious [a]	serious [b]	none	⨁⨁◯◯ LOW	1/10 (10.0%)	1/10 (10.0%)	**OR 1.00** (0.05 to 18.57)	100 per 1,000	**0 fewer per 1,000** (94 fewer to 574 more)
Severe Adverse Events - 50 million cells											
20 (1 RCT)	not serious	not serious	serious [a]	serious [b]	none	⨁⨁◯◯ LOW	1/10 (10.0%)	1/10 (10.0%)	**OR 1.00** (0.05 to 18.57)	100 per 1,000	**0 fewer per 1,000** (94 fewer to 574 more)
Severe Adverse Events - 75 million cells											

Table 1. Stem cells compared to control injection for Osteoarthritis											
Certainty assessment							Summary of findings				
20 (1 RCT)	not serious	not serious	serious [a]	serious [b]	none	⨁⨁◯◯ LOW	1/10 (10.0%)	1/10 (10.0%)	**OR 1.00** (0.05 to 18.57)	100 per 1,000	**0 fewer per 1,000** (94 fewer to 574 more)
Severe Adverse Events - 150 million cells											
20 (1 RCT)	not serious	not serious	serious [a]	serious [b]	none	⨁⨁◯◯ LOW	1/10 (10.0%)	1/10 (10.0%)	**OR 1.00** (0.05 to 18.57)	100 per 1,000	**0 fewer per 1,000** (94 fewer to 574 more)

CI: Confidence interval; **MD:** Mean difference; **OR:** Odds ratio

Explanations

a. Stem Cells vs. Placebo injection; NSAID use permitted but not directly compared

b. Wide 95% CI that overlaps with the line of no effect

c. Differential findings: stem cells favored at 1 month; control favored at 3 months and 12 months; no difference at 6 months

d. Differential findings: control favored at 1 month, 3 months; stem cells favored at 6 months and 12 months

e. Differential findings: stem cells favored at 1 month, 3 months; control favored at 6 months and 12 months

Table 2. Additional RCT data not suitable for combined analysis with other studies

Ref ID, Author, year	Study type	Duration	Population Description	Treatment given to relevant population	Results
8661 Kim et al. 2018	RCT	12 months	163 patients with knee OA (Kellgren-	Intra-articular TissueGene-C (TG-C) chondrocytes or placebo saline injection	**VAS pain** at 26 and 39 weeks favored TG-C (p=0.02 and 0.004, respectively). **KOOS pain** at 26, 39, and 52 weels favored TG-C (p=0.002, 0.003, and 0.001, respectively).

			Lawrence grade 3)		**KOOS ADL** significantly favored TG-C only at 26 weeks (p = 0.02). **Serious adverse events**: TG-C: 11 vs saline: 0 (p = 0.0003 favoring saline placebo).

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PICO 44: Intra-articular dextrose prolotherapy compared to oral NSAIDs for knee or hip OA

Summary: The literature search identified two RCTs[1,2] that addressed this PICO question. The RCTs provided indirect evidence by comparing dextrose prolotherapy to saline injection for osteoarthritis; one study discouraged NSAID use during the study period and the other[2] did not comment on NSAID use. Rabago et al.[1] found that dextrose prolotherapy had a lower mean difference in WOMAC pain and function compared to saline placebo. In patients with and without anterior cruciate ligament laxity (ACL)[2], dextrose prolotherapy was associated with better outcomes (pain at rest, pain with walking, pain with stair use, swelling, buckling episodes, and flexion range; p=0.015).

Quality of evidence across all critical outcomes: Low

Table 1. Dextrose prolotherapy compared to saline injection for knee OA

Certainty assessment							Summary of findings		
№ of participants		**Inconsistency**	**Indirectness**	**Imprecision**	**Publication bias**	**Overall certainty**	**Number of patients**	**Relative effect**	**Anticipated absolute effects**

Table 1. Dextrose prolotherapy compared to saline injection for knee OA											
Certainty assessment							**Summary of findings**				
(studies) Follow-up	**Risk of bias**					**of evidence**	**With saline injection control**	**With dextrose prolotherapy**	**(95% CI)**	**Risk with saline injection control**	**Risk difference with dextrose prolotherapy**
WOMAC pain (0-100, lower scores indicate improvement)											
51 (1 RCT)	not serious	not serious	serious[a]	serious[b]	none	⨁⨁◯◯ LOW	24	27	-	-	MD **5.99 lower** (8 lower to 3.98 lower) **Favors prolotherapy**
WOMAC function (0-100, lower scores indicate improvement)											
51 (1 RCT)	not serious	not serious	serious[a]	serious[b]	none	⨁⨁◯◯ LOW	24	27	-	-	MD **7.97 lower** (9.85 lower to 6.09 lower) **Favors prolotherapy**

CI: Confidence interval; **MD:** Mean difference

Explanations

[a]Indirect comparison – PRP vs saline
[b]Single study with small number of patients

Table 2. Additional RCT data

Ref ID, Author, year	Study type	Duration	Population Description	Treatment given to relevant population	Results
6736, Reeves, 2000	RCT	12 months	68 patients with knee OA with and without ACL laxity. ACL laxity+ group: 13 trx with dextrose. **Note total group (n=68) findings (table 1) did not report pts per group and could not be entered into revman. ACL subgroup findings (Table 3) included open-label phase and also couldn't be put in Revman.	Three bimonthly injections of 9 cc of either 10% dextrose and .075% lidocaine in bacteriostatic water (active solution) versus an identical control solution absent 10% dextrose. The dextrose - treated joints then received 3 further bimonthly injections of 10% dextrose in open-label fashion.	ACL laxity+ at 6 months: Pain VAS at rest: (dextrose, n=13)) 1.61 (1.71) vs (saline control, n=12) 1.69 (1.73). Pain VAS walking: (dextrose, n=13)) 2.56 (1.97) vs (saline control, n=12) 2.85 (2.2). Total group findings (w/ w/o ACL laxity): Hotelling multivariate analysis of paired observations between 0 and 6 months for active and control solution including all nonradiographic variables (pain at rest, pain with walking, pain with stair use, swelling, buckling episodes, and flexion range) demonstrated a statistically superior effect of active solution (P = .015).

*Note PICO 44 is compared to oral NSAIDs.

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PICO 45: Intra-articular botulinum compared to oral NSAIDs for knee or hip OA

Summary: The literature search identified four randomized controlled trials that addressed this PICO question[1-4]. The RCTs provided indirect evidence by comparing intra-articular botulinum injections to either an educational control with Tylenol use permitted or intra-articular saline injection[2,3,4]. One study also provided therapeutic exercise to patients in all groups.[4] The study by Hsieh et al.[1] was not blinded and had a small number of patients (n=41) but did show a small difference in pain VAS scores favoring intra-articular botulinum injections compared to education control. Bao et al. also showed a between-group difference in VAS pain favoring botulinum plus exercise over saline plus exercise, as well as improvements in WOMAC pain and function[4] (Table 1). However, the RCTs by Nielsen[2] and McAlindon[3] did not find a between-group difference for WOMAC or VAS pain scores. While McAlindon found no significant between-group difference in serious adverse events, Nielsen found a significantly higher number of serious adverse events in the botulinum group (11 vs 0) (Table 2).

Quality of evidence across all critical outcomes: Very low

Table 1. Intra-articular Botulinum Compared to Control for Osteoarthritis

Certainty assessment							Summary of findings				
№ of participants (studies) Follow-up	**Risk of bias**	**Inconsistency**	**Indirectness**	**Imprecision**	**Publication bias**	**Overall certainty of evidence**	**Number of patients**		**Relative effect (95% CI)**	**Anticipated absolute effects**	
							With control	**With IA Bot**		**Risk with control**	**Risk difference with IA Bot**
Pain VAS (0-10, lower scores indicate improvement)											
81 (2 RCTs)	serious [a]	not serious	serious [b]	serious [c]	none	⨁◯◯◯ VERY LOW	40	41	-	-	MD **1.94 lower** (2.37 lower to 1.51 lower) **Favors botulinum**

Table 1. Intra-articular Botulinum Compared to Control for Osteoarthritis											
Certainty assessment							Summary of findings				
WOMAC Pain (0-100, lower scores indicate improvement)											
40 (1 RCT)	serious [d]	not serious	serious [b]	serious [c]	none	⨁◯◯◯ VERY LOW	20	20	-	-	**MD 30.30 lower** (33 lower to 27.60 lower) **Favors botulinum**
WOMAC Function (0-100, lower scores indicate improvement)											
40 (1 RCT)	serious [d]	not serious	serious [b]	serious [c]	none	⨁◯◯◯ VERY LOW	20	20	-	-	**MD 11.20 lower** (13.48 lower to 8.92 lower) **Favors botulinum**

CI: Confidence interval; **MD:** Mean difference

Explanations

a. Patient blinded; personnel and observer not blinded.

b. IA Botulinum vs education control, IA bot vs saline control with both groups receiving exercise. Tylenol use permitted; NSAIDs not mentioned.

c. Small number of patients, findings not supported by studies in Table 2.

Table 2. RCT data not suitable for effect size calculation or combining with other data

Ref ID, Author, year	Study type	Duration	Population Description	Treatment given to relevant population	Results
9028 McAlindon 2018	RCT	8 weeks	Patients (N = 176) with chronic idiopathic knee OA	intra-articular onabotA 400 U or 200 U or sline placebo.	**VAS daily pain score** (between-group difference): 0.22, 95% CI -0.33 to 0.76, p=0.437. **WOMAC pain** (between-group difference): 0.0 (95% CI -0.61 to 0.59, p=0.979). **Serious AEs**: onabotA 9 vs placebo 6
4754, Nielsen, 2017	RCT	12 weeks	Patients (N = 121) with idiopathic knee OA according to American College of Rheumatology (ACR) modified clinical classification criteria verified radiographically as Kellgren–Lawrence (K&L) grade I to III. Bot group (n=61) 62.5 yrs (8.6); placebo group (n=60) 62.1 yrs (8.6). *Population was subgrouped (nociceptive, neuropathic, and mixed/uncertain)	Randomized to receive onabotA US-guided IA injection (200 units)(n = 61) or placebo (2 mL of 0.9% saline)(n = 60).	"No significant between-group difference was demonstrated for any of the clinical data analysed." Values (or graph) for WOMAC or pain VAS not reported in article.

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PICO 46: Intra-articular corticosteroids compared to intra-articular saline for knee or hip OA

Summary: The literature search identified nine RCTs that directly addressed this comparison.[1-9] Three RCTs addressed this question for patients with hip OA (Tables 1 and 2).[1-3] The study by Lambert et al.[1] was an RCT with a small number of participants and the only study with data suitable for RevMan (Table 1). Lambert et al.[1] found lower WOMAC pain and function scores at one and two months status post intra-articular corticosteroid injections compared to saline control. Likewise, the study by Atachia et al.[2] found significant reductions in WOMAC pain and function compared to saline at week eight s/p injection. Qvistgaard et al.[3] found improvements in pain VAS on walking for corticosteroid injections compared to saline injections after 14 and 28 days; effects were no longer seen at three months (Table 2).

Six RCTs addressed this comparison in patients with knee OA (Table 3).[4-9] McAlindon et al. and Raynauld et al.[4,6] found no significant between-group difference in WOMAC pain at two years. Conflicting results were noted on a shorter time schedule (3 weeks and 6 weeks s/p injections) by Jones et al.[7] and Gaffney et al.[9] in which mean pain VAS scores were lower for corticosteroid injections compared to saline injections. However, these findings were inconclusive due to wide CIs that crossed the line of no effect. At 12 weeks[8] and 24 weeks[6] s/p injection, various corticosteroids (triamcinolone, betamethasone, methylprednisolone, cortivazol) were associated with lower mean pain VAS scores, although the finding was imprecise at 24 weeks. There were no significant differences between groups in WOMAC function or the chair stand test for knee function.

Quality of evidence across all critical outcomes: Low

Table 1. Intra-articular corticosteroid compared to saline for patients with (hip) osteoarthritis

Certainty assessment							Summary of findings				
№ of participants (studies) Follow-up	**Risk of bias**	**Inconsistency**	**Indirectness**	**Imprecision**	**Publication bias**	**Overall certainty of evidence**	**Number of patients**		**Relative effect (95% CI)**	**Anticipated absolute effects**	
							With saline (hip)	**With IA corticosteroid**		**Risk with saline (hip)**	**Risk difference with IA corticosteroid**
WOMAC pain- 1 mo (0-500, lower scores indicate improvement)											
52 (1 RCT)	not serious	not serious	not serious	serious [a]	none	⨁⨁⨁◯ MODERATE	21	31	-	-	MD **126.8 lower** (194.82 lower to 58.78 lower) **Favors steroid**

Table 1. Intra-articular corticosteroid compared to saline for patients with (hip) osteoarthritis											
Certainty assessment							**Summary of findings**				
WOMAC pain- 2 mo (0-500, lower scores indicate improvement)											
52 (1 RCT)	not serious	not serious	not serious	serious [a]	none	⨁⨁⨁◯ MODERATE	21	31	-	-	MD **149.1 lower** (217.6 lower to 80.6 lower) **Favors steroid**
WOMAC function- 1 mo (0-1700, lower scores indicate improvement)											
52 (1 RCT)	not serious	not serious	not serious	serious [a]	none	⨁⨁⨁◯ MODERATE	21	31	-	-	MD **381.4 lower** (590.24 lower to 172.56 lower) **Favors steroid**
WOMAC function- 2 mo (0-1500, lower scores indicate improvement)											
52 (1 RCT)	not serious	not serious	not serious	serious [a]	none	⨁⨁⨁◯ MODERATE	21	31	-	-	MD **410.6 lower** (616.72 lower to 204.48 lower) **Favors steroid**

CI: Confidence interval; **MD:** Mean difference

Explanations

a. Single study with small number of patients

Table 2. RCT data not suitable for effect size calculation or combining with other data

Ref ID, Author, year	Study type	Duration	Population Description	Treatment given to relevant population	Results
3320, Atachia, 2010	RCT	16 weeks	Patients with primary hip osteoarthritis. HA group (n=18, 7 males) 69 yrs ± 9; placebo (saline) (n=18, 7 males) 70 yrs ± 10	standard care (non-injection group); normal saline (3 ml); non-animal stabilised hyaluronic acid (durolane, 3 ml/60 mg licensed for single injection) or methylprednisolone acetate (depomedrone, 3 ml/120 mg).	Estimated from graph: WOMAC function at 56 days Saline= 7 Steroid= 5 HA=6 No-injection= 6.5 (p=0.04) WOMAC pain at 56 days saline= 6.5 Steroid=5 HA=5.5 No-injection= 6.0 P=0.06 The effect size (calculated as the mean change from baseline divided by the baseline SD) of the benefit from corticosteroid was large, becoming moderate by week 8: 1.5, 1.0 and 0.5 for NRS pain; 1.9, 1.1 and 0.6 for WOMAC pain; and 1.3, 0.9 and 0.4 for WOMAC function, at weeks 1, 4 and 8, respectively. There was a non-significant trend for improvement with saline injection at week 1 (effect size of 0.44 and 0.41 for NRS pain and WOMAC pain, respectively), which was not apparent at later assessments. Adverse events: There was one confirmed case of post-arthroplasty infection (durolane group). Four patients in the durolane group had significant flare of symptoms within a few days of the injection. In one case septic arthritis had to be excluded and a diagnostic aspiration was performed at week 1, which excluded infection. The symptoms settled within a few days of the aspiration

Ref ID, Author, year	Study type	Duration	Population Description	Treatment given to relevant population	Results
4774, Qvistgaard, 2006	RCT	90 days	Hip OA as defined by the ACR criteria, radiographic changes of hip OA30, age above 18 years, stable medication for at least 3 weeks before inclusion. HA group (n=33, 61% females) 65 yrs (14), Control (n=36, 61% females) 64 yrs (11).	Patients were randomized to (1) one injection with 1 mL (40 mg Depo-medrol) methylprednisolone corticosteroid followed by two sham injections, (2) three injections of 2 mL HA (Hyalgan), or (3) three intra-articular injections of 2 mL saline water. Secondary outcome measures were WOMAC total scale and PGA VAS.	Estimated from graph: Pain on walking (VAS) at 90 days Corticosteroids:37 mm Saline (control): 41 mm "there was a significant treatment effect across all time-points (P Z 0.044), due to a significant improvement following corticosteroid compared to saline, SMD Steroid Z 0.6 (95% CI: 0.1e1.1, P Z 0.021) whereas HA compared to saline was SMDHA Z 0.4 (0.1 to 0.9; P Z 0.13). The difference between placebo (saline) and corticosteroid was significant at 14 and 28 days but vanished after 3 months (P14 days Z 0.006; P28 days Z 0.006; P3 months Z 0.58)."

Table 3. Intra-articular corticosteroid compared to saline (knee) for Osteoarthritis

Certainty assessment							Summary of findings				
№ of participants (studies) Follow-up	Risk of bias	Inconsistency	Indirectness	Imprecision	Publication bias	Overall certainty of evidence	Number of patients		Relative effect (95% CI)	Anticipated absolute effects	
							With saline (knee)	With IA corticosteroid		Risk with saline (knee)	Risk difference with IA corticosteroid
WOMAC pain- 2 years (lower scores indicate improvement)											

Table 3. Intra-articular corticosteroid compared to saline (knee) for Osteoarthritis											
Certainty assessment							Summary of findings				
206 (2 RCTs)	not serious	not serious	not serious	not serious	none	⨁⨁⨁⨁ HIGH	103	103	-	-	SMD **0.21 higher** (0.06 lower to 0.49 higher)
Pain VAS at 3 weeks (0-100, lower scores indicate improvement)											
59 (1 RCT)	serious [b]	not serious	not serious	serious [c]	none	⨁⨁◯◯ LOW	29	30	-	-	MD **4.75 lower** (16.89 lower to 7.39 higher)
Pain VAS- 6 weeks (0-100, lower scores indicate improvement)											
84 (1 RCT)	serious [e]	not serious	not serious	serious [c]	none	⨁⨁◯◯ LOW	42	42	-	-	MD **7.1 lower** (18.39 lower to 4.19 higher)
Pain VAS 12 weeks – Triamcinolone (0-10, lower scores indicate improvement)											
60 (1 RCT)	very serious [d]	not serious	not serious	not serious	none	⨁⨁◯◯ LOW	30	30	-	-	MD **1.7 lower** (2.51 lower to 0.89 lower) **Favors steroid**
Pain VAS 12 weeks – Betamethasone (0-10, lower scores indicate improvement)											

Table 3. Intra-articular corticosteroid compared to saline (knee) for Osteoarthritis											
Certainty assessment							**Summary of findings**				
60 (1 RCT)	very serious [d]	not serious	not serious	not serious	none	⨁⨁◯◯ LOW	30	30	-	-	MD **1.8 lower** (2.54 lower to 1.06 lower) **Favors steroid**
Pain VAS 12 weeks – Methylprednisolone (0-10, lower scores indicate improvement)											
60 (1 RCT)	very serious [d]	not serious	not serious	not serious	none	⨁⨁◯◯ LOW	30	30	-	-	MD **2.4 lower** (3.17 lower to 1.63 lower) **Favors steroid**
Pain VAS- 24 weeks, Cortivazol (0-100, lower scores indicate improvement)											
53 (1 RCT)	serious [a]	not serious	not serious	serious [c]	none	⨁⨁◯◯ LOW	28	25	-	-	MD **7 lower** (22.44 lower to 8.44 higher)
WOMAC function- 2 years (lower scores indicate improvement)											
206 (2 RCTs)	not serious	not serious	not serious	not serious	none	⨁⨁⨁⨁ HIGH	103	103	-	-	SMD **0.07 higher** (0.20 lower to 0.35 higher)
Chair Stand (higher scores indicate improvement)											

Table 3. Intra-articular corticosteroid compared to saline (knee) for Osteoarthritis											
Certainty assessment							Summary of findings				
140 (1 RCT)	not serious	not serious	not serious	not serious	none	⨁⨁⨁⨁ HIGH	70	70	-	-	MD **0.1 higher** (3.1 lower to 3.3 higher)

CI: Confidence interval; **MD:** Mean difference

Explanations

a. unclear allocation concealment, unclear attrition

b. unclear sequence generation, allocation concealment, reporting bias

c. wide 95% confidence interval that crosses line of no effect

d. unclear sequence generation, concealment, unblinded, unclear attrition, reporting bias

e. unclear sequence generation, allocation concealment, attrition bias

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PICO 47: Intra-articular hyaluronic acid compared to intra-articular corticosteroids for knee or hip OA

Summary: Knee: The literature search identified 16 randomized controlled trials[1-16] that addressed this PICO question. The RCTs provided direct evidence by comparing intra-articular hyaluronic acid compared to intra-articular corticosteroid injections for osteoarthritis. Of note, the studies by Tascioglu et al.[1] and Shimizu et al.[12] were unblinded, open label studies of three weekly or five weekly injections of hyaluronic acid, respectively. Intra-articular hyaluronic acid compared to intra-articular corticosteroids had significantly lower WOMAC pain scores at three and six months for a series of three injections,[10] although the difference was small and not clinically significant. A meta-analysis of 8 RCTs found that corticosteroids led to significantly greater global pain VAS improvement than HA at one month[1,4,5,8,12,16], but the difference was not clinically significant. No significant between-group difference in VAS pain was found at 3 months[1-5,8,10,,11]. At 6 months, a small but statistically significant-between-group difference favored HA[1,3,5,8,10,12,16], but the difference was not clinically significant. These findings did not change when studies with open label or unclear blinding were removed from the analyses. There was no between group difference in WOMAC function scores at 3 months[4] or 6 months[8,9]. There was no significant between-group difference in adverse events; however, a higher proportion of patients receiving intra-articular corticosteroids developed secondary adrenal insufficiency compared to hyaluronic acid[15]. A literature search update in August 2018 identified one additional relevant RCT in patients with knee OA[17]. This study's data did not alter the findings of Table 1 below.

Hip: Atchia et al.[13] found slightly lower mean (hip) WOMAC pain and function scores at 56 days with corticosteroid injections compared to hyaluronic acid at 56 days; data was insufficient to include in meta-analysis. Qvistgaard et al.[14] did not find any between group differences in (hip) pain VAS on walking at 90 days.

Quality of evidence across all critical outcomes: Moderate

Table 1. Intra-articular Hyaluronic Acid compared to Intra-articular Corticosteroid for Knee OA

Certainty assessment							Summary of findings				
№ of participants (studies) Follow-up	**Risk of bias**	**Inconsistency**	**Indirectness**	**Imprecision**	**Publication bias**	**Overall certainty of evidence**	**Number of patients**		**Relative effect (95% CI)**	**Anticipated absolute effects**	
							With IA steroid (knee)	**With IA HA**		**Risk with IA steroid (knee)**	**Risk difference with IA HA**
WOMAC Pain- 3 months (0-20, lower scores indicate improvement)											
356 (2 RCTs)	serious [a]	not serious	not serious	not serious	none	⨁⨁⨁◯ MODERATE	172	184	-	-	MD **0.19 lower** (0.94 lower to 0.56 higher)
WOMAC Pain- 3 months - 1 HA injection (0-20, lower scores indicate improvement)											
140 (1 RCT)	not serious	not serious	not serious	not serious	none	⨁⨁⨁⨁ HIGH	69	71	-	-	MD **0.51 higher** (0.81 lower to 1.83 higher)
WOMAC Pain- 3 months - 3 HA injections (0-20, lower scores indicate improvement)											
216 (1 RCT)	serious [b]	not serious	not serious	not serious	none	⨁⨁⨁◯ MODERATE	103	113	-	-	MD **0.4 lower** (0.43 lower to 0.37 lower) **Favors HA**
WOMAC Pain- 6 months (0-20, lower scores indicate improvement)											

Table 1. Intra-articular Hyaluronic Acid compared to Intra-articular Corticosteroid for Knee OA											
Certainty assessment							**Summary of findings**				
216 (1 RCT)	serious [b]	not serious	not serious	not serious	none	⨁⨁⨁◯ MODERATE	103	113	-	-	MD **1.1 lower** (1.13 lower to 1.07 lower) **Favors HA**
Pain VAS – 1 month (0-10, lower scores indicate improvement)											
484 (6 RCTs)	serious [d]	not serious	not serious	not serious	none	⨁⨁⨁◯ MODERATE	250	234	-	-	MD **0.67 higher** (0.07 higher to 1,27 higher) **Favors corticostheroids**
Pain VAS – 3 months (0-10, lower scores indicate improvement)											
800 (8 RCTs)	serious [d]	not serious	not serious	not serious	none	⨁⨁⨁◯ MODERATE	410	390	-	-	**MD 0.46 lower** (1.31 lower to 0.39 higher)
Pain VAS- 6 months (0-10, lower scores indicate improvement)											
646 (7 RCTs)	serious [f]	serious	not serious	not serious	none	⨁⨁⨁◯ MODERATE	339	307	-	-	MD **0.73 lower** (1.25 lower to 0.21 lower) **Favors HA**
WOMAC Function- 3 months (0-20, lower scores indicate improvement)											

Table 1. Intra-articular Hyaluronic Acid compared to Intra-articular Corticosteroid for Knee OA											
Certainty assessment							**Summary of findings**				
140 (1 RCT)	not serious	not serious	not serious	not serious	none	⨁⨁⨁⨁ HIGH	69	71	-	-	MD **0.25 higher** (3.69 lower to 4.19 higher)
WOMAC function 6 months (0-20, lower scores indicate improvement)											
541 (2 RCTs)	not serious	not serious	not serious	not serious	none	⨁⨁⨁⨁ HIGH	270	271	-	-	MD **1.34 lower** (2.7 lower to 0.01 higher)
Total Adverse Events											
521 (1 RCT)	not serious	not serious	not serious	serious [e]	none	⨁⨁⨁◯ MODERATE	16/262 (6.1%)	10/259 (3.9%)	**OR 0.62** (0.28 to 1.39)	61 per 1,000	**22 fewer per 1,000** (43 fewer to 22 more)

CI: Confidence interval; **MD:** Mean difference; **OR:** Odds ratio

Explanations

a. several categories of unclear risk of bias; Caborn 6796 had unblinded participants and injectors

b. Caborn 6796 had unblinded participants and injectors

c. Several categories of unclear risk of bias. Bisicchia 4233 had unblinded injectors and patients.

d. I2 >75%. Bisicchia 4233 favored IA HA, Skwara 789 & Skwara 3994 favored IA steroid.

e. Wide 95% confidence interval that overlaps line of no effect.

f. Several categories of unclear risk of bias. Bisicchia 4233 had unblinded injectors and patients; Shimizu 855 was completely unblinded

g. Tascioglu 3400 unblinded

Table 2. RCT data not suitable for effect size calculation or combining with other data

Ref ID, Author, year	Study type	Duration	Population Description	Treatment given to relevant population	Results
HIP					
3320, Atachia, 2010	RCT	16 weeks	Patients with primary hip osteoarthritis. HA group (n=18, 7 males) 69 yrs ± 9; placebo (saline) (n=18, 7 males) 70 yrs ± 10	Standard care (non-injection group); normal saline (3 ml); non-animal stabilised hyaluronic acid (durolane, 3 ml/60 mg licensed for single injection) or methylprednisolone acetate (depomedrone, 3 ml/120 mg).	Estimated from graph: WOMAC function at 56 days Control (saline)= 7 Steroid= 5 HA=6 No-injection= 6.5 (p=0.04) WOMAC pain at 56 days Control (saline)= 6.5 Steroid=5 HA=5.5 No-injection= 6.0 P=0.06 The effect size (calculated as the mean change from baseline divided by the baseline SD) of the benefit from corticosteroid was large, becoming moderate by week 8: 1.5, 1.0 and 0.5 for NRS pain; 1.9, 1.1 and 0.6 for WOMAC pain; and 1.3, 0.9 and 0.4 for WOMAC function, at weeks 1, 4 and 8, respectively. There was a non-significant trend for improvement with saline injection at week 1 (effect size of 0.44 and 0.41 for NRS pain and WOMAC pain, respectively), which was not apparent at later assessments. Adverse: There was one confirmed case of post-arthroplasty infection (durolane group). Four patients in the durolane group had signifi cant fl are of symptoms within a few days of the injection. In one case septic arthritis had to be excluded and a diagnostic aspiration was performed at week 1, which excluded infection. The symptoms settled within a few days of the aspiration
4774, Qvistgaard, 2006	RCT	90 days	Hip OA as defined by the ACR criteria29, radiographic	Patients were randomized to (1) one injection with 1 mL (40 mg Depo-	Estimated from graph: Pain on walking (VAS) at 90 days Corticosteroids:37 mm HA group: 37 mm

Ref ID, Author, year	Study type	Duration	Population Description	Treatment given to relevant population	Results
			changes of hip OA30, age above 18 years, stable medication for at least 3 weeks before inclusion. HA group (n=33, 61% females) 65 yrs (14), Control (n=36, 61% females) 64 yrs (11).	medrol) methylprednisolone corticosteroid followed by two sham injections, (2) three injections of 2 mL HA (Hyalgan), or (3) three intra-articular injections of 2 mL saline water. Secondary outcome measures were WOMAC total scale and PGA VAS.	Saline (control): 41 mm "there was a significant treatment effect across all time-points (P Z 0.044), due to a significant improvement following corticosteroid compared to saline, SMD Steroid Z 0.6 (95% CI: 0.1e1.1, P Z 0.021) whereas HA compared to saline was SMD HA Z 0.4 (0.1 to 0.9; P Z 0.13). The difference between placebo (saline) and corticosteroid was significant at 14 and 28 days but vanished after 3 months (P14 days Z 0.006; P28 days Z 0.006; P3 months Z 0.58)."
KNEE					
4705, Vaishya, 2017	RCT	24 weeks	Patients with moderate OA knee, Kellgren–Lawrence (KL) grade II and III were enrolled in the study: 40 patients in steroid (15 males) and 42 patients in HA group (13 males). *Ages not provided. 40 patients (68 knees) were	IA 40 mg triamcinolone or IA 6 ml of Synvisc. Either one or both knees were injected.* **ROB in Revman	Standard deviations or CIs not provided in article. For global VAS score After 1 week: Steroid group 1.75 vs HA group 1.87 (p=0.34) After 4th week: : Steroid group 2.07 vs HA group 1.95 (p=0.26) **After 12 weeks: Steroid group 2.8 vs HA group 2.34 (p<0.01)** **After 24 weeks: Steroid group 3.6 vs HA group 3.14 (p=0.03)**

Ref ID, Author, year	Study type	Duration	Population Description	Treatment given to relevant population	Results
			included in the steroid group. 42 patients (72 knees) were included in the HA group.		
4751, Habib, 2014	RCT	8 weeks	20 patients in HA group were 50.9 yrs±11.8 (15 males). 20 patients in steroid group were 53.3 yrs±13.1 (12 males).	Group 1 patients had an IACI of 80 mg of MPA at the knee joint and group 2 patients had an intra-articular injection (IAI) of 6 ml (60 mg) of sodium hyaluronate (control group)	**Primary goal of study was to evaluate HPA axis. Pain VAS was recorded but not specifically reported- "Eighty-five percent of the patients from group 1 had a favorable clinical response at week 1 vs. 50 % of the patients in group 2 (p =0.018). After that, the results were comparable." In the steroid group, 25 % of patients had secondary adrenal insufficiency vs. none in HA group (p = 0.0471). The earliest SAI was observed at week 2, and latest SAI was observed at week 4. SAI was observed at one time point, two consecutive time points, or two separate time points in the same patient.

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PICO 48: Intra-articular PRP vs. Intra-articular corticosteroids for OA of the hip / knee

Summary. This PICO was addressed by 2 RCTs [1,2]. There was no significant difference between groups in KOOS – Pain and the 20 meter walk test, although the findings were inconclusive due to wide CIs that included the possibility of a between-group difference. The KOOS – ADL showed a significant difference between groups.

Quality of evidence across all critical outcomes: Low

PRP compared to CS at 6 months for OA of Hip / Knee											
Certainty assessment							Summary of findings				
№ of participants (studies) Follow-up	Risk of bias	Inconsistency	Indirectness	Imprecision	Publication bias	Overall certainty of evidence	Number of Patients		Relative effect (95% CI)	Anticipated absolute effects	
							With CS at 6 months	With PRP		Risk with CS at 6 months	Risk difference with PRP
KOOS - Pain Relief (0-100, higher scores indicate improvement)											
103 (2 RCTs)	not serious	serious [a]	not serious	serious [b]	none	⨁⨁◯◯ LOW	46	57	-	-	MD **13.64 higher** (5.99 lower to 33.27 higher)
KOOS – ADL (0-100, higher scores indicate improvement)											
103 (2 RCTs)	not serious	not serious	not serious	not serious	none	⨁⨁⨁⨁ HIGH	46	57	-	-	MD **10.73 higher** (2.71 higher to 18.76 higher) **Favors PRP**
20 meter walk test (seconds) (lower scores indicate improvement)											
39 (1 RCT)	not serious	not serious	not serious	serious [b]	none	⨁⨁⨁◯ MODERATE	16	23	-	-	MD **2.6 lower** (5.63 lower to 0.43 higher)

CI: Confidence interval; **MD:** Mean difference

Explanations

a. High between-study heterogeneity

b. Wide 95% CI crosses line of no effect

References

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PICO 49. Intra-articular mesenchymal stem cells compared to intra-articular corticosteroid for patients with knee or hip OA

Summary. The literature searches did not identify any studies that addressed this question.

Quality of evidence across all critical outcomes: Very low

PICO 50. Intra-articular prolotherapy comparared to intra-articular corticosteroid for patients with knee or hip OA

Summary. The literature searches did not identify any studies that addressed this question.

Quality of evidence across all critical outcomes: Very low

PICO 51: Intra-articular botox vs. intra-articular corticosteroids for OA of hip/knee

Summary. This PICO was addressed by 1 RCT [1]. There was no significant difference between groups in WOMAC pain, WOMAC function, and 40 meter walk time, but these estimates were imprecise due to the small sample size and wide CIs around the effect sizes.

Quality of evidence across all critical outcomes: Moderate

BoNT-A 100 units compared to Methylprednisone 40mg (at 8 weeks) for OA of hip/knee									
Certainty assessment							Summary of findings		
		Inconsistency	Indirectness	Imprecision			Number of Patients		Anticipated absolute effects

BoNT-A 100 units compared to Methylprednisone 40mg (at 8 weeks) for OA of hip/knee											
Certainty assessment							Summary of findings				
№ of participants (studies) Follow-up	**Risk of bias**				**Publication bias**	**Overall certainty of evidence**	**With Methylprednisone 40mg (at 8 weeks)**	**With BoNT-A 100 units**	**Relative effect (95% CI)**	**Risk with Methylprednisone 40mg (at 8 weeks)**	**Risk difference with BoNT-A 100 units**
WOMAC pain (0-20, lower scores indicate improvement)											
40 (1 RCT)	not serious	not serious	not serious	serious [a]	none	⨁⨁⨁◯ MODERATE	20	20	-	-	MD **0.3 lower** (2.19 lower to 1.59 higher)
WOMAC function (0-20, lower scores indicate improvement)											
40 (1 RCT)	not serious	not serious	not serious	serious [a]	none	⨁⨁⨁◯ MODERATE	20	20	-	-	MD **2.1 lower** (8.98 lower to 4.78 higher)
40m walk (seconds) (lower scores indicate improvement)											
40 (1 RCT)	not serious	not serious	not serious	serious [a]	none	⨁⨁⨁◯ MODERATE	20	20	-	-	MD **6 higher** (2.42 lower to 14.42 higher)

CI: Confidence interval; **MD:** Mean difference

Explanations

a. Small study and 95% CI crosses no effect line

BoNT-A 200 units compared to Methylprednisone 40mg (at 8 weeks) for OA of hip/knee											
Certainty assessment							**Summary of findings**				
№ of participants (studies) Follow-up	**Risk of bias**	**Inconsistency**	**Indirectness**	**Imprecision**	**Publication bias**	**Overall certainty of evidence**	**Number of Patients**		**Relative effect (95% CI)**	**Anticipated absolute effects**	
							With Methylprednisone 40mg (at 8 weeks)	**With BoNT-A 200 units**		**Risk with Methylprednisone 40mg (at 8 weeks)**	**Risk difference with BoNT-A 200 units**
WOMAC pain (0-20, lower scores indicate improvement)											
40 (1 RCT)	not serious	not serious	not serious	serious [a]	none	⨁⨁⨁◯ MODERATE	20	20	-	-	MD **1.2 higher** (0.69 lower to 3.09 higher)
WOMAC function (0-20, lower scores indicate improvement)											
40 (1 RCT)	not serious	not serious	not serious	serious [a]	none	⨁⨁⨁◯ MODERATE	20	20	-	-	MD **5.2 higher** (1.78 lower to 12.18 higher)
40m walk (seconds) (lower scores indicate improvement)											
40 (1 RCT)	not serious	not serious	not serious	serious [a]	none	⨁⨁⨁◯ MODERATE	20	20	-	-	MD **0.9 higher** (2.03 lower to 3.83 higher)

CI: Confidence interval; **MD:** Mean difference

Explanations

a. Small study and 95% CI crosses no effect line

References

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PICO 52. Intra-articular anesthetic compared to intra-articular corticosteroid for patients with knee or hip OA

Summary. The literature searches did not identify any studies that addressed this question.

Quality of evidence across all critical outcomes: Very low

PICO 53. Intra-articular corticosteroids plus intra-articular anesthetic compared to intra-articular corticosteroid for patients with knee or hip OA

Summary. The literature searches did not identify any studies that addressed this question.

Quality of evidence across all critical outcomes: Very low

PICO 54: Long acting intra-articular corticosteroids vs. short acting intra-articular corticosteroids in OA hip/knee

Summary. This PICO was addressed by 2 RCTs [1]. Bodick et al. used three formulations of the long acting CS (TCA ER 10mg, 40mg, and 60mg) compared to short-acting CS (TCA IR 40 mg), while Conaghan et al. compared FX006 (32 mg) to TCA IR 40 mg. There were no significant between-group differences in pain or function for TCA ER 10 mg or 60 mg versus TCA IR 40 mg (Table 1 and Table 3). There were significant between-group differences in WOMAC pain and function between TCA ER (32 and 40 mg) versus TCA IR 40 mg, but the differences were small

and not clinically significant (Table 2). There was no significant difference in SAE between long acting CS (any dose) and short acting CS, but the number of events were too small to definitively rule out the possibility of a difference.

Quality of evidence across all critical outcomes: Moderate

Table 1. TCA ER 10mg compared to TCA IR 40mg for OA knee

Certainty assessment							Summary of findings				
№ of participants (studies) Follow-up	**Risk of bias**	**Inconsistency**	**Indirectness**	**Imprecision**	**Publication bias**	**Overall certainty of evidence**	**Number of Patients**		**Relative effect (95% CI)**	**Anticipated absolute effects**	
							With TCA IR 40mg	**With TCA ER 10mg**		**Risk with TCA IR 40mg**	**Risk difference with TCA ER 10mg**
WOMAC Pain (0-20, change from baseline) (lower scores indicate improvement)											
109 (1 RCT)	not serious	not serious	not serious	serious [a]	none	⨁⨁⨁◯ MODERATE	51	58	-	-	MD **0.27 lower** (0.56 lower to 0.02 higher)
WOMAC Function (0-68, change from baseline) (lower scores indicate improvement)											
109 (1 RCT)	not serious	not serious	not serious	serious [a]	none	⨁⨁⨁◯ MODERATE	51	58	-	-	MD **0.28 lower** (0.56 lower to 0.00 higher)
NRS mean daily pain (change from baseline to 12 weeks)											
109 (1 RCT)	not serious	not serious	not serious	serious [a]	none	⨁⨁⨁◯ MODERATE	51	58	-	-	**MD 0.30 lower** (1.13 lower to 0.53 higher)
Serious adverse events											

Table 1. TCA ER 10mg compared to TCA IR 40mg for OA knee											
Certainty assessment							**Summary of findings**				
109 (1 RCT)	not serious	not serious	not serious	serious [a]	none	⨁⨁⨁◯ MODERATE	2/51 (3.9%)	1/58 (1.7%)	**OR 0.43** (0.04 to 4.89)	39 per 1,000	**22 fewer per 1,000** (38 fewer to 127 more)

CI: Confidence interval; **MD:** Mean difference; **OR:** Odds ratio

Explanations

a. Wide 95% CI crosses line of no effect

Table 2. TCA ER 40mg compared to TCA IR 40mg for OA knee											
Certainty assessment							**Summary of findings**				
№ of participants (studies) Follow-up	**Risk of bias**	**Inconsistency**	**Indirectness**	**Imprecision**	**Publication bias**	**Overall certainty of evidence**	**Number of Patients**		**Relative effect (95% CI)**	**Anticipated absolute effects**	
							With TCA IR 40mg	**With TCA ER 40mg**		**Risk with TCA IR 40mg**	**Risk difference with TCA ER 40mg**
WOMAC Pain (0-20, change from baseline) (lower scores indicate improvement)											
432 (2 RCTs)	not serious	not serious	not serious	not serious	none	⨁⨁⨁⨁ HIGH	212	220	-	-	MD **0.24 lower** (0.42 lower to 0.05 lower) **Favprs TCA ER**
WOMAC Function (0-68, change from baseline) (lower scores indicate improvement)											

Table 2. TCA ER 40mg compared to TCA IR 40mg for OA knee											
Certainty assessment							Summary of findings				
432 (2 RCTs)	not serious	not serious	not serious	not serious	none	⨁⨁⨁⨁ HIGH	212	220	-	-	MD **0.26 lower** (0.40 lower to 0.12 lower) **Favprs TCA ER**
NRS mean daily pain (change from baseline to 12 weeks)											
432 (2 RCTs)	not serious	not serious	not serious	not serious	none	⨁⨁⨁⨁ HIGH	212	220	-	-	**MD 0.30 lower** (0.77 lower to 0.16 higher)
Serious adverse events											
432 (2 RCTs)	not serious	not serious	not serious	serious [a]	none	⨁⨁⨁◯ MODERATE	6/212 (2.8%)	5/220 (2.3%)	**OR 0.75** (0.13 to 4.18)	28 per 1,000	**5 fewer per 1,000** (24 fewer to 117 more)

CI: Confidence interval; **MD:** Mean difference; **OR:** Odds ratio

Explanations

a. Wide 95% CI crosses line of no effect

Table 3. TCA ER 60mg compared to TCA IR 40mg for OA knee									
Certainty assessment							Summary of findings		
№ of participants	**Risk of bias**	**Inconsistency**	**Indirectness**	**Imprecision**	**Publication bias**	**Overall certainty**	**Number of Patients**		**Anticipated absolute effects**

Table 3. TCA ER 60mg compared to TCA IR 40mg for OA knee											
Certainty assessment							Summary of findings				
(studies) Follow-up						of evidence	With TCA IR 40mg	With TCA ER 60mg	Relative effect (95% CI)	Risk with TCA IR 40mg	Risk difference with TCA ER 60mg
WOMAC Pain (0-20, change from baseline) (lower scores indicate improvement)											
111 (1 RCT)	not serious	not serious	not serious	serious [a]	none	⨁⨁⨁◯ MODERATE	51	60	-	-	MD **0.2 lower** (0.48 lower to 0.08 higher)
WOMAC Function (0-68, change from baseline) (lower scores indicate improvement)											
111 (1 RCT)	not serious	not serious	not serious	serious [a]	none	⨁⨁⨁◯ MODERATE	51	60	-	-	MD **0.19 lower** (0.47 lower to 0.09 higher)
NRS mean daily pain (change from baseline to 12 weeks)											
111 (1 RCT)	not serious	not serious	not serious	serious [a]	none	⨁⨁⨁◯ MODERATE	51	60	-	-	**MD 0.10 higher** (0.73 lower to 0.93 higher)
Serious adverse events											
111 (1 RCT)	not serious	not serious	not serious	serious [a]	none	⨁⨁⨁◯ MODERATE	2/51 (3.9%)	0/60 (0.0%)	**OR 0.16** (0.01 to 3.49)	39 per 1,000	**33 fewer per 1,000** (39 fewer to 85 more)

CI: Confidence interval; **MD:** Mean difference; **OR:** Odds ratio

Explanations

a. Wide 95% CI crosses line of no effect

References

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PICO 55. High-dose compared to low-dose intra-articular corticosteroid in patients with knee or hip OA

Summary. The literature searches did not identify any studies that addressed this question.

Quality of evidence across all critical outcomes: Very low

PICO 56: NSAIDs vs. no treatment for people with knee and/or hip OA.

Summary: The literature search identified 73 RCTs to evaluate this PICO question. Eight RCTs [1-8] were conducted in adults with hip OA only, 48 RCTs[9-53,68-70] were conducted in adults with knee OA only, and 16 studies were conducted in adults with hip or knee OA [59-67,71,72]. Follow-up ranged from 12 to 16 weeks for hip OA-only studies, 2 weeks to 6 months for knee OA-only studies, and 6 to 13 weeks for combined hip and knee OA studies.

Meta-analyses found significant between-group differences favoring NSAIDs over placebo for pain (WOMAC Pain and 100mm VAS) and self-reported function (WOMAC Function) in patients with hip OA (Table 1). Serious adverse events did not show a significant between-group difference at 12 to 16 week follow-up, but the findings were inconclusive due to a wide 95% CI that included the possibility of a between-group difference. One study[4] found an increase in gastrointestinal adverse events in the NSAID group, but the results were inconclusive due to the small number of events and wide CI that crossed the line of no effect.

Meta-analyses found significant between-group differences for pain (WOMAC Pain and global knee pain [VAS]) and self-reported function outcomes for knee OA at up to 24 weeks follow-up (Table 2). Petersen et al.[35] reported significant between-group differences in performance-related outcomes of gait speed, stair negotiation and sit-to-stand, but results were imprecise due to small study size. The reported risk of serious adverse events was inconsistent across studies and therefore results were inconclusive. Gastrointestinal adverse events occurred more frequently in the NSAID group. Similar findings were observed in studies that included both hip and knee OA patients (Table 3).

A Cochrane systematic review of RCTs comparing rofecoxib and placebo reported a significant increase in serious adverse events for patients in the rofecoxib arms when combined in a meta-analysis (Table 6).[66]

The quality of evidence was low, due primarily to serious risk of bias in the majority of the included studies and wide confidence intervals associated with the effect estimates for some critical outcomes.

Quality of evidence across all critical outcomes: Moderate

Table 1. Oral NSAIDs vs. placebo in hip OA

Certainty assessment							Summary of findings				
№ of participants (studies) Follow-up	**Risk of bias**	**Inconsistency**	**Indirectness**	**Imprecision**	**Publication bias**	**Overall certainty of evidence**	**Study event rates (%)**		**Relative effect (95% CI)**	**Anticipated absolute effects**	
							With placebo	**With Oral NSAIDs v placebo in hip OA**		**Risk with placebo**	**Risk difference with Oral NSAIDs v placebo in hip OA**
WOMAC Pain subscale (Likert/100mm) 12-16 wks (lower scores indicate improvement)											
1322 (2 RCTs)	serious [a]	not serious	not serious	not serious	none	⨁⨁⨁◯ MODERATE	747	575	-	-	SMD **0.29 lower** (0.41 lower to 0.18 lower) **Favors NSAIDs**
WOMAC function subscale (Likert/100mm) 12-16 wks (lower scores indicate improvement)											
1322 (2 RCTs)	serious [a]	not serious	not serious	not serious	none	⨁⨁⨁◯ MODERATE	747	575	-	-	SMD **0.3 lower** (0.41 lower to 0.19 lower) **Favors NSAIDs**
Total number of pts with serious AE											
1677 (4 RCTs)	serious [a]	not serious	not serious	serious [b]	none	⨁⨁◯◯ LOW	23/921 (2.5%)	18/756 (2.4%)	**OR 0.93** (0.40 to 2.17)	25 per 1,000	**2 fewer per 1,000** (15 fewer to 28 more)

Table 1. Oral NSAIDs vs. placebo in hip OA											
Certainty assessment							Summary of findings				
Gastrointestinal AE (perforation, ulcer, bleed)											
316 (1 RCT)	serious [a]	not serious	not serious	serious [b]	none	⨁⨁◯◯ LOW	0/155 (0.0%)	3/161 (1.9%)	**OR 6.87** (0.35 to 134.05)	0 per 1,000	**0 fewer per 1,000** (0 fewer to 0 fewer)

CI: Confidence interval; **MD:** Mean difference; **OR:** Odds ratio

Explanations

a. Lack of clarity regarding blinding of assessors and allocation concealment, randomization methods not described

b. Wide CI, small number of events

Table 2. Oral NSAIDs compared to placebo in knee OA

Certainty assessment							Summary of findings				
№ of participants (studies) Follow-up	**Risk of bias**	**Inconsistency**	**Indirectness**	**Imprecision**	**Publication bias**	**Overall certainty of evidence**	**Study event rates (%)**		**Relative effect (95% CI)**	**Anticipated absolute effects**	
							With placebo in knee OA	**With Oral NSAIDs**		**Risk with placebo in knee OA**	**Risk difference with Oral NSAIDs**
WOMAC Pain subscale (Likert/100mm) <12 wks (lower scores indicate improvement)											
5105 (13 RCTs)	serious [a]	not serious	not serious	not serious	none	⨁⨁⨁◯ MODERATE	2092	3013	-	-	SMD **0.47 lower** (0.68 lower to 0.27 lower) **Favors NSAIDs**
WOMAC Pain subscale (Likert/100mm) 12-24 wks (lower scores indicate improvement)											
8125 (14 RCTs)	serious [a]	not serious	not serious	not serious	none	⨁⨁⨁◯ MODERATE	3596	4529	-	-	SMD **0.35 lower** (0.43 lower to 0.27 lower) **Favors NSAIDs**
WOMAC Function subscale (Likert/100mm) <12 wks (lower scores indicate improvement)											

Table 2. Oral NSAIDs compared to placebo in knee OA											
Certainty assessment							Summary of findings				
3835 (10 RCTs)	serious [a]	not serious	not serious	not serious	none	⨁⨁⨁◯ MODERATE	1481	2354	-	-	SMD **0.28 lower** (0.35 lower to 0.21 lower) **Favors NSAIDs**
WOMAC Function subscale (Likert/100mm) 12-24 wks (lower scores indicate improvement)											
8119 (14 RCTs)	serious [a]	not serious	not serious	not serious	none	⨁⨁⨁◯ MODERATE	3592	4527	-	-	SMD **0.4 lower** (0.51 lower to 0.3 lower) **Favors NSAIDs**
Global knee pain (100mm VAS) <12 wks (lower scores indicate improvement)											
1020 (5 RCTs)	serious [a]	not serious	not serious	not serious	none	⨁⨁⨁◯ MODERATE	389	631	-	-	MD **4.44 lower** (7.43 lower to 1.46 lower) **Favors NSAIDs**
Global knee pain (100mm VAS) 12-16 wks (lower scores indicate improvement)											

Table 2. Oral NSAIDs compared to placebo in knee OA											
Certainty assessment							Summary of findings				
1133 (3 RCTs)	serious [a]	not serious	not serious	not serious	none	⨁⨁⨁◯ MODERATE	559	574	-	-	MD **9.57 lower** (14.35 lower to 4.78 lower) **Favors NSAIDs**
Global knee pain (100mm VAS), 6 months (lower scores indicate improvement)											
345 (1 RCT)	serious [a]	not serious	not serious	not serious	none	⨁⨁⨁◯ MODERATE	172	173	-	-	MD **6.3 lower** (11.01 lower to 1.59 lower) **Favors NSAIDs**
Gait speed (higher scores indicate improvement)											
23 (1 RCT)	not serious	not serious	not serious	serious [c]	none	⨁⨁⨁◯ MODERATE	12	11	-	-	MD **0.11 higher** (0.06 higher to 0.16 higher) **Favors NSAIDs**
Stair negotiation (climb time) (lower scores indicate improvement)											

Table 2. Oral NSAIDs compared to placebo in knee OA											
Certainty assessment							Summary of findings				
23 (1 RCT)	not serious	not serious	not serious	serious [c]	none	⨁⨁⨁◯ MODERATE	12	11	-	-	MD **0.26 lower** (0.02 lower to 0.50 lower) **Favors NSAIDs**
Sit-to-stand (reps/30sec) (higher scores indicate improvement)											
23 (1 RCT)	not serious	not serious	not serious	serious [c]	none	⨁⨁⨁◯ MODERATE	12	11	-	-	MD **1 higher** (0.64 lower to 2.64 higher)
Total number of patients with serious AE											
13799 (26 RCTs)	serious [a]	serious [d]	not serious	not serious	none	⨁⨁◯◯ LOW	115/5678 (2.0%)	121/8121 (1.5%)	**OR 0.83** (0.62 to 1.11)	19 per 1,000	**3 fewer per 1,000** (7 fewer to 2 more)
Gastrointestinal AE (perforation, ulcer, bleed)											
3508 (8 RCTs)	serious [a]	not serious	not serious	serious [b]	none	⨁⨁◯◯ LOW	2/1611 (0.1%)	18/1897 (0.9%)	**OR 2.68** (1.02 to 7.01)	1 per 1,000	**2 more per 1,000** (0 fewer to 7 more) **Favors placebo**
Cardiovascular AE											

Table 2. Oral NSAIDs compared to placebo in knee OA											
Certainty assessment							**Summary of findings**				
2204 (5 RCTs)	serious [a]	not serious	not serious	serious [b]	none	⨁⨁◯◯ LOW	2/952 (0.2%)	3/1252 (0.2%)	**OR 0.94** (0.22 to 3.93)	2 per 1,000	**0 fewer per 1000** (2 fewer to 6 more)

CI: Confidence interval; **SMD:** Standardised mean difference; **MD:** Mean difference; **OR:** Odds ratio

Explanations

a. Majority of studies had lack of clarity in blinding of assessors and allocation concealment; randomization methods not described

b. Wide CI that crosses the line of no effect

c. Small single study

d. Variation in direction of effect across studies

Table 3. Oral NSAIDs compared to placebo in hip and knee OA

Certainty assessment							Summary of findings				
№ of participants (studies) Follow-up	**Risk of bias**	**Inconsistency**	**Indirectness**	**Imprecision**	**Publication bias**	**Overall certainty of evidence**	**Number of Patients**		**Relative effect (95% CI)**	**Anticipated absolute effects**	
							With Placebo	**With NSAID**		**Risk with Placebo**	**Risk difference with NSAID**
WOMAC pain at 6 weeks (0-100, change from baseline) (lower scores indicate improvement)											
2275 (4 RCTs)	not serious	not serious	not serious	not serious	none	⨁⨁⨁⨁ HIGH	528	1747	-	-	MD **11.67 lower** (13.61 lower to 9.72 lower) **Favors NSAIDs**
WOMAC Pain at 12-13 weeks (0-100, change from baseline) (lower scores indicate improvement)											
1805 (6 RCTs)	not serious	not serious	not serious	not serious	none	⨁⨁⨁⨁ HIGH	717	1088	-	-	MD **10.14 lower** (12.54 lower to 7.74 lower) **Favors NSAIDs**
Global Pain (VAS) (0-100, lower scores indicate improvement)											
245 (1 RCT)	not serious	not serious	not serious	not serious	none	⨁⨁⨁⨁ HIGH	154	91	-	-	MD **13 lower** (19.73 lower to 6.27 lower) **Favors NSAIDs**

Table 3. Oral NSAIDs compared to placebo in hip and knee OA

Certainty assessment							Summary of findings				
Global Pain (VAS) (change from baseline) (0-100, lower scores indicate improvement)											
245 (1 RCT)	not serious	not serious	not serious	not serious	none	⨁⨁⨁⨁ HIGH	91	154	-	-	MD **0.61 lower** (0.93 lower to 0.29 lower) **Favors NSAIDs**
WOMAC function at 6 weeks (change from baseline) (0-100, lower scores indicate improvement)											
2330 (5 RCTs)	not serious	not serious	not serious	not serious	none	⨁⨁⨁⨁ HIGH	555	1775	-	-	MD **9.16 lower** (12.71 lower to 5.62 lower) **Favors NSAIDs**
WOMAC Function at 12-13 weeks (0-100, change from baseline) (lower scores indicate improvement)											
1104 (4 RCTs)	not serious	not serious	not serious	not serious	none	⨁⨁⨁⨁ HIGH	369	735	-	-	MD **8.16 lower** (11.12 lower to 5.20 lower) **Favors NSAIDs**
Total number of patients with serious AE											

Table 3. Oral NSAIDs compared to placebo in hip and knee OA											
Certainty assessment							Summary of findings				
2333 (5 RCTs)	not serious	not serious	not serious	serious [a]	none	⨁⨁⨁◯ MODERATE	9/675 (1.3%)	27/1658 (1.6%)	**OR 1.40** (0.44 to 4.46)	13 per 1,000	**5 more per 1,000** (7 fewer to 44 more)
Serious AE - Gastroduodenal ulcer											
218 (1 RCT)	not serious	not serious	not serious	not serious	none	⨁⨁⨁⨁ HIGH	3/80 (3.8%)	23/138 (16.7%)	**OR 5.13** (1.49 to 17.69)	38 per 1,000	**129 more per 1,000** (17 more to 371 more)

CI: Confidence interval; **MD:** Mean difference; **OR:** Odds ratio

Explanations

a. Wide 95% CI crosses line of no effect

Table 4. RCT data not suitable for effect size calculation or combining with other data (hip OA)

Ref ID, Author, year	Study type	Duration	Population Description	Treatment given to relevant population	Results
[1130, Kivitz, 2001]	RCT	12 weeks	1061 patients with hip OA	Celecoxib, 200mg/day (n=207)* or naproxen 1000mg/day (n=207) or placebo (n=218) *Data tabled for 200mg vs. placebo only, which represents usual daily dose.	<u>Global pain (VAS/100mm) Least square mean improvement from baseline at 12 weeks:</u> Celecoxib: -23.3 Naproxen: -22.3 Placebo: -11.1 2 total serious adverse events were reported, both were GI bleeds (naproxen =1, placebo =1).
[3371, Mejjad, 2000]	RCT, crossover	3 hours each crossover	16 outpatients	Etodolac, 300mg, single dose or placebo. All 16 patients were given a single	VAS (100mm) scores decreased significantly between t0 and t180 for etodolac and placebo groups (P<0.0009 and P<0.03, respectively). At t0, VAS scores were significantly higher for the

Ref ID, Author, year	Study type	Duration	Population Description	Treatment given to relevant population	Results
			(8M, 8F) with hip OA	dose of drug or placebo, then analyses were done hourly for 3 hours, After a 7-day washout period the crossover medication was given and analyses again were recorded hourly for 3 hours.	etodolac group (m±SD: 54.8±19.3 mm) than the placebo group (m±SD: 37.2±20.4 mm) (P<0.01); by t180, the mean VAS scores for the two treatment groups had become statistically comparable. No serious adverse events were reported by the investigators.
[4322, Quiding, 1992]	RCT, crossover	10 days total for 3-way crossover, 32hours each drug dose cycle with 48 hour washout between	27 outpatients with hip OA	Ibuprofen, 200mg or placebo, 6 total doses starting at 10.00h, then 18.00h, then every 4th hour. Study groups also included ibuprofen/codeine combination treatment arm. Since that combination is not on our list of interventions, we did not report data from that treatment arm.	<u>Global pain (100mm VAS):</u> **8 hour mean intensity values: (recorded hourly for 8 hours after the 1st and 6th doses):** Pretreatment VAS score was 31-37mm After 1st dose: ibuprofen 27mm placebo 26mm After 6th dose: ibuprofen 17mm placebo 29mm **Pain intensity index (mm/h):** After 1st dose: ibuprofen 3.3 placebo 3.4 After 6th dose: ibuprofen 2.1 placebo 3.9 No serious adverse events were reported by the investigators.
[3878, Hodgkinson, 1973]	RCT	5 years	45 outpatients with hip OA	Indomethacin, (dose starting at 25mg twice daily, increased by 25mg daily each week until optimum dose was reached) or placebo. Dosage adjustment 10-12 weeks.	<u>Serious adverse events:</u> GI bleed: 1 Perforated gastric ulcer: 2 Deaths: 8 (includes 4 coronary occlusions, 1 congestive heart failure, 2 cerebrovascular accidents)

Table 5. RCT data not suitable for effect size calculation or combining with other data (knee OA)

Ref ID, Author, year	Study type	Duration	Population Description	Treatment given to relevant population	Results
[6742, Mayorga, 2017]	RCT crossover	3 treatment periods of 7 days	33 patients with painful knee OA	500mg naproxen twice daily or placebo in 3-way crossover. * Study groups also included mavatrep treatment arm. Since that drug is not on our list of interventions, we did not report data from that treatment arm.	7 day mean (SD) average daily current NRS scores (11 point, 0-10 scale) Naproxen: 3.49 (1.544) Placebo: 4.9 (1.413) No statistically significant difference (p=0.271) 4 hour postdose sum of pain intensity (SPID scores): Pain after stair climbing, mean (SD): Naproxen: 2.1 (2.66) Placebo: 1.2 (2.07) No statistically significant between-group difference (p=0.229). Pain at rest, mean (SD) before stair climbing: Naproxen: 1.9 (3.37) Placebo: 0.8 (2.21) No statistically significant between-group difference (p=0.364). No deaths or serious adverse events were reported by the investigators.
[899, Sawitzke, 2010]	RCT	2 years	662 patients from GAIT trial aged ≥ years with painful knee OA for six months	Population is a subset of GAIT trial, longer term follow up from original study. Patients randomized to receive celecoxib 200mg/day (n=142) or placebo (n=131).	WOMAC Pain subscale over 24 months vs. placebo Decline in pain score: Celecoxib 32.80 vs placebo 30.21, 95% CI (-7.18 to 1.77) WOMAC Function subscale over 24 months vs. placebo: Celecoxib 24.07 vs placebo 23.14, 95% CI (-6.02 to 4.16) Total patients with SAE reported: Celecoxib: 4

Ref ID, Author, year	Study type	Duration	Population Description	Treatment given to relevant population	Results
				Data is reported elsewhere for glucosamine/chondroitin /combination arms (total n=389)	Placebo: 3 2 CVA were reported in the celecoxib group 1 abdominal wall abscess was reported in the celecoxib group.

[3262, Asmus, 2014]	2 identical RCTs	6 weeks	Patients aged ≥40 years with OA of the knee in a flare state, who had failed prior treatment with both prescription strength naproxen (at least 750 mg/day for 2 weeks) and ibuprofen (at least 1200 mg/day for 2 weeks) within the past 5 years due to either lack of efficacy	Celecoxib 200mg/day or placebo
				
				Study 1:
				celecoxib, n = 186;
				placebo, n = 184
				
				Study 2:
				celecoxib, n = 194;
				placebo, n = 186
					Study 1: Improvement from baseline to week 6 was significantly better for celecoxib than placebo for all WOMAC subscales (p < 0.001)
					One serious adverse event was reported for each group.
					
					Study 2: Improvement from baseline to week 6 was significantly better for celecoxib and placebo for the WOMAC physical function subscale, but the difference in the pain subscale was not significant.
					
					One serious adverse event was reported for each group.
					
					WOMAC Pain subscale least squares mean change (SE) from baseline to week 6:
					
					Study 1: -2.3 (0.42) 95% CI (-3.2 to -1.5), p= <0.001, favors celecoxib
					Study 2: -0.8 (0.39) 95% CI (-1.5 to 0.008), p= 0.052, favors celecoxib
					
					WOMAC function subscale least squares mean change from baseline to week 6:
					Study 1: -7.5 (1.4) 95% CI (-10.3 to -4.6), p= <0.001, favors celecoxib
					Study 2: -2.4 (1.2) 95% CI (-4.9 to -0.006), p= 0.049, favors celecoxib

Ref ID, Author, year	Study type	Duration	Population Description	Treatment given to relevant population	Results
			and/or tolerability Study 1: n=380 Study 2: n=388		
[3517, Huggins, 2012]	RCT	2 weeks	114 patients aged 18-75 years, with knee OA	Naproxen 500mg twice daily (n=36) or placebo (n=70) Study groups also included investigational drug PF-04457845 treatment arm (n=37). Since that drug is not on our list of interventions, we did not report data from that treatment arm.	<u>Mean differences (80% confidence intervals) from placebo in WOMAC scores at end of treatment:</u> Pain (out of 20): -1.13 (-1.79, -0.47) Function (out of 48): -4.49 (-9.04, -3.27) No serious adverse events were reported by the investigators.
[3884, Hochberg, 2011]	2 identical RCTs	12 weeks	Patients aged ≥50 years with a 6-month history of symptomatic, clinically diagnosed OA of the knee	Celecoxib 200mg once daily or placebo Study 1: celecoxib, n = 247; placebo, n = 124 Study 2: celecoxib, n = 247; placebo, n = 124	<u>Least mean change compared with placebo at 12 weeks:</u> **WOMAC pain subscale:** Study 1: -6.1, 95% CI (-11.8, -0.5), p=0.032, favors celecoxib Study 2: -4.6, 95% CI (-10.3, 1.2), p=0.118, favors celecoxib **WOMAC function subscale:** Study 1: -5.7, 95% CI (-11.2, -0.1), p=0.045, favors celecoxib Study 2: -4.5, 95% CI (-10.3, 1.3), p=0.131, favors celecoxib <u>Patients with one or more serious adverse events reported:</u> Study 1: celecoxib 5 (2.1%) vs. placebo 0 Study 2: celecoxib 3 (1.2%) vs. placebo 1 (0.8%)

Ref ID, Author, year	Study type	Duration	Population Description	Treatment given to relevant population	Results
			Study 1: n=619 Study 2: n=615		
[8177, Peeva, 2010]	RCT crossover	3 days	22 patients aged ≥45 years of age with knee OA >6 months	naproxen 500 mg bid or placebo in each of three periods * Study groups also included tramadol/acetaminophen treatment arm. Since that drug combination is not on our list of interventions, we did not report data from that treatment arm.	<u>WOMAC pain subscale score mean changes from baseline</u>: Day 1: naproxen -5.8, placebo -5.6 Day 3: naproxen -23.8, placebo -6.8 <u>WOMAC function subscale score mean changes from baseline:</u> Day 1: naproxen -6.9, placebo -5.2 Day 3: naproxen -22.1, placebo -6.2 No serious adverse events were reported by the investigators.
[1349, Schnitzer, 2005]	RCT	6 weeks	672 patients, aged 40 years or older, with knee OA	Rofecoxib 25mg/day (n=98) or naproxen 500mg/bid (n=117) or placebo (n=104) * Study groups also included investigational drug AZD3582 treatment arms. Since that drug is not on our list of interventions, we did not report data from those treatment arms.	<u>Adverse events:</u> Rofecoxib: 1 upper GI hemorrhage Naproxen: 1 upper GI hemorrhage, 1 myocardial infarction, 2 other SAEs Placebo: 1 myocardial infarction
[1612, McKenna, 2001]	RCT	6 weeks	182 patients, aged 40 years or	celecoxib 200mg/day (n=63) or rofecoxib	<u>Global pain VAS (100mm) least squares mean change from baseline at 6 weeks:</u> Celecoxib: -39

Ref ID, Author, year	Study type	Duration	Population Description	Treatment given to relevant population	Results
			older, with knee OA	25mg/day (n=59) or placebo (n=60)	Rofecoxib: -40 Placebo: -25 <u>Pain on walking VAS (100mm) least squares mean change from baseline at 6 weeks:</u> Celecoxib: -38 Rofecoxib: -38 Placebo: -25 One serious adverse event was reported in the celecoxib group.
[5147, Scott, 2000]	RCT	Up to 5 years; assessments reported after 4 weeks	812 patients with knee OA	Indomethacin, 25mg three times daily (n=202) or placebo (n=303). Study groups also included tiaprofenic acid treatment arm (n=307). Since that drug is not on our list of interventions, we did not report data from that treatment arm.	<u>Mean change in overall VAS Pain score at 4 weeks:</u> Indomethacin: -4.8 Placebo: -0.2 <u>Number of patients with severe overall pain at baseline vs. 4 weeks:</u> Indomethacin: 75/187 (40%) vs. 37/141 (21%) Placebo: 106/262 (40%) vs. 101/155 (39%) Investigators reported that after 4 weeks there were no further significant differences in overall pain between active treatment and placebo groups. Patients who remained on treatment for 12 months or longer also showed no measureable benefit from active treatment. Only one serious adverse event was reported, a GI bleed in the indomethacin group.
[6401, Simon, 1998]	RCT	2 weeks	293 patients with knee OA in flare	Celecoxib 200mg twice daily (n=73) or placebo (n=71). Data tabled for 200mg vs. placebo only, which	<u>Global pain (100mm VAS) mean change from baseline at 2 weeks:</u> Celecoxib: -30.52mm Placebo: -15.48mm

Ref ID, Author, year	Study type	Duration	Population Description	Treatment given to relevant population	Results
				represents usual daily dose.	
[3511, Makarowski, 1996]	RCT	6 weeks	347 patients with knee OA	Oxaprozin 1200 mg/day (n=116) or nabumetone 1500 mg/day (n=115) or placebo (n=116)	Knee pain on weight bearing, mean % change from baseline at 6 weeks: Oxaprozin - 47% vs. 30% placebo, $P \leq 0.05$ Nabumetone – 40% vs. 30% placebo, $P \leq 0.05$ Knee pain on motion, mean % change from baseline at 6 weeks: Oxaprozin - 56% vs. 34.5% placebo, $P \leq 0.05$ Nabumetone – 50.5% vs. 34.5% placebo, $P \leq 0.05$ No serious adverse events were reported by the investigators.
[7954, Dieppe, 1993]	RCT	2 years	89 patients with knee OA	51 patients completed the study. ITT was not attempted. Diclofenac slow release 100mg once daily (n=31) or placebo (n=21)	Number of patients with functional difficulty at entry and at study completion (2 years) **Walking:** Diclofenac: 6 (19%) vs. 7 (23%) Placebo: 2 (10%) vs. 8 (40%) **Stairs:** Diclofenac: 26 (84%) vs. 21 (68%) Placebo: 18 (90%) vs. 16 (80%)

Table 6. RCT data not suitable for effect size calculation or combining with other data (hip and knee OA)

Ref ID, Author, year	Study type	Duration	Population Description	Treatment given to relevant population	Results
[7134, Yocum, 2000]	Double blind RCT	12 weeks	OA of hip or knee	Meloxicam 7.5mg PO QD (n=153) Meloxicam 15mg PO QD (n=156)	**WOMAC pain (change from baseline)** Meloxicam 7.5mg = -3.4 Meloxicam 15mg = -14.5 Diclofenac 50mg bid = -4.5 Placebo = -2.2

				Diclofenac50mg PO BID (n=152) Placebo (n=155)	**WOMAC function (change from baseline)** Meloxicam 7.5mg = -10.4 Meloxicam 15mg = --12.6 Diclofenac 50mg bid = -14.9 Placebo = -7.2
[7041, Garner, 2005]	Cochrane Systematic Review	6 weeks	OA of hip or knee	Rofecoxib 12.5mg Rofecoxib 25mg Rofecoxib 125mg Placebo	**SAE** Rofecoxib 12.5mg 6 weeks 3 RCTs with 1388 participants Risk Ratio (M-H, Fixed, 95% CI) Effect Size 3.95 [1.06, 14.63] Rofecoxib 25mg 4 RCTs with 658 participants Risk Ratio (M-H, Fixed, 95% CI) Effect Size 0.47 [0.11, 2.08] Rofecoxib 125mg 1 RCT with 146 participants Risk Ratio (M-H, Fixed, 95% CI) Effect Size 6.81 [0.36, 129.61]
[3662, Zhao, 1999]	Double blind RCT	12 week	OA of knee	Celecoxib 100mg bid (n=197) Naproxen 500mg bid (n=198) Placebo (n=203)	**WOMAC pain (change from baseline)** Celecoxib 100mg bid = -3.1 Naproxen 500mg bid = -2.4 Placebo = -1.2 **WOMAC function (change from baseline)** Celecoxib 100mg bid = -9.5 Naproxen 500mg bid = -7.8 Placebo = -3.9

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PICO 57: Acetaminophen vs. no treatment for people with knee and/or hip OA.

Summary: The literature search identified 7 RCTs to evaluate this PICO question. Foure RCTs[1-3,7] were conducted in adults with symptomatic knee OA and three RCTs[4-6] were conducted in adults with knee or hip OA. Follow-up ranged from eight days to 24 weeks. Four studies[3-6] observed that participants in the acetaminophen group had greater improvements in pain (WOMAC Pain and 100mm VAS) than the placebo group with knee or hip OA. Micelli-Richard et al.[2] found no between-group difference in either pain or self-reported function. Findings of self-reported function were inconsistent between studies. Altman et al.[5] and Prior et al.[4] found greater improvements in self-reported function in the acetaminophen group, while conversely Case et al.[3] reported improvements favoring the placebo group, but results were imprecise due to wide confidence intervals and small study size. However, combined data analysis found a significant between-group difference in WOMAC function improvement favoring acetaminophen. The risk of serious adverse events overall and hepatotoxicity in particular was observed to be greater in the acetaminophen group, but the findings were inconclusive due to wide confidence intervals that cross the line of no effect. The quality of evidence was low, due primarily to variations in the magnitude of effects across studies and wide confidence intervals associated with

the effect estimates. A literature search update in August 2018 identified two additional relevant RCTs[8,9] that did not alter the findings in the table below.

Quality of evidence across all critical outcomes: Low

Acetaminophen compared to placebo for hip and knee OA											
Certainty assessment							Summary of findings				
№ of participants (studies) Follow-up	Risk of bias	Inconsistency	Indirectness	Imprecision	Publication bias	Overall certainty of evidence	Study event rates (%)		Relative effect (95% CI)	Anticipated absolute effects	
							With placebo	With acetaminophen		Risk with placebo	Risk difference with acetaminophen
WOMAC Pain subscale (Likert) 12 wks to 24 wks (lower scores indicate improvement)											
1136 (4 RCTs)	serious [a]	not serious	not serious	not serious	none	⨁⨁⨁◯ MODERATE	468	456	-	-	SMD **0.2 lower** (0.31 lower to 0.08 lower) **Favors acetaminophen**
WOMAC Function subscale (Likert/100mm), <12 wks (lower scores indicate improvement)											
779 (1 RCT)	serious [b]	not serious	not serious	not serious	none	⨁⨁⨁◯ MODERATE	374	405	-	-	SMD **0** (0.14 lower to 0.14 higher)
WOMAC Function subscale (Likert/100mm), 12 wks to 24 wks (lower scores indicate improvement)											
1136 (4 RCTs)	serious [a]	not serious	not serious	not serious	none	⨁⨁⨁◯ MODERATE	468	456	-	-	SMD **0.23 lower** (0.36 lower to 0.11 lower) **Favors acetaminophen**
Global pain (100mm VAS) (lower scores indicate improvement)											

Acetaminophen compared to placebo for hip and knee OA											
Certainty assessment							Summary of findings				
1489 (3 RCTs)	serious [b]	not serious	not serious	serious [c]	none	⨁⨁◯◯ LOW	728	761	-	-	SMD **0.16 lower** (0.34 lower to 0.03 higher)
Hepatic transaminases exceeded 3 x ULN											
867 (2 RCTs)	serious [d]	not serious	not serious	serious [e]	none	⨁⨁◯◯ LOW	1/440 (0.2%)	10/427 (2.3%)	**OR 7.37** (1.32 to 41.00)	2 per 1,000	**14 more per 1,000** (1 more to 83 more) **Favors placebo**
Total number of patients with serious adverse events											
3354 (7 RCTs)	serious [b]	not serious	not serious	serious [c]	none	⨁⨁◯◯ LOW	21/1531 (1.4%)	30/1611 (1.9%)	**OR 1.30** (0.76 to 2.21)	14 per 1,000	**5 more per 1,000** (3 fewer to 20 more)

CI: Confidence interval; **SMD:** Standardised mean difference; **OR:** Odds ratio

Explanations

a. 2/3 studies had lack of clarity about blinding of assessors and allocation concealment, and high attrition.

b. Randomization methods not described, lack of clarity about blinding of assessors and allocation concealment.

c. Wide 95% CI that crosses line of no effect.

d. 1/2 studies had lack of clarity about blinding of assessors and allocation concealment, and randomization methods not described.

e. Wide 95% CI and small number of events

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PICO 58: Bisphosphonates vs. no treatment for OA hip/knee

Summary. This PICO was addressed by 4 RCTs [1-4]. They showed no significant difference in WOMAC pain and function. VAS pain showed a significant improvement favoring bisphosphonate over no treatment; however, it was a small study with a wide CI.

Quality of evidence across all critical outcomes: Moderate

Table 1. Bisphosphonates compared to Placebo for OA of hip or knee											
Certainty assessment							**Summary of findings**				
№ of participants (studies) Follow-up	**Risk of bias**	**Inconsistency**	**Indirectness**	**Imprecision**	**Publication bias**	**Overall certainty of evidence**	**Number of Patients**		**Relative effect (95% CI)**	**Anticipated absolute effects**	
							With Placebo	**With Bisphosphonates**		**Risk with Placebo**	**Risk difference with Bisphosphonates**
WOMAC pain (change from baseline) >/= 12 months (lower scores indicate improvement)											
1010 (2 RCTs)	serious [a]	serious [b]	not serious	not serious	none	⨁⨁⨁◯ MODERATE	487	523	-	-	SMD **0.07 lower** (0.28 lower to 0.13 higher)
VAS pain (6 months) (0-100, lower scores indicate improvement)											
59 (1 RCT)	not serious	not serious	not serious	serious [c]	none	⨁⨁⨁◯ MODERATE	28	31	-	-	MD **15 lower** (29.35 lower to 0.65 lower) **Favors bisphosphanates**
WOMAC function (change from baseline) >/= 12 months (0-100, lower scores indicate improvement)											
968 (1 RCT)	serious [d]	not serious	not serious	not serious	none	⨁⨁⨁◯ MODERATE	475	493	-	-	MD **0.52 higher** (2.38 lower to 3.42 higher)

CI: Confidence interval; **SMD:** Standardised mean difference; **MD:** Mean difference

Explanations

a. Neither RCT provided information on randomization method or allocation concealment, and they provided no information or incomplete information on blinding.

b. High I^2 due to study effect sizes in different directions

c. Small study with wide 95% CI

d. No information on randomization method, allocation concealment, or blinding of outcome assessors.

Table 2. RCT data not suitable for effect size calculation or combining with other data

Ref ID, Author, year	Study type	Duration	Population Description	Treatment given to relevant population	Results
2218, Jokar, 2010	Double blind RCT	24 weeks	OA knee	Alendronate 70mg/week n=20 Placebo N=19	**WOMAC pain (change from baseline)** Alendronate = -2.4 Placebo = -2.9 **WOMAC function (change from baseline)** Alendronate = -2.9 Placebo = -2.55

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PICO 59: Duloxetine vs. no treatment in OA hip/knee

Summary. This PICO was addressed by 4 RCTs [1-4]. They showed a significant improvement in WOMAC pain and function favoring duloxetine over placebo. There was no difference in serious adverse events, although the wide 95% CI means that the possibility of a difference could not be

ruled out. A literature search update in August 2018 identified two additional relevant RCTs[5,6]; these studies did not alter the findings in the table below.

Quality of evidence across all critical outcomes: Moderate

Duloxetine compared to Placebo for OA hip or knee											
Certainty assessment							Summary of findings				
№ of participants (studies) Follow-up	Risk of bias	Inconsistency	Indirectness	Imprecision	Publication bias	Overall certainty of evidence	Number of Patients		Relative effect (95% CI)	Anticipated absolute effects	
							With Placebo	With Duloxetine		Risk with Placebo	Risk difference with Duloxetine
WOMAC Pain (0-20, lower scores indicate improvement)											
878 (3 RCTs)	not serious	not serious	not serious	not serious	none	⨁⨁⨁⨁ HIGH	443	435	-	-	MD **1.41 lower** (2.38 lower to 0.45 lower) **Favors duloxetine**
WOMAC Function (0-68, lower scores indicate improvement)											
1069 (3 RCTs)	not serious	not serious	not serious	not serious	none	⨁⨁⨁⨁ HIGH	454	615	-	-	MD **3.83 lower** (6.1 lower to 1.56 lower) **Favors duloxetine**
SAE											

Duloxetine compared to Placebo for OA hip or knee											
Certainty assessment							Summary of findings				
894 (3 RCTs)	not serious	not serious	not serious	serious [a]	none	⨁⨁⨁◯ MODERATE	8/450 (1.8%)	6/444 (1.4%)	**OR 0.92** (0.30 to 2.81)	18 per 1,000	**1 fewer per 1,000** (12 fewer to 31 more)

CI: Confidence interval; **MD:** Mean difference; **OR:** Odds ratio

Explanations

a. Wide 95% CI crosses line of no effect

References

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PICO 60. Other serotonin norepinephrine reuptake inhibitors compared to no treatment in patients with knee or hip OA

Summary. The literature searches did not identify any studies that addressed this question.

Quality of evidence across all critical outcomes: Very low

PICO 61. Tricyclic antidepressants compared to no treatment in patients with knee or hip OA

Summary. The literature searches did not identify any studies that addressed this question.

Quality of evidence across all critical outcomes: Very low

PICO 62: Tramadol vs. no treatment in OA hip/knee

Summary. This PICO was addressed by 8 RCTs [1-8]. They found a significant improvement in WOMAC pain, WOMAC function, and pain intensity in the tramadol group compared to the placebo group. Although there was no significant difference between the groups in regard to serious adverse events, the wide 95% CI around the summary effect size means that the possibility of a between-group difference could not be ruled out.

Quality of evidence across all critical outcomes: Moderate

Tramadol 100mg - 400mg daily compared to Placebo for patients with knee or hip OA											
Certainty assessment							**Summary of findings**				
№ of participants (studies) Follow-up	**Risk of bias**	**Inconsistency**	**Indirectness**	**Imprecision**	**Publication bias**	**Overall certainty of evidence**	**Number of Patients**		**Relative effect (95% CI)**	**Anticipated absolute effects**	
							With Placebo	**With Tramadol 100mg - 400mg daily**		**Risk with Placebo**	**Risk difference with Tramadol 100mg - 400mg daily**
WOMAC Pain (0-20, lower scores indicate improvement)											
129 (1 RCT)	not serious	not serious	not serious	not serious	none	⨁⨁⨁⨁ HIGH	66	63	-	-	MD **0.97 lower** (1.74 lower to 0.2 lower) **Favors tramadol**

Tramadol 100mg - 400mg daily compared to Placebo for patients with knee or hip OA											
Certainty assessment							Summary of findings				
WOMAC Pain (change from baseline) (0-500, lower scores indicate improvement)											
406 (1 RCT)	not serious	not serious	not serious	not serious	none	⨁⨁⨁⨁ HIGH	205	201	-	-	MD **37.3 lower** (61.14 lower to 13.46 lower) **Favors tramadol**
WOMAC Function (0-20, lower scores indicate improvement)											
129 (1 RCT)	not serious	not serious	not serious	not serious	none	⨁⨁⨁⨁ HIGH	66	63	-	-	MD **0.73 lower** (1.48 lower to 0.02 higher)
WOMAC Function (change from baseline) (0-1500, lower scores indicate improvement)											
406 (1 RCT)	not serious	not serious	not serious	not serious	none	⨁⨁⨁⨁ HIGH	205	201	-	-	MD **115.9 lower** (195.04 lower to 36.76 lower) **Favors tramadol**
Pain Intensity - NRS (absolute improvement) (lower scores indicate improvement)											

Tramadol 100mg - 400mg daily compared to Placebo for patients with knee or hip OA											
Certainty assessment							Summary of findings				
589 (1 RCT)	not serious	not serious	not serious	not serious	none	⨁⨁⨁⨁ HIGH	196	393	-	-	MD **0.74 higher** (0.39 higher to 1.09 higher) **Favors tramadol**
SAE											
1785 (3 RCTs)	not serious	not serious	not serious	serious [a]	none	⨁⨁⨁◯ MODERATE	5/485 (1.0%)	26/1300 (2.0%)	**OR 1.81** (0.43 to 7.65)	10 per 1,000	**8 more per 1,000** (6 fewer to 63 more)

CI: Confidence interval; **MD:** Mean difference; **OR:** Odds ratio

Explanations

a. Wide CI crosses no effect line

Table 2. RCT data not suitable for effect size calculation or combining with other data

Ref ID, Author, year	Study type	Duration	Population Description	Treatment given to relevant population	Results
3173, Babul, 2004	Double blind RCT	12 weeks	OA knee	Tramadol ER 200mg – 400mg daily n=124 Placebo N=122	**WOMAC pain (LS mean change from baseline)** Tramadol = -120.1 mm Placebo = -69.0 mm P-value = <0.001 **WOMAC function (LS mean change from baseline)** Tramadol = -407.0 mm Placebo = -208.5 mm P-Value = <0.001
3286, Malonne,	Double blind RCT	2 week	OA hip or knee Age=45-80	Tramadol LP 200mg daily n=85	**Global Pain Score (VAS) Change** Tramadol = -2.34 cm

2004				Placebo N=112	Placebo = -1.55 cm P=value = 0.010 **SAE** Tramadol = 0 Placebo = 1 (died suddenly unknown cause; 71y/o woman)
3131, Fishman, 2007	Double blind RCT	12 weeks	OA knee Age=40-75	Tramadol 100mg daily n=99 Tramadol 200mg daily n=107 Tramadol 300mg daily n=104 Placebo N=223	**WOMAC Pain improvement from baseline (%)** Tramadol 100mg daily Mean ± SD = 41.6 ± 50.2 Tramadol 200mg daily Mean ± SD = 42.8 ± 46.4 Tramadol 300mg daily Mean ± SD = 46.0 ± 39.9 Placebo Mean ± SD = 32.3 ± 48.2 **SAE** Tramadol 100mg = 1 Tramadol 300mg = 1 Placebo = 2
8258, Kean, 2009	Double blind RCT	12 weeks	OA knee Women Age=40-75	Tramadol 100mg daily WOMAC Pain n=69 WOMAC Function n=68 Tramadol 200mg daily WOMAC Pain n=70 WOMAC Function n=68 Tramadol 300mg daily WOMAC Pain n=63 WOMAC Function n=61 Placebo WOMAC Pain n=176	**WOMAC Pain improvement from baseline (%)** Tramadol 100mg daily Mean ± SD = 58.8 ± 37.1 Tramadol 200mg daily Mean ± SD = 53.0 ± 38.5 Tramadol 300mg daily Mean ± SD = 58.9 ± 38.8 Placebo Mean ± SD = 45.2 ± 43.8 **WOMAC Function improvement from baseline (%)**

				WOMAC Function n=168	Tramadol 100mg daily Mean ± SD = 56.9 ± 36.4 Tramadol 200mg daily Mean ± SD = 54.0 ± 33.8 Tramadol 300mg daily Mean ± SD = 53.4 ± 41.4 Placebo Mean ± SD = 41.9 ± 40.8

References

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PICO 63: Non-tramadol opioids vs. no treatment in OA hip/knee

Summary. This PICO was addressed by 15 placebo-controlled RCTs [1-15]. Meta-analysis of 12 RCTs found a small but statistically significant difference in WOMAC pain and function favoring non-tramadol opioids, but the difference was not clinically significant. There was a significant increase in serious adverse events in patients receiving non-tramadol opioids. A systematic review that included unpublished trials and trials published only as abstracts showed similar findings.[16]

Quality of evidence across all critical outcomes: Low

Non-tramadol Opioids compared to Placebo for Knee or Hip OA											
Certainty assessment							Summary of findings				
№ of participants (studies) Follow-up	Risk of bias	Inconsistency	Indirectness	Imprecision	Publication bias	Overall certainty of evidence	Number of Patients		Relative effect (95% CI)	Anticipated absolute effects	
							With Placebo	With Nontramadol opioids		Risk with Placebo	Risk difference with Nontramadol opiods
WOMAC Pain (change from baseline) (lower scores indicate improvement)											
2522 (12 RCTs)	serious [a]	serious [b]	not serious	not serious	none	⨁⨁◯◯ LOW	1326	1196	-	-	SMD **0.17 lower** (0.31 lower to 0.03 lower) **Favors opioids**
WOMAC Function (change from baseline) (lower scores indicate improvement)											
2054 (10 RCTs)	serious [a]	serious [b]	not serious	not serious	none	⨁⨁◯◯ LOW	1110	944	-	-	SMD **0.17 lower** (0.33 lower to 0.01 lower) **Favors opioids**
SAE											

Non-tramadol Opioids compared to Placebo for Knee or Hip OA											
Certainty assessment							Summary of findings				
3292 (9 RCTs)	serious [a]	not serious	not serious	not serious	none	⨁⨁⨁◯ MODERATE	30/1649 (1.8%)	49/1643 (3.0%)	**OR 1.66** (1.04 to 2.66)	18 per 1,000	**12 more per 1,000** (1 more to 29 more) **Favors placebo**

CI: Confidence interval; **SMD:** Standardised mean difference; **OR:** Odds ratio

Explanations

a. Some studies did not report randomization method or allocation concealment, several studies had high attrition

b. High I^2 due to study effect size variation

Table 2. Systematic review or RCT data not suitable for effect size calculation or combining with other data

Ref ID, Author, year	Study type	Duration	Population Description	Treatment given to relevant population	Results
Da Costa 2014	Systematic review	Median duration 1 month (range 3 days to 6 months)	OA knee or hip	Non-tramadol opioids vs. placebo	**Pain (SMD)(22 RCTs)** SMD -0.28 (95% CI -0.35 to -0.20), favors opioids **Function (SMD)(12 RCTs)** SMD -0.26 (95% CI -0.35 to -0.17), favors opioids
Zautra and Smith 2005	Double blind RCT	2 weeks	OA	Oxycodone (controlled release) vs placebo	**Pain (0-10)** P<0.0002 significant pain reduction favoring opioids
Kjaersgaard-Andersen 1990	Double blind RCT	1 month	OA hip	Codeine plus acetaminophen vs acetaminophen alone	**Percent patients with less pain at 4 weeks compared to baseline** Codeine/acetaminophen 45% vs acetaminophen 40%, p = not significant.

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PICO 64. Gabapentin compared to no treatment in patients with knee or hip OA

Summary. The literature searches did not identify any studies that addressed this question.

Quality of evidence across all critical outcomes: Very low

PICO 65. Pregabalin compared to no treatment in patients with knee or hip OA

Summary. The literature searches did not identify any studies that addressed this question.

Quality of evidence across all critical outcomes: Very low

PICO 66. Methotrexate compared to no treatment in patients with knee or hip OA

Summary. The literature searches did not identify any studies that addressed this question.

Quality of evidence across all critical outcomes: Very low

PICO 67: Colchicine vs. no treatment in patients with knee OA

This PICO was addressed by 3 double-blind RCTs [1-3]. They were small studies that showed conflicting findings regarding the impact of colchicine on improvement in pain; when combined in a meta-analysis, there was serious inconsistency and very serious imprecision in the effect estimate. One study reported no significant between-group difference in WOMAC function.

Quality of evidence across all critical outcomes: Very low

Colchicine 0.5mg BID compared to Placebo for OA of the knee											
Certainty assessment							**Summary of findings**				
№ of participants (studies) Follow-up	**Risk of bias**	**Inconsistency**	**Indirectness**	**Imprecision**	**Publication bias**	**Overall certainty of evidence**	**Number of patients**		**Relative effect (95% CI)**	**Anticipated absolute effects**	
							With Placebo	**With Colchicine 0.5mg BID**		**Risk with Placebo**	**Risk difference with Colchicine 0.5mg BID**
Pain (combines different pain measures) – 16 -20 weeks											
203 (3 RCTs)	not serious	serious[a]	not serious	very serious[b]	none	⨁◯◯◯ VERY LOW	101	102	-	-	**SMD 0.24 higher** (1.12 lower to 1.61 higher)
WOMAC Pain (0-100) – change from baseline to 16 weeks											
109 (1 RCT)	not serious	not serious	not serious	serious[c]	none	⨁⨁⨁◯ MODERATE	55	54	-	-	**MD 3.10 higher** (4.11 lower to 10.31 higher)
WOMAC Function (0-100) – change from baseline to 16 weeks											
109 (1 RCT)	not serious	not serious	not serious	serious[c]	none	⨁⨁⨁◯ MODERATE	55	54	-	-	**MD 1.10 lower** (8.03 lower to 5.83 higher)
VAS Pain (0-15, lower scores indicate improvement)											

Colchicine 0.5mg BID compared to Placebo for OA of the knee											
Certainty assessment							Summary of findings				
36 (1 RCT)	not serious	not serious	not serious	serious[d]	none	⨁⨁⨁◯ MODERATE	17	19	-	-	MD **3.4 lower** (5.3 lower to 1.5 lower) **Favors colchicine**
Physician global assessment (VAS)(0-15, higher scores indicate improvement)											
58 (1 RCT)	not serious	not serious	not serious	serious[d]	none	⨁⨁⨁⨁ MODERATE	29	29	-	-	MD **6.11 higher** (4.26 higher to 7.96 higher) **Favors colchicine**

CI: Confidence interval; **MD:** Mean difference

Explanations

a. I^2 = 95%

b. Very wide 95% CI includes possibility of a large effect in either direction.

c. Wide 95% CI

d. Single small study

References

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PICO 68. Glucosamine compared to no treatment for hip or knee OA

Summary: This PICO question is addressed by 17 direct RCTs.[1-17] However, since between-group differences favoring glucosamine only appeared in studies funded by industry, those studies were removed from our analyses based on evidence of industry bias. For the remaining studies,[1-3,6-8,12-16] the results for WOMAC pain and function from 3 to 24 months showed no significant between-group differences (Table 1). Serious adverse events did not differ significantly between groups, but the findings were imprecise due to the small number of events.

Quality of Evidence across all critical outcomes: Moderate.

Table 1. Glucosamine compared to Placebo for Hip or Knee OA

Certainty assessment							Summary of findings				
№ of participants (studies) Follow-up	**Risk of bias**	**Inconsistency**	**Indirectness**	**Imprecision**	**Publication bias**	**Overall certainty of evidence**	**Number of patients**		**Relative effect (95% CI)**	**Anticipated absolute effects**	
							With Placebo	**With Glucosamine**		**Risk with Placebo**	**Risk difference with Glucosamine**
WOMAC pain overall (0-20, lower scores indicate improvement)											
427 (2 RCTs)	not serious	not serious	not serious	not serious	none	⨁⨁⨁⨁ HIGH	215	212	-	-	MD **0.55 lower** (1.51 lower to 0.41 higher)
WOMAC pain 3 months (0-20, lower scores indicate improvement)											
541 (3 RCTs)	not serious	not serious	not serious	not serious	none	⨁⨁⨁⨁ HIGH	274	267	-	-	MD **0.69 higher** (0.72 lower to 2.1 higher)

Table 1. Glucosamine compared to Placebo for Hip or Knee OA											
Certainty assessment							Summary of findings				
WOMAC pain 6 months (0-20, lower scores indicate improvement)											
1178 (4 RCTs)	not serious	not serious	not serious	not serious	none	⨁⨁⨁⨁ HIGH	586	592	-	-	MD **0.76 lower** (1.74 lower to 0.21 higher)
WOMAC pain 12 months (0-20, lower scores indicate improvement)											
525 (2 RCTs)	not serious	not serious	not serious	not serious	none	⨁⨁⨁⨁ HIGH	262	263	-	-	MD **0.19 lower** (1.02 lower to 0.65 higher)
WOMAC pain 24 months (0-20, lower scores indicate improvement)											
790 (3 RCTs)	serious [a]	not serious	not serious	not serious	none	⨁⨁⨁⨁ HIGH	393	397	-	-	MD **0.16 lower** (0.95 lower to 0.63 higher)
WOMAC function overall (0-68, lower scores indicate improvement)											
427 (2 RCTs)	not serious	serious [c]	not serious	serious [d]	none	⨁⨁◯◯ LOW	215	212	-	-	MD **1.06 lower** (3.6 lower to 1.47 higher)
WOMAC Function 3 months (0-68, lower scores indicate improvement)											

Table 1. Glucosamine compared to Placebo for Hip or Knee OA											
Certainty assessment							Summary of findings				
541 (3 RCTs)	not serious	not serious	not serious	serious [d]	none	⨁⨁⨁◯ MODERATE	274	267	-	-	MD **0.69 higher** (3.38 lower to 4.76 higher)
WOMAC function 6 months (0-68, lower scores indicate improvement)											
1178 (4 RCTs)	not serious	not serious	not serious	serious [d]	none	⨁⨁⨁◯ MODERATE	586	592	-	-	MD **0.47 lower** (6.31 lower to 5.36 higher)
WOMAC Function 12 months (0-68, lower scores indicate improvement)											
222 (1 RCT)	not serious	not serious	not serious	serious [d]	none	⨁⨁⨁◯ MODERATE	111	111	-	-	MD **0.1 higher** (4.19 lower to 4.39 higher)
WOMAC Function 24 months (0-68, lower scores indicate improvement)											
487 (2 RCTs)	not serious	not serious	not serious	serious [d]	none	⨁⨁⨁◯ MODERATE	242	245	-	-	MD **1.15 lower** (4.81 lower to 2.51 higher)

Table 1. Glucosamine compared to Placebo for Hip or Knee OA											
Certainty assessment							**Summary of findings**				
SAE											
222 (1 RCT)	not serious	not serious	not serious	serious [d]	none	⨁⨁⨁◯ MODERATE	2/111 (1.8%)	4/111 (3.6%)	**OR 2.04** (0.37 to 11.36)	18 per 1,000	**18 more per 1,000** (11 fewer to 154 more)

CI: Confidence interval; **MD:** Mean difference; **OR:** Odds ratio; **SMD**: Standardized mean difference

Explanations

a. One study had selective outcome reporting

b. One or more studies had selective outcome reporting or inadequate allocation concealment

c. I-squared is 75%, mean values of both studies on the opposite sides of a no-effect line

d. Wide 95% CI crossing line of no effect

Table 2. RCT data not suitable for effect size calculation or combining with other data

Author, year	Study type	Duration	Population Description	Treatment given to relevant population	Results
993 Rovati 1992	Double-blind RCT	6 weeks	OA knee patients	Group A: Glucosamine 1500 mg/day or Group B: placebo	Lequsene's index response rate (ITT analysis): 4 weeks: Group A 66/126 (52%); Group B 46/126 (37%) 6 weeks: Group A 40/79 (51%); Group B 23/76 (32%)

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PICO 69: Chondroitin versus no treatment for hip or knee OA

Summary: This PICO question is addressed by 18 direct RCTs[1-18]. However, as with glucosamine there was clear evidence of industry bias; only industry-funded trials found positive results for pain and function favoring chondroitin over placebo. Therefore, these studies were removed from our analyses. For the remaining 4 RCTs,[3,9,17,18] WOMAC pain and function subscales found no significant between-group difference at any time point from 6 to 24 months. Serious adverse events did not differ significantly between groups, but the findings are imprecise.

Quality of Evidence across all critical outcomes: Moderate.

Table 1. Chondroitin compared to placebo for OA of the knee or hip

Certainty assessment							Summary of findings				
№ of participants (studies) Follow-up	Risk of bias	Inconsistency	Indirectness	Imprecision	Publication bias	Overall certainty of evidence	Number of patients		Relative effect (95% CI)	Anticipated absolute effects	
							With placebo	With Chondroitin		Risk with placebo	Risk difference with Chondroitin
WOMAC pain, 6 months (0-500, lower scores indicate improvement)											

Table 1. Chondroitin compared to placebo for OA of the knee or hip											
Certainty assessment							Summary of findings				
631 (1 RCT)	not serious	not serious	not serious	serious [a]	none	⨁⨁⨁◯ MODERATE	313	318	-	-	MD **2.2 higher** (15.02 lower to 19.42 higher)
WOMAC pain, 12 months (0-20, lower scores indicate improvement)											
302 (1 RCT)	not serious	not serious	not serious	not serious	none	⨁⨁⨁⨁ HIGH	151	151	-	-	MD **0.2 higher** (0.64 lower to 1.04 higher)
WOMAC pain, 2 years (lower scores indicate improvement)											
859 (3 RCTs)	not serious	not serious	not serious	not serious	none	⨁⨁⨁⨁ HIGH	432	427	-	-	SMD **0.01 lower** (0.14 lower to 0.12 higher)
WOMAC function, 6 months (0-1500, lower scores indicate improvement)											
631 (1 RCT)	not serious	not serious	not serious	serious [a]	none	⨁⨁⨁◯ MODERATE	313	318	-	-	MD **8.2 lower** (63.57 lower to 47.17 higher)

Table 1. Chondroitin compared to placebo for OA of the knee or hip											
Certainty assessment							**Summary of findings**				
WOMAC function, 12 months (0-20, lower scores indicate improvement)											
302 (1 RCT)	not serious	not serious	not serious	not serious	none	⨁⨁⨁⨁ HIGH	151	151	-	-	MD **0.3 lower** (3.07 lower to 2.47 higher)
WOMAC function, 2 years (lower scores indicate improvement)											
859 (3 RCTs)	not serious	not serious	not serious	not serious	none	⨁⨁⨁⨁ HIGH	432	427	-	-	SMD **0.03 lower** (0.16 lower to 0.11 higher)
SAE											
612 (3 RCTs)	not serious	not serious	not serious	serious [a]	none	⨁⨁⨁◯ MODERATE	11/306 (3.6%)	13/306 (4.2%)	OR 1.19 (0.52 to 2.72)	36 per 1,000	**7 more per 1,000** (17 fewer to 56 more)

CI: Confidence interval; **MD:** Mean difference; **OR:** Odds ratio

Explanations

a. Wide 95% CI crossing line of no effect

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PICO 70: Glucosamine + chondroitin versus no treatment for hip or knee OA

Summary: This PICO question is addressed by 10 direct RCTs[1-10]. However, as noted for PICO 68 and 69, there was some evidence of industry bias in that the only positive findings for glucosamine plus chondroitin came from industry-funded studies. Therefore, we removed these studies from the analysis. For the remaining studies,[2,7-10] the results across all outcomes show no significant difference between glucosamine/chondroitin and placebo in pain, function, or serious adverse events. All findings were inconclusive due to imprecision in effect estimates.

Quality of Evidence across outcomes: Moderate

Glucosamine plus Chondroitin compared to Placebo for Knee or Hip OA											
Certainty assessment							**Summary of findings**				
№ of participants (studies) Follow-up	**Risk of bias**	**Inconsistency**	**Indirectness**	**Imprecision**	**Publication bias**	**Overall certainty of evidence**	**Number of patients**		**Relative effect (95% CI)**	**Anticipated absolute effects**	
							With Placebo	**With Glucosamine plus Chondroitin**		**Risk with Placebo**	**Risk difference with Glucosamine plus Chondroitin**
WOMAC pain, 6 months (lower scores indicate improvement)											
630 (1 study)	not serious	not serious	not serious	serious [a]	none	⨁⨁⨁◯ MODERATE	313	317	-	-	SMD **0.13 lower** (0.28 lower to 0.03 higher)
WOMAC pain 12 months (lower scores indicate improvement)											
303 (1 study)	not serious	not serious	not serious	serious [a]	none	⨁⨁⨁◯ MODERATE	151	152	-	-	SMD **0.05 lower** (0.28 lower to 0.17 higher)
WOMAC pain 24 months (lower scores indicate improvement)											
563 (2 studies)	not serious	not serious	not serious	serious [a]	none	⨁⨁⨁◯ MODERATE	282	281	-	-	SMD **0.01 lower** (0.17 lower to 0.16 higher)
WOMAC total score, 6 months (lower scores indicate improvement)											

Glucosamine plus Chondroitin compared to Placebo for Knee or Hip OA											
Certainty assessment							Summary of findings				
99 (1 study)	not serious	not serious	not serious	serious [a]	none	⨁⨁⨁◯ MODERATE	50	49	-	-	SMD **0.04 lower** (0.43 lower to 0.36 higher)
HAQ pain, 6 months (lower scores indicate improvement)											
630 (1 study)	not serious	not serious	not serious	serious [a]	none	⨁⨁⨁◯ MODERATE	313	317	-	-	MD **4.2 lower** (8.64 lower to 0.24 higher)
WOMAC function, 6 months (lower scores indicate improvement)											
630 (1 study)	not serious	not serious	not serious	serious [a]	none	⨁⨁⨁◯ MODERATE	313	317	-	-	SMD **0.14 lower** (0.29 lower to 0.02 higher)
WOMAC function 24 months (lower scores indicate improvement)											
260 (1 study)	not serious	not serious	not serious	serious [a]	none	⨁⨁⨁◯ MODERATE	131	129	-	-	SMD **0.14 higher** (0.1 lower to 0.39 higher)
SAE, 6 months											

Glucosamine plus Chondroitin compared to Placebo for Knee or Hip OA											
Certainty assessment							Summary of findings				
158 (1 study)	not serious	not serious	not serious	serious [a]	none	⨁⨁⨁◯ MODERATE	2/78 (2.6%)	2/80 (2.5%)	**OR 0.97** (0.13 to 7.09)	26 per 1,000	**1 fewer per 1,000** (22 fewer to 132 more)

CI: Confidence interval; **SMD:** Standardised mean difference; **OR:** Odds ratio; **MD:** Mean difference

Explanations

a. Wide CI crossing significant effect and no-effect lines

b. I-squared is 99%

c. I-squared is 90%

d. Wide CI from small to very significant effect, small sample

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PICO 71: Vitamin D versus no treatment for hip or knee OA

Summary: This PICO question is addressed by 4 direct RCTs [1-4]. The results for WOMAC pain and function subscales at different time points were slightly in favor of vitamin D over placebo, although at most time points the findings were imprecise. Combining data from all studies revealed a small statistically significant difference favoring vitamin D, but the difference may not be clinically significant and the heterogeneity in effect sizes among different studies is high. The results for SAE at 6 months and 3 years had high imprecision due to wide 95% CIs around the effect estimates.

Quality of Evidence across outcomes: Low

Vitamin D compared to Placebo for Knee or Hip OA

Certainty assessment							Summary of findings				
№ of participants (studies) Follow-up	**Risk of bias**	**Inconsistency**	**Indirectness**	**Imprecision**	**Publication bias**	**Overall certainty of evidence**	**Number of patients**		**Relative effect (95% CI)**	**Anticipated absolute effects**	
							With Placebo	**With Vitamin D**		**Risk with Placebo**	**Risk difference with Vitamin D**
WOMAC Pain (combined different scales) 6 to 36 months											
1130 (4 RCTs)	not serious	serious[a]	not serious	serious[b]	none	⨁⨁◯◯ LOW	570	560	-	-	**SMD 0.32 lower** (0.63 lower to 0.02 lower) **Favors vitamin D**
WOMAC Pain (combined different scales) 6 to 36 months											
1130 (4 RCTs)	not serious	serious[a]	not serious	serious[b]	none	⨁⨁◯◯ LOW	570	560	-	-	**SMD 0.34 lower** (0.61 lower to 0.07 lower) **Favors vitamin D**
WOMAC pain, 6 months (0-500, lower scores indicate improvement)											

Vitamin D compared to Placebo for Knee or Hip OA											
Certainty assessment							**Summary of findings**				
413 (1 RCT)	not serious	not serious	not serious	serious [c]	none	⨁⨁⨁◯ MODERATE	204	209	-	-	MD **14.8 lower** (32.38 lower to 2.78 higher)
WOMAC pain, 12 months (0-20, lower scores indicate improvement)											
103 (1 RCT)	not serious	not serious	not serious	serious [d]	none	⨁⨁⨁◯ MODERATE	51	52	-	-	MD **1.71 lower** (3.28 lower to 0.14 lower) **Favors vitamin D**
WOMAC pain, 2 years (0-20, lower scores indicate improvement)											
146 (1 RCT)	not serious	not serious	not serious	serious [c]	none	⨁⨁⨁◯ MODERATE	73	73	-	-	MD **0.85 lower** (2.1 lower to 0.4 higher)
WOMAC pain, 3 years (0-20, lower scores indicate improvement)											
474 (1 RCT)	not serious	not serious	not serious	serious [c]	none	⨁⨁⨁◯ MODERATE	237	237	-	-	MD **0.79 lower** (2.31 lower to 0.73 higher)

Vitamin D compared to Placebo for Knee or Hip OA											
Certainty assessment							**Summary of findings**				
WOMAC function, 6 months (0-1700, lower scores indicate improvement)											
413 (1 RCT)	not serious	not serious	not serious	not serious	none	⨁⨁⨁⨁ HIGH	204	209	-	-	MD **72.9 lower** (126.05 lower to 19.75 lower) **Favors vitamin D**
WOMAC function, 12 months (0-68, lower scores indicate improvement)											
103 (1 RCT)	not serious	not serious	not serious	serious [c]	none	⨁⨁⨁◯ MODERATE	51	52	-	-	MD **2.05 lower** (2.91 lower to 1.19 lower) **Favors vitamin D**
WOMAC function, 2 years (0-68, lower scores indicate improvement)											
146 (1 RCT)	not serious	not serious	not serious	serious [c]	none	⨁⨁⨁◯ MODERATE	73	73	-	-	MD **3.15 lower** (6.61 lower to 0.31 higher)
WOMAC function, 3 years (0-68, lower scores indicate improvement)											

Vitamin D compared to Placebo for Knee or Hip OA											
Certainty assessment							**Summary of findings**				
474 (1 RCT)	not serious	not serious	not serious	not serious	none	⨁⨁⨁⨁ HIGH	237	237	-	-	MD **0.65 lower** (2.09 lower to 0.79 higher)
SAE, 6 months											
413 (1 RCT)	not serious	not serious	not serious	serious [c]	none	⨁⨁⨁◯ MODERATE	7/204 (3.4%)	11/209 (5.3%)	**OR 1.56** (0.59 to 4.12)	34 per 1,000	**18 more per 1,000** (14 fewer to 93 more)
SAE, 3 years											
474 (1 RCT)	not serious	not serious	not serious	serious [c]	none	⨁⨁⨁◯ MODERATE	64/237 (27.0%)	59/237 (24.9%)	**OR 0.90** (0.59 to 1.35)	270 per 1,000	**20 fewer per 1,000** (91 fewer to 63 more)

CI: Confidence interval; **MD:** Mean difference; **OR:** Odds ratio

Explanations

a. I^2 = 82%

b. Wide CI that includes possibility of no meaningful effect.

c. Wide CI crossing line of no effect

d. small sample size, wide 95% CI close to the line of no effect

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PICO 72. Fish oil compared to no treatment in patients with knee or hip OA

Summary. The literature searches identified one study that compared high-dose fish oil (4.5 g omega-3 fatty acids) 15 ml/day vs low-dose fish oil (0.45 g omega-3 fatty acids) 15 ml/day in patients with knee OA. At 2 year follow-up, WOMAC pain and function showed significantly greater improvement in the low dose group, although the difference is probably not clinically significant. Adverse events did not differ between groups.

Quality of evidence across all critical outcomes: Moderate

Table 1. RCT data not suitable for effect size calculation

Author, year	Study type	Duration	Population Description	Treatment given to relevant population	Results
3872 Hill 2016	Double-blind RCT	2 years	202 OA knee patients	High-dose fish oil (4.5 g omega-3 fatty acids) 15 ml/day vs low-dose fish oil (0.45 g omega-3 fatty acids) 15 ml/day.	WOMAC pain at 2 years (intention to treat analysis) High dose – low dose Adjusted Mean (SE): 3.1 (1.3), p=0.014 WOMAC function at 2 years (intention to treat analysis) High dose – low dose Adjusted Mean (SE): 7.9 (4.0). p=0.046 Adverse events were common and did not occur more frequently in either group. Serious adverse events were primarily non-elective hospital admissions (overall hospital admissions did not differ (37 in low-dose, 38 in high dose).

References:

1. Hill CL, March LM, Aitken D, Lester SE, Battersby R, Hynes K, et al. Fish oil in knee osteoarthritis: a randomised clinical trial of low dose versus high dose. Ann Rheum Dis 2016; 75:23-29.

PICO 73: Anti-nerve growth factor vs. no treatment in hip or knee OA

Summary. This PICO was addressed by 8 RCTs [1-8]. Tanezumab (4 RCTs) showed a significant difference in WOMAC pain (p=0.01) and function (p=0.005) indicating improvement but not in pain during walking (VAS). Fulranumab (1 RCT) and Fusinumab (1 RCT) showed no difference in WOMAC pain (p=0.85 and p=0.77 respectively) or function (p=0.81 and p=0.74 respectively). In our meta-analysis of 7 RCTs, serious adverse events were slightly and significantly higher in the Anti-nerve growth factor arms compared to no treatment arms, but the finding was imprecise because of the wide 95% CI that nearly crossed the line of no effect. A literature search update in August 2018 identified an additional relevant RCT of tanezumab[9], but the study did not alter the findings in the table below.

Quality of evidence across all critical outcomes: Moderate

Table 1. Anti-nerve growth factor compared to placebo for knee or hip OA

Certainty assessment							Summary of findings				
№ of participants (studies) Follow-up	**Risk of bias**	**Inconsistency**	**Indirectness**	**Imprecision**	**Publication bias**	**Overall certainty of evidence**	**Number of Patients**		**Relative effect (95% CI)**	**Anticipated absolute effects**	
							With placebo	**With Anti-nerve growth factor**		**Risk with placebo**	**Risk difference with Anti-nerve growth factor**
WOMAC pain, mean change at 16 to 24 wks followup (lower scores indicate improvement)											
1265 (6 RCTs)	not serious	not serious	not serious	serious [a]	none	⨁⨁⨁◯ MODERATE	625	640	-	-	SMD **0.19 lower** (0.37 lower to 0.01 lower) **Favors ANGF**
Pain during walking (VAS) change from baseline (0-100, lower scores indicate improvement)											

Table 1. Anti-nerve growth factor compared to placebo for knee or hip OA											
Certainty assessment							Summary of findings				
29 (1 RCT)	not serious	not serious	not serious	serious [b]	none	⨁⨁⨁◯ MODERATE	14	15	-	-	MD **4 lower** (20.08 lower to 12.08 higher)
WOMAC function, mean change at 16 to 24 wks followup (lower scores indicate improvement)											
1265 (6 RCTs)	not serious	not serious	not serious	serious [a]	none	⨁⨁⨁◯ MODERATE	625	640	-	-	SMD **0.24 lower** (0.46 lower to 0.01 lower) **Favors ANGF**
SAEs (serious adverse events)											
1387 (7 RCTs)	not serious	not serious	not serious	serious [a]	none	⨁⨁⨁◯ MODERATE	26/684 (3.8%)	43/703 (6.1%)	**OR 1.76** (1.04 to 2.99)	38 per 1,000	**27 more per 1,000** (1 more to 68 more) **Favors placebo**
severe adverse events											
148 (1 RCT)	not serious	not serious	not serious	serious [b]	none	⨁⨁⨁◯ MODERATE	2/74 (2.7%)	3/74 (4.1%)	**OR 1.52** (0.25 to 9.38)	27 per 1,000	**13 more per 1,000** (20 fewer to 180 more)
osteonecrosis											
309 (1 RCT)	not serious	not serious	not serious	serious [b]	none	⨁⨁⨁◯ MODERATE	0/155 (0.0%)	1/154 (0.6%)	**OR 3.04** (0.12 to 75.18)	0 per 1,000	**0 fewer per 1,000** (0 fewer to 0 fewer)

Table 1. Anti-nerve growth factor compared to placebo for knee or hip OA											
Certainty assessment							Summary of findings				
clinically significant neurologic AE											
653 (2 studies)	not serious	not serious	not serious	serious [b]	none	⨁⨁⨁◯ MODERATE	2/327 (0.6%)	2/326 (0.6%)	**OR 0.96** (0.14 to 6.57)	6 per 1,000	**0 fewer per 1,000** (5 fewer to 33 more)

CI: Confidence interval; **SMD:** Standardised mean difference; **MD:** Mean difference; **OR:** Odds ratio

Explanations

a. Very close to no effect line

b. Crosses no effect line

Table 2. RevMan data not suitable for GRADEPro

Ref ID, Author, year	Study type	Duration	Population Description	Treatment given to relevant population	Results
5173, Sanga, 2017	Double blind RCT	49 weeks	OA hip or knee 40-80y/o	Fulranumab 3mg Q4weeks N=68 Placebo N=59	**WOMAC pain score** Fulranumab 13 week = 71 Fulranumab 25 week = 61 Fulranumab 49 week = 45 Placebo 13 week = 66 Placebo 25 week = 48 Placebo 49 week = 40 **WOMAC function score** Fulranumab 13 week = 71 Fulranumab 25 week = 61 Fulranumab 49 week = 45

					Placebo 13 week = 66 Placebo 25 week = 48 Placebo 49 week = 40

References

1. Sanga P, Katz N, Polverejan E, Wang S, Kelly KM, Haeussler J, et al. Long-Term Safety and Efficacy of Fulranumab in Patients With Moderate-to-Severe Osteoarthritis Pain: A Phase II Randomized, Double-Blind, Placebo-Controlled Extension Study. Arthritis Rheumatol. 2017;69(4):763-773.
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PICO 74. Tumor necrosis factor inhibitor compared to no treatment in patients with knee or hip OA

Summary. The literature searches identified one RCT[1] and one observational comparative study[2] that indirectly addressed this question by comparing intra-articular TNFi knee injection (10 mg etanercept or adalimumab) to intra-articular HA injection (25 mg). A combined analysis revealed no significant between-group differences in VAS pain or WOMAC pain and function at 4 weeks post-injection. One study reported no

adverse events, while the RCT reported one serious adverse event (pulmonary infection) in the adalimumab group. However, all findings were inconclusive due to imprecision in the effect estimates.

Quality of evidence across all critical outcomes: Very low

TNF Inhibitor compared to HA for Knee OA											
Certainty assessment							Summary of findings				
№ of participants (studies) Follow-up	Risk of bias	Inconsistency	Indirectness	Imprecision	Publication bias	Overall certainty of evidence	Number of patients		Relative effect (95% CI)	Anticipated absolute effects	
							With HA	With TNF Inhibitor		Risk with HA	Risk difference with TNF Inhibitor
VAS pain (0-10, 4 weeks)											
95 (1 RCT, 1 observational study)	very serious [a]	not serious	serious [b]	serious [c]	none	⨁◯◯◯ VERY LOW	48	47	-	-	MD **1.68 lower** (4.31 lower to 0.95 higher)
WOMAC pain (0-20, 4 weeks)											
95 (1 RCT, 1 observational study)	very serious [a]	not serious	serious [b]	serious [c]	none	⨁◯◯◯ VERY LOW	48	47	-	-	MD **3.68 lower** (8.27 lower to 0.91 higher)
WOMAC function (0-68, 4 weeks)											
95 (1 RCT, 1 observational study)	very serious [a]	not serious	serious [b]	serious [c]	none	⨁◯◯◯ VERY LOW	48	47	-	-	MD **10.35 lower** (21.11 lower to 0.41 higher)

TNF Inhibitor compared to HA for Knee OA											
Certainty assessment							**Summary of findings**				
Serious adverse events											
56 (1 RCT)	serious [d]	not serious	serious [b]	very serious [e]	none	⨁◯◯◯ VERY LOW	0/28 (0.0%)	1/28 (3.6%)	**OR 3.11** (0.12 to 79.64)	0 per 1,000	**0 fewer per 1,000** (0 fewer to 0 fewer)

CI: Confidence interval; **MD:** Mean difference; **OR:** Odds ratio

Explanations

a. One study not randomized, neither study blinded

b. The comparator of interest is no treatment, not HA

c. Wide 95% CI that overlaps line of no effect

d. No blinding

e. Only 1 event, extreme imprecision in effect estimate

References

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2. Ohtori S, Orita S, Yamauchi K, Eguchi Y, Ochiai N, Kishida S, et al. Efficacy of direct injection of etanercept into knee joints for pain in moderate and severe knee osteoarthritis. Yonsei Med J 2015;56(5):1379-1383.

PICO 75. Interleukin 1 receptor antagonist compared to no treatment for knee OA

Summary. Our searches identified one RCT that compared intra-articular injection of Anakinra to intra-articular saline injections in patients with knee OA.[1] Anakinra (150mg) did not show a significant difference from saline in terms of reducing VAS pain at 4 to 12 weeks, or in serious adverse event rates (see Table below). A lower dose of Anakinra (50 mg) showed similar results (data not shown).

Overall quality of evidence across all critical outcomes: Low

IL-1 compared to saline for knee OA											
Certainty assessment							**Summary of findings**				
№ of participants (studies) Follow-up	**Risk of bias**	**Inconsistency**	**Indirectness**	**Imprecision**	**Publication bias**	**Overall certainty of evidence**	**Number of patients**		**Relative effect (95% CI)**	**Anticipated absolute effects**	
							With saline	**With IL-1**		**Risk with saline**	**Risk difference with IL-1**
VAS pain at 4 weeks, change scores (0-100, lower scores indicate improvement)											
136 (1 RCT)	not serious	not serious	not serious	serious [a]	none	⨁⨁⨁◯ MODERATE	69	67	-	-	MD **4.5 lower** (13.53 lower to 4.53 higher)
VAS pain at 12 weeks, change scores (0-100, lower scores indicate improvement)											
136 (1 RCT)	not serious	not serious	not serious	serious [a]	none	⨁⨁⨁◯ MODERATE	69	67	-	-	MD **4.2 lower** (13.38 lower to 4.98 higher)
SAEs											
136 (1 RCT)	not serious	not serious	not serious	very serious [b]	none	⨁⨁◯◯ LOW	1/69 (1.4%)	1/67 (1.5%)	**OR 1.03** (0.06 to 16.82)	14 per 1,000	**1 more per 1,000** (13 fewer to 235 more)

CI: Confidence interval; **MD:** Mean difference; **OR:** Odds ratio

Explanations

a. Wide 95% CI that overlaps line of no effect
b. Very wide CI and very few events

References

1. Chevalier X1, Goupille P, Beaulieu AD, Burch FX, Bensen WG, Conrozier T, et al. Intraarticular injection of anakinra in osteoarthritis of the knee: a multicenter, randomized, double-blind, placebo-controlled study. Arthritis Rheum. 2009 Mar 15;61(3):344-352.

PICO 76. NSAIDs compared to acetaminophen for patients with knee and/or hip OA

Summary: Fifteen RCTs met inclusion criteria for this comparison. Pain (Table 1): There was heterogeneity among RCTs comparing pain and function with oral nsaids vs acetaminophen with respect to how pain was assessed. In summary, RCTs evaluating pain level post intervention found lower statistically significant WOMAC pain[1] with oral nsaids use compared to acetaminophen use, but not significantly when pain level was assessed by KOOS[2] or VAS at movement.[3] When change in pain from baseline was assessed, there was insignificant lower pain with oral nsaid use when measured by WOMAC[4-6] or HAQ pain[7,8] scale but significantly lower pain when assessed using VAS pain scale[9]. While the majority of the evidence comes from RCTs that were double blinded, the major limitation of these studies was lack of a description of allocation concealment which can introduce bias. An RCT assessing pain using a different pain scale (0-4) with activity and rest found naproxen use with greater improvement than acetaminophen (Table 3).[10] In another RCT, lower mean WOMAC pain level was noted for rofecoxib (cox-2 inhibitor) 25mg use compared to acetaminophen but no SD or Confidence Interval (CI) were provided which limited the interpretation of this study.[11] Similarly, greater improvement in WOMAC pain was reported by another study with rofecoxib 25 mg use compared to acetaminophen but again without SD or CI, results could not be interpreted.[12]

Function (Table 1): RCTs assessing self-report function post intervention with oral nsaids vs acetaminophen found a significantly improved function level with nsaid use when assessed using WOMAC[1] but not when using KOOS[2]. When assessing change in function from baseline, greater improvement in WOMAC score was reported with nsaid use, although results did not reach statistical significance[4-6]. No meaningful change in function was noted when assessed using HAQ[7,8]. When function was assessed objectively, no between-group difference was noted for 50 meter walk time.[3]

Adverse events (Table 1): One RCT found no significant between-group difference in the risk of serious adverse effects, gastrointestinal or cardiovascular side effects,[10] but the study was underpowered to detect a statistically significant difference. Another study that was not included in this evidence table reported greater serious adverse effects with acetaminophen and rofecoxib 25mg compared to celcoxib and rofecoxib 12.5mg. This study also reported no difference in cardiovascular adverse effects between any of the 4 groups (acetaminophen, celecoxib, rofecoxib 12.5mg and rofecoxib 25mg)(Table 2). [13]

Quality of evidence across all critical outcomes: Low

Table 1: NSAIDS compared to acetaminophen pain and function outcomes for patients with knee or hip OA

Certainty assessment							Summary of findings				
№ of participants (studies) Follow-up	**Risk of bias**	**Inconsistency**	**Indirectness**	**Imprecision**	**Publication bias**	**Overall certainty of evidence**	**Number of participants**		**Relative effect (95% CI)**	**Anticipated absolute effects**	
							With acetaminophen pain and function outcomes	**With NSAIDS**		**Risk with acetaminophen pain and function outcomes**	**Risk difference with NSAIDS**
WOMAC pain (mean, post)(0-100, lower scores indicate improvement)											
217 (1 RCT)	serious [a]	not serious	not serious	not serious	none	⨁⨁⨁◯ MODERATE	109	108	-	-	MD **8.5 lower** (13.16 lower to 3.84 lower) **Favors NSAIDs**
WOMAC pain (mean change from baseline)(lower scores indicate improvement)											
543 (3 RCTs)	serious [a]	not serious	not serious	not serious	none	⨁⨁⨁◯ MODERATE	259	284	-	-	SMD **0.14 lower** (0.31 lower to 0.02 higher)
KOOS pain (mean, post)(0-100, higher scores indicate improvement)											
104 (1 RCT)	serious [b]	not serious	not serious	serious [c]	none	⨁⨁◯◯ LOW	52	52	-	-	MD **2.6 higher** (5.17 lower to 10.37 higher)
VAS pain on movement (mean, post)(0-20, lower scores indicate improvement)											

178 (1 RCT)	serious [a]	not serious	not serious	not serious	none	⨁⨁⨁◯ MODERATE	88	90	-	-	MD **0.21 higher** (0.66 lower to 1.08 higher)
VAS pain (mean change from baseline)(0-100, lower scores indicate improvement)											
839 (2 RCTs)	serious [a]	not serious	not serious	not serious	none	⨁⨁⨁◯ MODERATE	368	471	-	-	MD **5.6 lower** (8.15 lower to 3.05 lower) **Favors NSAIDs**
HAQ pain mean change (lower scores indicate improvement)											
207 (2 RCTs)	serious [a]	not serious	not serious	not serious	none	⨁⨁⨁◯ MODERATE	104	103	-	-	MD **0.06 lower** (0.29 lower to 0.16 higher)
WOMAC function (mean, post)(0-100, lower scores indicate improvement)											
217 (1 RCT)	serious [a]	not serious	not serious	not serious	none	⨁⨁⨁◯ MODERATE	109	108	-	-	MD **7.5 lower** (11.51 lower to 3.49 lower) **Favors NSAIDs**
WOMAC function (mean change from baseline)(lower scores indicate improvement)											
536 (3 RCTs)	serious [a]	not serious	not serious	not serious	none	⨁⨁⨁◯ MODERATE	256	280	-	-	SMD **0.20 lower** (0.47 lower to 0.06 higher)

KOOS function (mean, post)(0-100, higher scores indicate improvement)											
104 (1 RCT)	serious [b]	not serious	not serious	serious [c]	none	⊕⊕◯◯ LOW	52	52	-	-	MD **3 higher** (4.63 lower to 10.63 higher)
HAQ disability (mean change)(lower scores indicate improvement)											
207 (2 RCTs)	serious [a]	not serious	not serious	not serious	none	⊕⊕⊕◯ MODERATE	104	103	-	-	MD **0.06 higher** (0.05 lower to 0.17 higher)
50 meter walk time (lower scores indicate improvement)											
178 (1 RCT)	serious [a]	not serious	not serious	serious [d]	none	⊕⊕◯◯ LOW	88	90	-	-	MD **0.01 higher** (2.61 lower to 2.63 higher)
Serious adverse effects (n/N)											
309 (1 RCT)	serious [a]	not serious	not serious	serious [c]	none	⊕⊕◯◯ LOW	10/148 (6.8%)	7/161 (4.3%)	**OR 0.63** (0.23 to 1.69)	68 per 1,000	**24 fewer per 1,000** (51 fewer to 42 more)
GI side effects											
309 (1 RCT)	serious [a]	not serious	not serious	serious [c]	none	⊕⊕◯◯ LOW	31/148 (20.9%)	39/161 (24.2%)	**RR 1.16** (0.76 to 1.75)	209 per 1,000	**34 more per 1,000** (50 fewer to 157 more)
Cardiac side effects											

309 (1 RCT)	serious [a]	not serious	not serious	serious [c]	none	⨁⨁◯◯ LOW	1/148 (0.7%)	0/161 (0.0%)	**OR 0.30** (0.01 to 7.53)	7 per 1,000	**5 fewer per 1,000** (7 fewer to 42 more)

CI: Confidence interval; **MD:** Mean difference

Explanations

a. Allocation concealment not described

b. Blinding not described

c. Wide CI that crosses line of no effect

d. Not statistically significant, small effect estimate

Table 2. RCT data not suitable for effect size calculation or combining with other data

Ref ID, Author, year	Study type	Duration	Population Description	Treatment given to relevant population	Results
PICO76_1231_Bradley	RCT	4 week	Knee OA participants: Group 1: n=61, mean age 55.7 (13.7), mean weight 92.5 (22.8), 71 % females Group 2: n=62, mean age 56.7 (11.2), mean weight 94.5 (21.4), 79% females Group 3: n=61, mean age 57.2 (11.7), mean weight in Kg 92.8 (22.8), 74% female	Group 1: Ibuprofen 2400/day Group 2: ibuprofen 1200 mg/day Group 3: acetaminophen 4000 mg/day	**Mean change in HAQ pain score:** **Group 1:** 0.35 (0.13 to 0.57) **Group 2:** 0.30 (0.09 to 0.51) **Group 3:** 0.33 (0.14 to 0.52) **Mean change in walking pain score**: **Group 1**: 0.45 (0.21 to 0.69) **Group 2**: 0.31 (0.10 to 0.51) **Group 3**: 0.13 (-0.06 to 0.32) **Mean change in rest pain score**: **Group 1**: 0.40 (0.13 to 0.66) **Group 2**: 0.33 (0.25 to 0.50) **Group 3**: 0.06 (-0.08 to 0.19)

					Mean change in HAQ disability score: **Group 1**: 0.11 (-0.02 to 0.23) **Group 2**: 0.08 (-0.01 to 0.16) **Group 3**: 0.08 (0.00 to 0.16)
PICO76_13_ Schnitzer	RCT	4 weeks	Knee OA participants: Group 1: n=126 mean age 60.9 (10.8), 59.5% female, mean bmi 32.4 (7.7) Group 2: n=129, mean age 60.8 (10.2), 62.8% female, mean bmi 33.0 (7.2) Group 3: n=121, mean age 57.5 (11.5), 65.3 % female, mean bmi 33.7 (9.0)	Group 1: extended release acetaminophen1300 mg three times daily Group 2: rofecoxib 12.5mg once daily Group 3: rofecoxib 25mg once daily	**EFFICACY:** **Mean and mean change in WOMAC pain, NO SD or 95% CI provided:** **Group 1:** 150.35, 140.89 **Group 2**: 136.25, 147.64 **Group 3**: 127.98, 184.42 **Mean and mean change in WOMAC pain, NO SD or 95% CI provided:** **Group 1:** 530.63, 448.32 **Group 2**: 513.36, 470.95 **Group 3**: 465.84, 598.74 **SAFETY:** **Adverse events n (%):** **Group 1:** 59 (43.4) , no MI **Group 2:** 58 (42.0), 2 MIs **Group 3:** 55 (42.6), no MI
PICO76_263 _Shen	RCT	3 month	Group 1: n=10, age 60–77 yr, 4 males, 6 females Group 2: n=10, age 48–80 yr, 4 males, 6 females	Group 1: acetaminophen up to 4 g/day Group 2: rofecoxib 25 mg/day	**Change in mean WOMAC pain (NO SD or 95% CI provided):** **Group 1:** −0.74 **Group 2:** −1.12 **Change in mean WOMAC activity (NO SD or 95% CI provided):** **Group 1:** −1.06 **Group 2:** −0.98 NO safety data provided
PICO76_276 _Golden	RCT		464 adult patients, aged 25 years or older (87.1% aged 45 years or older), with knee OA	Group 1: 220mg naproxen sodium three times daily (patients aged	**Difference in pain at rest (0-4 points) from baseline:** **Group 1:** 0.5 **Group 2:** 0.2 **Group 3:** 0.2

				65 years and older took 220 mg twice daily) Group 2: 1000mg acetaminophen four times daily Group 3: placebo four times daily	P for group 1 vs group 2 and group 1 vs group 3 <0.05 **Difference in pain with weight bearing:** **Group 1:** 1.0 **Group 2:** 0.9 **Group 3:** 0.7 P for the above comparisons is <0.01
PICO76_ 3465_Geba	RCT	6 week	Group 1: mean age 63.1 (10.90), 70.2% females Group 2: mean age 62.6 (11.03), 64.9% females Group 3: mean age 63.4 (10.40), 65.6% females Group 4: mean age 61.3 (10.93), 72.6% females	Group 1:Acetaminophen, 4000 mg/d (n = 94) Group 2:Celecoxib, 200 mg/d (n = 97) Group 3:Rofecoxib 12.5 mg/d (n = 96); Group 4:Rofecoxib, 25 mg/d (n = 95)	**Change in mean WOMAC pain (95% CI)subscale score:** **Group 1 :** -24.9 (-29.5 to -20.3) **Group 2:** -28.6 (-33.2 to -24) **Group 3:** -28.0 (-33.6 to -23.4) **Group 4:** -35.4 (-40.0 to -30.8) Change in mean WOMAC function (95%CI) subscale: **Group 1 :** -19.5 (-24.1 to -14.9) **Group 2:** -24.9 (-29.3 to -20.5) **Group 3:** -24.3 (-28.7 to -9.9) **Group 4:** -29.7 (-34.1 to -25.3)
PICO76_ 3466_Schnitzer	RCT pooled VACT1 and VACt2		Group 1: mean age 61.9 (10.70), % female 66.2 Group 1:Mean age 61.4 (9.89), % female 68.1 Group 3: Mean age 62.8 (10.80), % female 65.3 Group 4: Mean age 62.7 (10.34), % female 68.3	Group 1 (n= 269): acetaminophen (4000 mg, 1000 mg qid) Group 2 (n=523): celecoxib (200 mg/day) Group 3 (n=259): rofecoxib (12.5 mg/day) Group 4 (n=527): rofecoxib (25 mg/day)	**Change in mean WOMAC pain (No SD or 95% CI provided) subscale score from the pooled study:** **Group 1 :** -24.7 **Group 2:** –29.4 **Group 3:** –30.8 **Group 4:** –33.0 **Change in mean WOMAC function (No SD or 95% CI provided) subscale score from the pooled study:** **Group 1 :** –19.9 **Group 2:** –25.6 **Group 3:** –26.7 **Group 4:** –28.8 **SAFETY:**

					AE: Significantly more rofecoxib 25 mg (6.3%) and acetaminophen (7.4%) patients than celecoxib patients (2.7%; $p < 0.05$) discontinued due to an AE, while rofecoxib 12.5 mg (5.4%) was not significantly different from celecoxib. EDEMA: No significant differences between acetaminophen (0.6%), celecoxib (0%), rofecoxib 12.5 mg (0%), and rofecoxib 25 mg (0.6%) in discontinuations due to edema or related AE. HYPERTENSION: No significant differences between acetaminophen (0.8%), celecoxib (0%), rofecoxib 12.5 mg (0.6%), and rofecoxib 25 mg (0.2%) in discontinuations due to ypertension related AE. CVD: The acetaminophen, celecoxib, rofecoxib 12.5 mg, and rofecoxib 25 mg treatment groups experienced a similar incidence of cardiovascular system AE (4.7%, 3.5%, 3.7%, and 3.2%, respectively) including events classified by the investigator specifically as hypertension (1.1%, 1.0%, 0.8%, and 0.8%, respectively)

References

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8. Bradley JD, Brandt KD, Katz BP, Kalasinski LA, Ryan SI. Treatment of knee osteoarthritis: relationship of clinical features of joint inflammation to the response to a nonsteroidal antiinflammatory drug or pure analgesic. J Rheumatol 1992;19:1950-4.
9. Pincus T, Koch G, Lei H, et al. Patient Preference for Placebo, Acetaminophen (paracetamol) or Celecoxib Efficacy Studies (PACES): two randomised, double blind, placebo controlled, crossover clinical trials in patients with knee or hip osteoarthritis. Ann Rheum Dis 2004;63:931-9.
10. Golden HE, Moskowitz RW, Minic M. Analgesic efficacy and safety of nonprescription doses of naproxen sodium compared with acetaminophen in the treatment of osteoarthritis of the knee. Am J Ther 2004;11:85-94.
11. Schnitzer TJ, Tesser JR, Cooper KM, Altman RD. A 4-week randomized study of acetaminophen extended-release vs rofecoxib in knee osteoarthritis. Osteoarthritis Cartilage 2009;17:1-7.
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PICO 77. Bisphosphonates compared to oral NSAIDs in patients with knee or hip OA

Summary. The literature searches did not identify any studies that addressed this question.

Quality of evidence across all critical outcomes: Very low

PICO 78. Duloxetine compared to oral NSAIDs for knee or hip OA

Summary. Our searches identified one RCT that indirectly addressed this comparison. Frakes et al. randomized 524 patients with knee OA to receive either flexible-dose duloxetine (60/120 mg per day) plus oral NSAIDs or placebo plus oral NSAIDs.[1] At 8 weeks, the study found a significant between-group difference in WOMAC pain and function improvement favoring duloxetine plus oral NSAIDs over oral NSAIDs alone. The rate of serious adverse events did not differ significantly between groups, although imprecision in the effect estimate means that the findings for this outcome are inconclusive.

Quality of evidence across all critical outcomes: Very low

Duloxetine plus oral NSAIDS compared to placebo plus oral NSAIDS for knee OA											
Certainty assessment							**Summary of findings**				
№ of participants (studies) Follow-up	**Risk of bias**	**Inconsistency**	**Indirectness**	**Imprecision**	**Publication bias**	**Overall certainty of evidence**	**Number of patients**		**Relative effect (95% CI)**	**Anticipated absolute effects**	
							With placebo plus oral NSAIDS	**With duloxetine plus oral NSAIDS**		**Risk with placebo plus oral NSAIDS**	**Risk difference with duloxetine plus oral NSAIDS**
WOMAC pain at 8 wk change score (0-100, lower scores indicate improvement)											
514 (1 RCT)	serious [a]	not serious	serious [b]	not serious	none	⨁⨁◯◯ LOW	256	258	-	-	MD **6.45 lower** (9.57 lower to 3.33 lower) **Favors duloxetine + NSAIDs**
WOMAC function change score at wk 8 (0-100, lower scores indicate improvement)											
504 (1 RCT)	serious [a]	not serious	serious [b]	not serious	none	⨁⨁◯◯ LOW	253	251	-	-	MD **7.29 lower** (10.42 lower to 4.16 lower) **Favors duloxetine + NSAIDs**

Duloxetine plus oral NSAIDS compared to placebo plus oral NSAIDS for knee OA											
Certainty assessment							**Summary of findings**				
SAEs											
524 (1 RCT)	serious [a]	not serious	serious [b]	serious [c]	none	⨁◯◯◯ VERY LOW	3/260 (1.2%)	5/264 (1.9%)	**OR 1.65** (0.39 to 6.99)	12 per 1,000	**7 more per 1,000** (7 fewer to 64 more)

CI: Confidence interval; **MD:** Mean difference; **OR:** Odds ratio

Explanations

a. 26% attrition, randomization method and allocation concealment not reported

b. Both groups received NSAIDs

c, Wide 95% CI that overlaps line of no effect

References

1. Frakes EP, Risser RC, Ball TD, Hochberg MC, Wohlreich MM. Duloxetine added to oral nonsteroidal anti-inflammatory drugs for treatment of knee pain due to osteoarthritis: results of a randomized, double-blind, placebo-controlled trial. Curr Med Res Opin. 2011;27(12):2361-2372.

PICO 79. Other serotonin norepinephrine inhibitors compared to oral NSAIDs in patients with knee or hip OA

Summary. The literature searches did not identify any studies that addressed this question.

Quality of evidence across all critical outcomes: Very low

PICO 80. Tricyclic antidepressants compared to oral NSAIDs in patients with knee or hip OA

Summary. The literature searches did not identify any studies that addressed this question.

Quality of evidence across all critical outcomes: Very low

PICO 81: Tramadol vs. Oral NSAIDs for hip or knee OA

Summary: Three RCTs have compared tramadol to oral NSAIDs for the treatment of hip and knee OA. Beaulieu[1] et al. compared tramadol (titrated up to 400mg/day) to diclofenac, while DeLemos[2] et al. compared tramadol (100-300mg, 300 used for meta-analysis) to celecoxib in adults with hip or knee OA. Combined, these studies no significant between-group difference in pain and self-reported function (Table 1). However, there was a serious risk of bias due to high attrition (25-44%), and the findings were inconclusive due to serious imprecision in the effect estimates. In a randomized crossover trial, Pavelka[3] also compared tramadol to diclofenac, and observed no difference in improvement of pain or self-reported function. The results were reported in medians (Table 2), and could not be combined in the meta-analysis.

Quality of evidence: Low

Table 1. Tramadol compared to Oral NSAIDs for Hip or Knee OA for Knee/Hip OA

Certainty assessment							Summary of findings				
№ of participants (studies) Follow-up	**Risk of bias**	**Inconsistency**	**Indirectness**	**Imprecision**	**Publication bias**	**Overall certainty of evidence**	**Number of patients**		**Relative effect (95% CI)**	**Anticipated absolute effects**	
							With Oral NSAIDs for Hip or Knee OA	**With Tramadol**		**Risk with Oral NSAIDs for Hip or Knee OA**	**Risk difference with Tramadol**
WOMAC Pain (lower scores indicate improvement)											
498 (2 RCTs)	serious [a]	not serious	not serious	serious [b]	none	⨁⨁◯◯ LOW	254	244	-	-	SMD **0.1 higher** (0.08 lower to 0.27 higher)

Table 1. Tramadol compared to Oral NSAIDs for Hip or Knee OA for Knee/Hip OA											
Certainty assessment							**Summary of findings**				
WOMAC Function (lower scores indicate improvement)											
498 (2 RCTs)	serious [a]	not serious	not serious	serious [b]	none	⨁⨁◯◯ LOW	254	244	-	-	SMD **0.14 higher** (0.04 lower to 0.31 higher)

CI: Confidence interval; **SMD:** Standardised mean difference

Explanations

a. Incomplete outcome data due to high attrition

b. Wide 95% CI that crosses line of no effect

Table 2. RCT data not suitable for effect size calculation or combining with other data

Ref ID, Author, year	Study type	Duration	Population Description	Treatment given to relevant population	Results
4819 Pavelka[3], 1998	Double blind crossover study, Moderate quality	4 weeks then cross over One week wash out between phases	Knee or Hip OA (KL grade>=2) n=60 randomized (8M:52F) age 44-85	Group 1. Tramadol (4 weeks) then diclofenac (4 weeks) Group 2. Diclofenac (4 weeks) then tramadol (4 weeks) Tramadol dose:1-2 50mg capsule, 3 times per day Diclofenac dose:1-2 25mg capsule, 3 times per day	Data estimated from period 1 boxplots 5th, 25th, 50th (median), 75th, 95th percentile WOMAC Pain: Tramadol: -12.5, 2, 8.5, 16, 39.5 Diclofenac: -1.5, 5, 8, 17.5, 29.5 WOMAC Function: Tramadol: -8.5, 0, 7, 11.5, 22.5 Diclofenac: 0, 2.5, 7, 13.5, 21

References

1. Beaulieu AD, Peloso PM, Haraoui B, Bensen W, Thomson G, Wade J, et al. Once-daily, controlled-release tramadol and sustained-release diclofenac relieve chronic pain due to osteoarthritis: a randomized controlled trial. Pain Res Manag. 2008;13(2):103-110.
2. DeLemos BP, Xiang J, Benson C, Gana TJ, Pascual ML, Rosanna R, et al. Tramadol hydrochloride extended-release once-daily in the treatment of osteoarthritis of the knee and/or hip: a double-blind, randomized, dose-ranging trial. Am J Ther. 2011;18(3):216-226.
3. Pavelka K, Peliskova Z, Stehlikova H, Ratcliffe S, Repas C. Intraindividual differences in pain relief and functional improvement in osteoarthritis with diclofenac or tramadol. Clin Drug Investig. 1998;16(6):421-429.

PICO 82. Non-tramadol opioids compared to oral NSAIDs in patients with knee or hip OA

Summary. The literature searches did not identify any studies that addressed this question.

Quality of evidence across all critical outcomes: Very low

PICO 83. Gabapentin compared to oral NSAIDs in patients with knee or hip OA

Summary. The literature searches did not identify any studies that addressed this question.

Quality of evidence across all critical outcomes: Very low

PICO 84. Pregabalin compared to oral NSAIDs for knee and hip OA

Summary. The literature searches identified one RCT that compared pregabalin (25 mg/day) to meloxicam (10 mg/day) for 4 weeks in 59 patients with knee OA grade 1 through 4.[1] The study found no significant between-group difference in WOMAC pain or function at 4 weeks, although serious imprecision in the effect estimates mean the findings are inconclusive.

Quality of evidence across all critical outcomes: Low

Pregabalin compared to oral NSAIDS for knee and hip OA											
Certainty assessment							**Summary of findings**				
№ of participants (studies) Follow-up	**Risk of bias**	**Inconsistency**	**Indirectness**	**Imprecision**	**Publication bias**	**Overall certainty of evidence**	**Number of patients**		**Relative effect (95% CI)**	**Anticipated absolute effects**	
							With oral NSAIDS	**With pregabalin**		**Risk with oral NSAIDS**	**Risk difference with pregabalin**
WOMAC pain at 4 wks, post scores (0-20, lower scores indicate improvement)											
59 (1 RCT)	serious [a]	not serious	not serious	serious [b]	none	⨁⨁◯◯ LOW	31	28	-	-	MD **0.3 higher** (1.07 lower to 1.67 higher)
WOMAC function, 4 wks, change score (0-68, lower scores indicate improvement)											
59 (1 RCT)	serious [a]	not serious	not serious	serious [b]	none	⨁⨁◯◯ LOW	31	28	-	-	MD **1 higher** (4.79 lower to 6.79 higher)

CI: Confidence interval; **MD:** Mean difference

Explanations

a. allocation concealment and blinding not reported

b. Wide 95% CI that overlaps line of no effect

References

1. Ohtori S, Inoue G, Orita S, Takaso M, Eguchi Y, Ochiai N, et al. Efficacy of combination of meloxicam and pregabalin for pain in knee osteoarthritis. Yonsei Med J. 2013;54(5):1253-1258.

PICO 85. Methotrexate compared to oral NSAIDs in patients with knee or hip OA

Summary. The literature searches did not identify any studies that addressed this question.

Quality of evidence across all critical outcomes: Very low

PICO 86. Colchicine compared to oral NSAIDs in patients with knee or hip OA

Summary. The literature searches did not identify any studies that addressed this question.

Quality of evidence across all critical outcomes: Very low

PICO 87: Glucosamine compared to oral NSAIDs in patients with knee or hip OA

Summary: This PICO question is addressed by 5 direct RCTs. The results for all pain and function outcomes showed no significant between-group differences, but all findings were inconclusive due to serious imprecision in effect estimates.

Quality of Evidence across all critical outcomes: Low.

Table 1. Glucosamine compared to NSAID for knee or hip OA

Certainty assessment							Summary of findings				
№ of participants (studies) Follow-up	Risk of bias	Inconsistency	Indirectness	Imprecision	Publication bias	Overall certainty of evidence	Number of patients		Relative effect (95% CI)	Anticipated absolute effects	
							With NSAID	With Glucosamine		Risk with NSAID	Risk difference with Glucosamine

Table 1. Glucosamine compared to NSAID for knee or hip OA											
Certainty assessment							Summary of findings				
WOMAC pain, 6 months (lower scores indicate improvement)											
855 (2 RCTs)	not serious	serious [a]	not serious	serious [b]	none	⨁⨁◯◯ LOW	428	427	-	-	**SMD 0.04 lower** (0.44 lower to 0.37 higher)
HAQ pain, 6 months (lower scores indicate improvement)											
635 (1 RCT)	not serious	not serious	not serious	serious [b]	none	⨁⨁⨁◯ MODERATE	318	317	-	-	**MD 4.2 higher** (0.2 lower to 8.6 higher)
VAS pain, 12 weeks (0-10, lower scores indicate improvement)											
24 (1 RCT)	not serious	not serious	not serious	serious [c]	none	⨁⨁⨁◯ MODERATE	12	12	-	-	**MD 0.04 higher** (0.24 lower to 0.32 higher)
Lequesne's index, 4 weeks (lower scores indicate improvement)											
199 (1 RCT)	not serious	not serious	not serious	serious [b]	none	⨁⨁⨁◯ MODERATE	99	100	-	-	**MD 0** (1.67 lower to 1.67 higher)
WOMAC function, 6 months (lower scores indicate improvement)											

Table 1. Glucosamine compared to NSAID for knee or hip OA											
Certainty assessment							**Summary of findings**				
855 (2 RCTs)	not serious	serious [a]	not serious	serious [b]	none	⨁⨁◯◯ LOW	428	427	-	-	**SMD 0.06 higher** (0.23 lower to 0.34 higher)

CI: Confidence interval; **MD:** Mean difference; **SMD**: Standardized mean difference

Explanations

a. High I-squared and Chi-squared values

b. Wide CI crossing significant effect and no-effect lines

c. Very small study with CI crossing line of no effect

Table 2. RCT data not suitable for effect size calculation or combining with other data

Author, year	Study type	Duration	Population Description	Treatment given to relevant population	Results
899 Sawitzke 2010	Double-blind RCT	24 months	662 patients with knee OA	glucosamine 500 mg three times daily, celecoxib 200 mg daily, or placebo over 24 months	Glucosamine WOMAC pain mean change at 24 months: -31.1 Celecoxib WOMAC pain mean change at 24 months: -32.8; MD -1.7 Glucosamine WOMAC function mean change at 24 months: -22.58 Celecoxib WOMAC function mean change at 24 months: -24.07; MD -3.49

References:

1. Qiu G., et al (1998). Efficacy and safety of glucosamine sulfate versus ibuprofen in patients with knee osteoarthritis. Arzneimittelforschung. 1998 May;48(5):469-74.
2. Chopra, A. A. S. (2013). Ayurvedic medicine offers a good alternative to glucosamine and celecoxib in the treatment of symptomatic knee osteoarthritis: a randomized, double-blind, controlled equivalence drug trial. Rheumatology (Oxford), 52(8), 1408-1417. doi:10.1093/rheumatology/kes414 10.1093/rheumatology/kes414. Epub 2013 Jan 30.
3. Muller-Fassbender, H. A. B. (1994). Glucosamine sulfate compared to ibuprofen in osteoarthritis of the knee. Osteoarthritis Cartilage, 2(1), 61-69.
4. Sawitzke, A. et al. (2010). Clinical effi cacy and safety of glucosamine, chondroitin sulphate, their combination, celecoxib or placebo taken to treat osteoarthritis of the knee: 2-year results from GAIT. Ann Rheum Dis 2010;69:1459–1464. doi:10.1136/ard.2009.120469
5. Clegg D., (2006). Glucosamine, Chondroitin Sulfate, and the Two in Combination for Painful Knee Osteoarthritis. N Engl J Med 2006;354:795-808

PICO 88: Chondroitin compared to oral NSAIDs in patients with hip or knee OA

Summary: This PICO question is addressed by 5 direct RCTs. The results for WOMAC pain, HAQ pain, Lequesne's index, VAS Huskisson's and WOMAC function were in favor of NSAIDs over Chondroitin, with low imprecision for HAQ pain, Lequesne's index, and WOMAC function, and serious imprecision for WOMAC pain and VAS Huskisson's. Serious adverse event rates did not differ significantly between groups, but the results are imprecise due to the low number of events.

Quality of Evidence across all critical outcomes: Moderate

Table 1. Chondroitin compared to NSAIDs for knee or hip OA

Certainty assessment							Summary of findings				
№ of participants (studies) Follow-up	Risk of bias	Inconsistency	Indirectness	Imprecision	Publication bias	Overall certainty of evidence	Number of patients		Relative effect (95% CI)	Anticipated absolute effects	
							With NSAIDs	With Chondroitin		Risk with NSAIDs	Risk difference with Chondroitin

Table 1. Chondroitin compared to NSAIDs for knee or hip OA											
Certainty assessment							Summary of findings				
WOMAC pain, 24 weeks (0-500, lower scores indicate improvement)											
636 (1 RCT)	not serious	not serious	not serious	serious [a]	none	⨁⨁⨁◯ MODERATE	318	318	-	-	MD **16.1 higher** (0.16 lower to 32.36 higher)
HAQ pain, 24 weeks (lower scores indicate improvement)											
636 (1 RCT)	not serious	not serious	not serious	not serious	none	⨁⨁⨁⨁ HIGH	318	318	-	-	MD **4.8 higher** (0.69 higher to 8.91 higher)
Lequesne's index, 4 weeks (lower scores indicate improvement)											
146 (1 RCT)	not serious	not serious	not serious	not serious	none	⨁⨁⨁⨁ HIGH	72	74	-	-	MD **2.1 higher** (1.05 higher to 3.15 higher) **Favors NSAIDs**
VAS Huskisson, 4 weeks (0-100, lower scores indicate improvement)											

Table 1. Chondroitin compared to NSAIDs for knee or hip OA											
Certainty assessment							Summary of findings				
146 (1 RCT)	not serious	not serious	not serious	serious [b]	none	⨁⨁⨁◯ MODERATE	72	74	-	-	MD **1.2 higher** (4.1 lower to 6.5 higher)
WOMAC function, 24 weeks (0-1700, lower scores indicate improvement)											
636 (1 RCT)	not serious	not serious	not serious	serious [a]	none	⨁⨁⨁◯ MODERATE	318	318	-	-	MD **53.7 higher** (0.28 higher to 107.12 higher) **Favors NSAIDs**
SAE, 24 months											
194 (1 RCT)	not serious	not serious	not serious	serious [b]	none	⨁⨁⨁◯ MODERATE	6/97 (6.2%)	10/97 (10.3%)	OR 1.74 (0.61 to 5.00)	62 per 1,000	**41 more per 1,000** (23 fewer to 186 more)

CI: Confidence interval; **MD:** Mean difference; **OR:** Odds ratio

Explanations

a. Very wide CI close to no-effect line

b. Wide CI crossing no-effect line

Table 2. RCT data not suitable for effect size calculation or combining with other data

Author, year	Study type	Duration	Population Description	Treatment given to relevant population	Results
899 Sawitzke 2010	Double-blind RCT	24 months	662 patients with knee OA	CS 400 mg three times daily, celecoxib 200 mg daily, or placebo over 24 months	Chondroitin WOMAC pain mean change at 24 months: -27.91 Celecoxib WOMAC pain mean change at 24 months: -32.8 ; MD -4.89 Chondroitin WOMAC function mean change at 24 months: -20.98 Celecoxib WOMAC function mean change at 24 months: -24.07; MD -4.09
811 Pelletier 2016	Double-blind RCT	30 days	662 patients with knee OA	CS 1200 mg/day versus 150 mg Diclofenac Sodium tablets/day for 30 days	Lequesne Index CS entry 7.8±3.5, 30 days 4.9±2.5, change -37.52%; DS entry 7.9±3.7, 30 days 2.9±2.3, change -63.43%. Huskisson (VAS) CS entry 56.4±16.6, 30 days 30.9±14.0, change -45.2%; DS entry 56.7±18.7, 30 days 30.0±15.0, change -47.1%.
6111 Reginster 2017	Double-blind RCT	6 months	604 patients aged 50 years or older with symptomatic knee OA	Chondroitin sulfate 800mg/day, oral celecoxib, 200mg once daily (n=200) or placebo (n=205)	VAS CS at baseline 71.2, at 6 months 28.6,change -42.6; Celecoxib at baseline 70.0 (0.8), at 6 months 30.5, change -39.5 Lequesne's Index CS at baseline 11.8, at 30 days 7.1, change -4.7; Celecoxib at baseline 11.6, at 30 days 7.0, change -4.6

References:

1. Morreale, P., Manopulo, R., Galati, M., Boccanera, L., Saponati, G., & Bocchi, L. (1996). Comparison of the antiinflammatory efficacy of chondroitin sulfate and diclofenac sodium in patients with knee osteoarthritis. J Rheumatol, 23(8), 1385-1391.
2. Pelletier, J. P. A. R. (2016). Chondroitin sulfate efficacy versus celecoxib on knee osteoarthritis structural changes using magnetic resonance imaging: a 2-year multicentre exploratory study. Arthritis Res Ther, 18(1), 256. doi:10.1186/s13075-016-1149-0
3. Reginster, J. Y. A. D. (2017). Pharmaceutical-grade chondroitin sulfate is as effective as celecoxib and superior to placebo in symptomatic knee osteoarthritis: The chondroitin vs celecoxib vs placebo trial (CONCEPT). Osteoporosis International, 28(1 Supplement 1), S56. doi:10.1007/s00198-017-3945-z

4. Sawitzke, A. et al. (2010). Clinical effi cacy and safety of glucosamine, chondroitin sulphate, their combination, celecoxib or placebo taken to treat osteoarthritis of the knee: 2-year results from GAIT. Ann Rheum Dis 2010;69:1459–1464. doi:10.1136/ard.2009.120469
5. Clegg D., (2006). Glucosamine, Chondroitin Sulfate, and the Two in Combination for Painful Knee Osteoarthritis. N Engl J Med 2006;354:795-808

PICO 89: Glucosamine + chondroitin compared to oral NSAIDs in patients with hip or knee OA

Summary: This PICO question is addressed by 4 direct RCTs [1-4]. The results across all outcomes showed no significant difference between treatments, but some of the findings were imprecise due to wide 95% CIs that included the possibility of a difference between treatments.

Quality of Evidence across outcomes: Moderate

Table 1. Glucosamine + chondroitin compared to oral NSAIDs for knee or hip OA

Certainty assessment							Summary of findings				
№ of participants (studies) Follow-up	**Risk of bias**	**Inconsistency**	**Indirectness**	**Imprecision**	**Publication bias**	**Overall certainty of evidence**	**Number of patients**		**Relative effect (95% CI)**	**Anticipated absolute effects**	
							With oral NSAIDs	**With glucosamine + chondroitin**		**Risk with oral NSAIDs**	**Risk difference with glucosamine + chondroitin**
WOMAC pain, 6 months (0-500, lower scores indicate improvement)											
1203 (2 RCTs)	not serious	not serious	not serious	not serious	none	⨁⨁⨁⨁ HIGH	600	603	-	-	MD **0.13 higher** (12.92 lower to 13.19 higher)
HAQ pain score, 6 months (lower scores indicate improvement)											

Table 1. Glucosamine + chondroitin compared to oral NSAIDs for knee or hip OA											
Certainty assessment							**Summary of findings**				
635 (1 RCT)	not serious	not serious	not serious	serious [a]	none	⨁⨁⨁◯ MODERATE	318	317	-	-	MD **0.6 lower** (4.97 lower to 3.77 higher)
Huskisson's VAS (0-100, lower scores indicate improvement)											
568 (1 RCT)	not serious	not serious	not serious	serious [a]	none	⨁⨁⨁◯ MODERATE	282	286	-	-	MD **0.2 higher** (4.38 lower to 4.78 higher)
WOMAC function, 6 months (0-1700, lower scores indicate improvement)											
1203 (2 RCTs)	not serious	not serious	not serious	not serious	none	⨁⨁⨁⨁ HIGH	600	603	-	-	MD **16.2 higher** (25.74 lower to 58.14 higher)
SAE											
568 (1 RCT)	not serious	not serious	not serious	serious [a]	none	⨁⨁⨁◯ MODERATE	10/282 (3.5%)	7/286 (2.4%)	OR 0.68 (0.26 to 1.82)	35 per 1,000	**11 fewer per 1,000** (26 fewer to 27 more)

CI: Confidence interval; **MD:** Mean difference; **OR:** Odds ratio

Explanations

a. Wide CI crossing line of no-effect. Note: WOMAC pain and function are not downgraded for imprecision because the scales used are large (0-500 for pain, 0-1700 for function).

Table 2. RCT data not suitable for effect size calculation or combining with other data

Author, year	Study type	Duration	Population Description	Treatment given to relevant population	Results
899 Sawitzke 2010	Double-blind RCT	24 months	662 patients with knee OA	glucosamine 500 mg three times daily, CS 400 mg three times daily, the combination of glucosamine and CS, celecoxib 200 mg daily, or placebo over 24 months	Glucosamine+Chondroitin WOMAC pain mean change at 24 months: -30 Celecoxib WOMAC pain mean change at 24 months: -32.8; MD -2.8 Glucosamine+Chondroitin WOMAC function mean change at 24 months: -19.94 Celecoxib WOMAC function mean change at 24 months: -24.07; MD -4.13

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PICO 90. Vitamin D compared to oral NSAIDs in patients with knee or hip OA

Summary. The literature searches did not identify any studies that addressed this question.

Quality of evidence across all critical outcomes: Very low

PICO 91. Fish oil compared to oral NSAIDs in patients with knee or hip OA

Summary. The literature searches did not identify any studies that addressed this question.

Quality of evidence across all critical outcomes: Very low

PICO 92: Anti-nerve growth factor vs. Oral NSAID for OA of hip/knee

Summary. This PICO was addressed by 2 RCTs. [1,2] One study directly compared tanezumab to oral NSAIDs (Table 1), while the other had some indirectness (tanezumab plus oral NSAID vs. oral NSAID alone, Table 2). Both studies showed a significant improvement in WOMAC pain and function in the tanezumab group compared to the NSAID group. Although there was no significant difference in serious adverse events, there was some imprecision in the effect estimates for both trials.

Quality of evidence across all critical outcomes: Moderate

Table 1. Anti-nerve growth factor compared to Oral NSAID for OA of Hip/Knee

Certainty assessment							Summary of findings				
№ of participants (studies) Follow-up	**Risk of bias**	**Inconsistency**	**Indirectness**	**Imprecision**	**Publication bias**	**Overall certainty of evidence**	**Number of Patients**		**Relative effect (95% CI)**	**Anticipated absolute effects**	
							With Oral NSAID	**With Anti-nerve growth factor**		**Risk with Oral NSAID**	**Risk difference with Anti-nerve growth factor**
WOMAC Pain (change from baseline) (0-11, lower scores indicate improvement)											
1080 (1 RCT)	not serious	not serious	not serious	not serious	none	⨁⨁⨁⨁ HIGH	539	541	-	-	MD **0.54 lower** (0.81 lower to 0.28 lower) **Favors ANGF**
WOMAC Function (change from baseline) (0-11, lower scores indicate improvement)											

Table 1. Anti-nerve growth factor compared to Oral NSAID for OA of Hip/Knee											
Certainty assessment							Summary of findings				
1080 (1 RCT)	not serious	not serious	not serious	not serious	none	⨁⨁⨁⨁ HIGH	539	541	-	-	MD **0.59 lower** (0.83 lower to 0.34 lower) **Favors ANGF**
SAE											
1080 (1 RCT)	not serious	not serious	not serious	serious [b]	none	⨁⨁⨁◯ MODERATE	43/539 (8.0%)	44/541 (8.1%)	**OR 1.02** (0.66 to 1.58)	80 per 1,000	**1 more per 1,000** (26 fewer to 41 more)

CI: Confidence interval; **MD:** Mean difference; **OR:** Odds ratio

Explanations

a. Wide 95% CI crosses line of no effect

Anti-nerve growth factor + Oral NSAID compared to Oral NSAID for OA of Hip / Knee										
Certainty assessment							Summary of findings			
№ of participants (studies) Follow-up	**Risk of bias**	**Inconsistency**	**Indirectness**	**Imprecision**	**Publication bias**	**Overall certainty of evidence**	**Number of Patients**		**Relative effect (95% CI)**	**Anticipated absolute effects**	
							With Oral NSAID	**With Anti-nerve growth factor + Oral NSAID**		**Risk with Oral NSAID**	**Risk difference with Anti-nerve growth factor + Oral NSAID**
WOMAC pain (change from baseline) (0-11, lower scores indicate improvement)											

Anti-nerve growth factor + Oral NSAID compared to Oral NSAID for OA of Hip / Knee										
Certainty assessment							Summary of findings			
302 (1 RCT)	not serious	not serious	serious [a]	not serious	none	⨁⨁⨁◯ MODERATE	152	150	-	-	MD **0.51 lower** (1.04 lower to 0.02 higher)
WOMAC function (change from baseline) (0-11, lower scores indicate improvement)										
302 (1 RCT)	not serious	not serious	serious [a]	not serious	none	⨁⨁⨁◯ MODERATE	152	150	-	-	MD **0.63 lower** (1.16 lower to 0.1 lower) **Favors ANGF**
SAE										
302 (1 RCT)	not serious	not serious	serious [a]	serious [b]	none	⨁⨁◯◯ LOW	8/152 (5.3%)	8/150 (5.3%)	**OR 1.01** (0.37 to 2.78)	53 per 1,000	**0 fewer per 1,000** (32 fewer to 81 more)

CI: Confidence interval; **MD:** Mean difference; **OR:** Odds ratio

Explanations

a. Anti-nerve growth factor + Oral NSAID vs. Oral NSAID

b. Wide 95% CI crosses line of no effect

References

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2. Schnitzer TJ, Ekman EF, Spierings EL, Greenberg HS, Smith MD, Brown MT, et al. Efficacy and safety of tanezumab monotherapy or combined with non-steroidal anti-inflammatory drugs in the treatment of knee or hip osteoarthritis pain. Ann Rheum Dis. 2015;74(6):1202-1211.

PICO 93. Tumor necrosis factor inhibitor compared to oral NSAIDs in patients with knee or hip OA

Summary. The literature searches did not identify any studies that addressed this question.

Quality of evidence across all critical outcomes: Very low

PICO 94. Interleukin-1 inhibitor compared to oral NSAIDs in patients with knee or hip OA

Summary. The literature searches did not identify any studies that addressed this question.

Quality of evidence across all critical outcomes: Very low

PICO 95. Tramadol compared to non-tramadol opioids in patients with knee or hip OA

Summary. The literature searches did not identify any studies that addressed this question.

Quality of evidence across all critical outcomes: Very low

PICO 96: Topical NSAIDs versus no treatment for patients with knee or hip OA

Summary: This PICO question is addressed by 17 direct RCTs. The results for all pain and function outcomes significantly favor treatment with topical NSAIDs over no treatment. The only outcome that favors placebo is serious adverse events, but the effect estimate is imprecise due to the small number of events.

Quality of Evidence across outcomes: Moderate.

Table 1. Topical NSAIDs compared to Placebo for symptomatic knee OA

Certainty assessment							Summary of findings				
№ of participants (studies) Follow-up	**Risk of bias**	**Inconsistency**	**Indirectness**	**Imprecision**	**Publication bias**	**Overall certainty of evidence**	**Number of patients**		**Relative effect (95% CI)**	**Anticipated absolute effects**	
							With Placebo	**With topical NSAIDs**		**Risk with Placebo**	**Risk difference with topical NSAIDs**
WOMAC pain, 12 weeks (lower scores indicate improvement)											
4263 (14 RCTs)	not serious	serious [a]	not serious	not serious	none	⨁⨁⨁◯ MODERATE	2131	2132	-	-	SMD **0.25 lower** (0.35 lower to 0.15 lower) **Favors topical NSAIDs**
Huskisson's VAS, 2 weeks (0-100, lower scores indicate improvement)											
155 (1 RCT)	not serious	not serious	not serious	serious [b]	none	⨁⨁⨁◯ MODERATE	77	78	-	-	MD **11.3 lower** (17.26 lower to 5.34 lower) **Favors topical NSAIDs**

Table 1. Topical NSAIDs compared to Placebo for symptomatic knee OA											
Certainty assessment							Summary of findings				
VAS pain, 3 weeks (0-100, lower scores indicate improvement)											
237 (1 RCT)	not serious	not serious	not serious	serious [b]	none	⨁⨁⨁◯ MODERATE	120	117	-	-	MD **9 lower** (15.37 lower to 2.63 lower) **Favors topical NSAIDs**
VAS pain at rest, 2 weeks (lower scores indicate improvement)											
164 (2 RCTs)	not serious	not serious	not serious	not serious	none	⨁⨁⨁⨁ HIGH	81	83	-	-	SMD **0.76 lower** (1.15 lower to 0.36 lower) **Favors topical NSAIDs**
VAS pain in motion, 12 weeks (lower scores indicate improvement)											

Table 1. Topical NSAIDs compared to Placebo for symptomatic knee OA											
Certainty assessment							**Summary of findings**				
1504 (7 RCTs)	not serious	not serious	not serious	not serious	none	⨁⨁⨁⨁ HIGH	747	757	-	-	SMD **0.32 lower** (0.46 lower to 0.18 lower) **Favors topical NSAIDs**
Lequesne's index, 2 weeks (lower scores indicate improvement)											
305 (3 RCTs)	not serious	not serious	not serious	not serious	none	⨁⨁⨁⨁ HIGH	152	153	-	-	MD **1.81 lower** (2.37 lower to 1.25 lower) **Favors topical NSAIDs**
WOMAC function, 12 weeks (lower scores indicate improvement)											
3366 (12 RCTs)	not serious	serious [a]	not serious	not serious	none	⨁⨁⨁◯ MODERATE	1677	1689	-	-	SMD **0.27 lower** (0.39 lower to 0.16 lower) **Favors topical NSAIDs**

Table 1. Topical NSAIDs compared to Placebo for symptomatic knee OA											
Certainty assessment							**Summary of findings**				
SAE, 12 weeks											
1929 (4 RCTs)	not serious	not serious	not serious	serious [c]	none	⨁⨁⨁◯ MODERATE	9/965 (0.9%)	16/964 (1.7%)	OR 1.59 (0.48 to 5.26)	9 per 1,000	**5 more per 1,000** (5 fewer to 38 more)

CI: Confidence interval; **MD:** Mean difference; **SMD:** Standardised mean difference; **OR:** Odds ratio

Explanations

a. I-squared and Chi-squared are high, no explanation

b. Small sample size

c. Wide CI crossing no-effect line

Table 2. RCT data not suitable for effect size calculation or combining with other data

Author, year	Study type	Duration	Population Description	Treatment given to relevant population	Results
24 Kneer 2013	RCT	12 weeks	866 patients with knee OA	100, 50, or 25 mg ketoprofen, or placebo twice daily for 12 weeks	WOMAC function mean change: Topical Ketoprofen 100 mg: -22.29 (−42.01% ± 35.69%) Placebo: -20.09 (-36% ± 39.02%)
3130 Trnavsky 2004	RCT	8 days	50 patients with knee OA	25 patients with ibuprofen and 25 with placebo	VAS pain mean change: Ibuprofen -22.6, Placebo -12.32

5506 Conaghan 2013	RCT	12 weeks	464 patients with knee OA	100 mg ketoprofen gel (n=230), placebo (n=234)	Change in WOMAC physical function subscore at week 12 with the 100 mg ketoprofen dose 38.7%, placebo 35.3%.

References:

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10. Rother, M., & Conaghan, P. G. (2013). A randomized, double-blind, phase III trial in moderate osteoarthritis knee pain comparing topical ketoprofen gel with ketoprofen-free gel. J Rheumatol, 40(10), 1742-1748. doi:10.3899/jrheum.130192

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PICO 97: Topical capsaicin versus no treatment in patients with knee or hip OA

Summary: This PICO question is addressed by 3 direct RCTs that compared capsaicin to placebo. The results across all outcomes were slightly in favor of capsaicin, but with serious imprecision for WOMAC pain and function. VAS pain showed a small pain reduction that fell within the bounds of a non-clinically significant improvement.

Quality of Evidence across outcomes: Moderate.

Table 1. Topical capsaicin compared to placebo for knee or hip OA

Certainty assessment							Summary of findings				
№ of participants (studies) Follow-up	**Risk of bias**	**Inconsistency**	**Indirectness**	**Imprecision**	**Publication bias**	**Overall certainty of evidence**	**Number of patients**		**Relative effect (95% CI)**	**Anticipated absolute effects**	
							With placebo	**With topical capsaicin**		**Risk with placebo**	**Risk difference with topical capsaicin**
WOMAC pain, 12 weeks (0-20, lower scores indicate improvement)											
893 (2 RCTs)	not serious	not serious	not serious	serious [a]	none	⨁⨁⨁◯ MODERATE	450	443	-	-	**MD 1.92 lower** (4.78 lower to 0.94 higher)
VAS score, 12 weeks (0-10, lower scores indicate improvement)											
198 (1 RCT)	not serious	not serious	not serious	not serious	none	⨁⨁⨁⨁ HIGH	99	99	-	-	**MD 0.73 lower** (1.27 lower to 0.19 lower) **Favors capsaicin**
WOMAC function, 12 weeks (0-68, lower scores indicate improvement)											

Table 1. Topical capsaicin compared to placebo for knee or hip OA											
Certainty assessment							Summary of findings				
893 (2 RCTs)	not serious	not serious	not serious	serious [a]	none	⨁⨁⨁◯ MODERATE	450	443	-	-	**MD 5.4 lower** (12.03 lower to 1.24 higher)

CI: Confidence interval; **MD:** Mean difference

Explanations

a. Wide CI crossing no-effect line

Table 2. Systematic review data not suitable for RevMan

Author, year	Study type	Duration	Population Description	Treatment given to relevant population	Results
709 Laslett 2014	SR	4 weeks	475 patients with knee OA from 5 RCTs	Capriacin or placebo over 4weeks	Pooled VAS pain score over 4 weeks from 5 studies: SMD 0.44 [0.25, 0.62]

References:

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PICO 98: Topical NSAIDs compared to oral NSAIDs in patients with knee or hip OA

Summary: This PICO question is addressed by 7 direct RCTs that compared topical NSAIDs to oral NSAIDs. The results showed no significant between-group difference for most pain and function outcomes, but for some of these outcomes the finding was imprecise due to wide CIs that included the possibility of a between-group difference. Severe adverse event rates did not differ significantly between groups but the finding was imprecise due to the low number of events.

Quality of Evidence across all critical outcomes: Low

Table 1. Topical NSAID compared to oral NSAID for knee and hip OA

Certainty assessment							Summary of findings				
№ of participants (studies) Follow-up	**Risk of bias**	**Inconsistency**	**Indirectness**	**Imprecision**	**Publication bias**	**Overall certainty of evidence**	**Number of patients**		**Relative effect (95% CI)**	**Anticipated absolute effects**	
							With oral NSAID	**With topical NSAID**		**Risk with oral NSAID**	**Risk difference with topical NSAID**
WOMAC pain, 2 weeks (0-500, lower scores indicate improvement)											
19 (1 RCT)	serious [a]	not serious	not serious	serious [b]	none	⨁⨁◯◯ LOW	9	10	-	-	MD **1.7 lower** (105.22 lower to 101.82 higher)
WOMAC pain, 12 weeks (lower scores indicate improvement)											

Table 1. Topical NSAID compared to oral NSAID for knee and hip OA											
Certainty assessment							**Summary of findings**				
1642 (4 studies)	not serious	not serious	not serious	not serious	none	⨁⨁⨁⨁ HIGH	817	825	-	-	SMD **0.07 higher** (0.03 lower to 0.17 higher)
pain on walking, 12 weeks (0-100, lower scores indicate improvement)											
604 (1 RCT)	not serious	not serious	not serious	serious [c]	none	⨁⨁⨁◯ MODERATE	301	303	-	-	MD **1.7 higher** (2.96 lower to 6.36 higher)
WOMAC function, 2 weeks (0-1700, lower scores indicate improvement)											
19 (1 RCT)	serious [a]	not serious	not serious	serious [b]	none	⨁⨁◯◯ LOW	9	10	-	-	MD **11.1 lower** (366.14 lower to 343.94 higher)
WOMAC function, 12 weeks (lower scores indicate improvement)											

Table 1. Topical NSAID compared to oral NSAID for knee and hip OA											
Certainty assessment							**Summary of findings**				
1179 (3 studies)	not serious	not serious	not serious	serious [c]	none	⨁⨁⨁◯ MODERATE	584	595	-	-	SMD **0.17 higher** (0.06 higher to 0.29 higher) **Favors oral NSAIDs**
WOMAC total, 12 months (0-100, lower scores indicate improvement)											
282 (1 RCT)	serious [d]	not serious	not serious	not serious	none	⨁⨁⨁◯ MODERATE	144	138	-	-	MD **1.6 higher** (2.37 lower to 5.57 higher)
SAE, 12 weeks											
463 (1 study)	serious [d]	not serious	not serious	serious [c]	none	⨁⨁◯◯ LOW	4/233 (1.7%)	3/230 (1.3%)	**OR 0.76** (0.17 to 3.42)	17 per 1,000	**4 fewer per 1,000** (14 fewer to 39 more)

CI: Confidence interval; **MD:** Mean difference

Explanations

a. Patients and personnel not blinded

b. Wide CI crossing no-effect line, small sample size

c. Wide CI crossing no-effect line

d. Data not fully reported

Table 2. RCT data not suitable for effect size calculation or combining with other data

Author, year	Study type	Duration	Population Description	Treatment given to relevant population	Results
198 Underwood 2007	RCT	12 months	282 patients with knee OA	topical (n=138) oral (n=144)	Change in WOMAC from baseline to 12 months, for topical minus oral treatment: Pain 1 (−4 to 6); function 3 (−2 to 7). Mean difference in SF-36 (topical-oral) in change from baseline to 12 months: Physical component score −1.6 (−3.5 to 0.3); Mental component score −1.0 (−3.4 to 1.3)
1158 Gor 2016	RCT	7 days	50 patients with knee OA	oral diclofenac 50 mg t.i.d. vs oral diclofenac 75 mg plus 10mg topical diclofenac t.i.d. for 7 days	VAS score mean change: -3.84 vs -4.6 Lequesne Index change: -4.68 (9.12 pre and 4.44 post) vs (3.6 post)

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PICO 99. Topical capsaicin compared to oral NSAIDs in patients with knee or hip OA

Summary. The literature searches did not identify any studies that addressed this question.

Quality of evidence across all critical outcomes: Very low

PICO 100: Topical lidocaine compared to oral NSAIDS for knee OA

Summary: The literature search identified one RCT[1] that directly compared topical lidocaine with oral NSAIDs for the treatment of knee OA. Kivitz et al.[1] compared a 5% lidocaine patch to celecoxib (200mg/d) over a 12-week treatment period. There was moderate certainty of no difference in pain or self-reported function at 12 weeks. There was also no difference in skin reactions between groups, however there was low certainty in this finding as the confidence interval was wide.

Quality of evidence across all critical outcomes**:** Low

Topical lidocaine compared to Oral NSAIDS for Knee OA									
Certainty assessment							**Summary of findings**		
№ of participants	**Risk of bias**	**Inconsistency**	**Indirectness**	**Imprecision**	**Publication bias**	**Overall certainty**	**Number of patients or Study event rates (%)**	**Relative effect (95% CI)**	**Anticipated absolute effects**

Topical lidocaine compared to Oral NSAIDS for Knee OA											
Certainty assessment							**Summary of findings**				
(studies) Follow-up						**of evidence**	**With Oral NSAIDS for Knee OA**	**With Topical lidocaine**		**Risk with Oral NSAIDS for Knee OA**	**Risk difference with Topical lidocaine**
WOMAC Pain (0-20, lower scores indicate improvement)											
143 (1 RCT)	serious [a]	not serious	not serious	not serious	none	⨁⨁⨁◯ MODERATE	74	69	-	-	MD **0.4 lower** (2.63 lower to 1.83 higher)
WOMAC function (0-68, lower scores indicate improvement)											
143 (1 RCT)	serious [a]	not serious	not serious	not serious	none	⨁⨁⨁◯ MODERATE	74	69	-	-	MD **1.6 higher** (5.57 lower to 8.77 higher)
Safety: Skin Reaction											
143 (1 RCT)	serious [a]	not serious	not serious	serious [b]	none	⨁⨁◯◯ LOW	3/74 (4.1%)	4/69 (5.8%)	**OR 1.46** (0.31 to 6.75)	41 per 1,000	**18 more per 1,000** (28 fewer to 181 more)

CI: Confidence interval; **MD:** Mean difference; **OR:** Odds ratio

Explanations

a. Blinding practices not described

b. Wide 95% confidence interval

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PICO 101. Topical capsaicin compared to topical NSAIDs in patients with knee or hip OA

Summary. The literature searches did not identify any studies that directly addressed this question. However, a recent network meta-analysis performed an indirect comparison of capsaicin and topical NSAIDs using 28 placebo-controlled trials (5 RCTs comparing capsaicin vs. placebo, 23 RCTs comparing topical NSAIDs vs. placebo). The primary outcome was pain at or nearest to 4 weeks, and the analysis found no significant difference between treatments. Average risk of bias was serious, and the quality of evidence was further downgraded by the indirect comparison and by imprecision in the effect estimate.

Quality of evidence across all critical outcomes: Very low

Table 1. Network meta-analysis data

Author, year	Study type	Duration	Population Description	Treatment given to relevant population	Results
Persson 2018	SR	4 weeks	Patients with knee OA	Capsaicin (5 RCTs, 206 patients) Topical NSAIDs (23 RCTs, 3693 patients)	Pain at or nearest to 4 weeks: SMD 0.04 (95% CI -0.26 to 0.33)

References

1. Persson MSM, Stocks J, Walsh DA, Doherty M, Zhang W. The relative efficacy of topical non-steroidal anti-inflammatory drugs and capsaicin in osteoarthritis: a network meta-analysis of randomised controlled trials. Osteoarth Cart 2018;26:1575-1582.

PICO 102: Ablation + usual care vs. Usual care for knee/hip OA

Summary: The search identified 2 RCTs that directly addressed this PICO question, and 2 that indirectly addressed the comparison. Radnovich et al.[1] randomized 180 patients with knee OA to receive either cryoneurolysis or a sham procedure. WOMAC pain and function showed a significant between-group difference favoring ablation at 4 weeks (the primary endpoint, Table 1) and 3 months (data not shown); the between-group difference became non-significant for both outcomes at 4 months (data not shown). Another RCT (Choi et al. 2011[2]) compared conventional RFA to a sham control group. The RFA group significantly improved VAS knee pain compared to controls at 3 months follow-up (Table 1). No AEs were reported. These two RCTs had low risk of bias. However, the smaller study by Choi et al. had a much larger effect size than Radnovich et al., so we did not perform a meta-analysis of pain data from these 2 trials.

For the intra-articular injection studies, one RCT (Shen et al. 2017[3]) compared conventional RFA plus intra-articular PRP and HA injections to a control group receiving intra-articular PRP and HA. At 3 months follow-up, the RFA group significantly improved knee pain and function compared to controls (measured using the VAS and SF-36)(Table 2). Walking and stair climbing similarly showed improvements favoring ablation. No serious AEs were reported. Davis et al.[4] compared cooled RFA to intra-articular steroid injection (control) and found a statistically significant between-group difference in NRS pain favoring ablation at 3 months (Table 2) and 6 months (data not shown). Although serious AEs did not differ significantly between groups, the event rates were too low to rule out the possibility of a between-group difference.

A literature search update in August 2018 identified one additional relevant RCT[5] comparing RFA to conventional oral analgesics (NSAIDs or acetaminophen). This study's findings were in agreement with the findings of the overall evidence base.

Quality of evidence across all critical outcomes: Moderate (for direct comparison data)

Table 1. Ablation compared to Sham Ablation for OA Knee

Certainty assessment							Summary of findings				
№ of participants (studies) Follow-up	Risk of bias	Inconsistency	Indirectness	Imprecision	Publication bias	Overall certainty of evidence	Number of patients		Relative effect (95% CI)	Anticipated absolute effects	
							With Placebo	With Ablation		Risk with Placebo	Risk difference with Ablation
VAS (0-100, 12 weeks)											

Table 1. Ablation compared to Sham Ablation for OA Knee											
Certainty assessment							Summary of findings				
35 (1 RCT)	not serious	not serious	not serious	serious[a]	none	⨁⨁⨁◯ MODERATE	18	17	-	-	MD **35.5 lower** (48.4 lower to 22.6 lower) **Favors ablation**
WOMAC pain (0-50, change from baseline) - 4 weeks											
180 (1 RCT)	not serious	not serious	not serious	not serious	none	⨁⨁⨁⨁ HIGH	59	121	-	-	MD **7.11 lower** (11.15 lower to 3.07 lower) **Favors ablation**
WOMAC function (0-170, change from baseline) - 4 weeks											
180 (1 RCT)	not serious	not serious	not serious	not serious	none	⨁⨁⨁⨁ HIGH	59	121	-	-	MD **21.3 lower** (34.46 lower to 8.14 lower) **Favors ablation**

CI: Confidence interval; **MD:** Mean difference

Explanations

a Small study with large effect size

Table 2. Ablation compared to intra-articular injections for OA Knee

Certainty assessment							Summary of findings				
№ of participants (studies) Follow-up	Risk of bias	Inconsistency	Indirectness	Imprecision	Publication bias	Overall certainty of evidence	Number of patients		Relative effect (95% CI)	Anticipated absolute effects	
							With intra-articular injections	With Ablation		Risk with intra-articular injections	Risk difference with Ablation
Pain (0-10, combined VAS and NRS) (at 3 months)											
187 (2 RCTs)	serious [a,b]	not serious	serious [c]	not serious	none	⨁⨁◯◯ LOW	95	92	-	-	MD **2.19 lower** (2.66 lower to 1.73 lower) **Favors ablation**
Pain VAS (0-10, 3 months) – Ablation + PRP + HA vs. PRP + HA											
54 (1 RCT)	serious [a]	not serious	serious [c]	not serious	none	⨁⨁◯◯ LOW	27	27	-	-	MD **2.04 lower** (2.65 lower to 1.43 lower) **Favors ablation**
Pain NRS (0-10, 3 months) - Ablation vs. Intra-articular CS											
133 (1 RCT)	serious [b]	not serious	serious [c]	not serious	none	⨁⨁◯◯ LOW	68	65	-	-	MD **2.4 lower** (3.12 lower to 1.68 lower) **Favors ablation**

Table 2. Ablation compared to intra-articular injections for OA Knee

Certainty assessment							Summary of findings				
SF - 36 physical function (0-100, 3 months) - Ablation + PRP + HA vs. PRP + HA											
54 (1 RCT)	serious [a]	not serious	serious [c]	not serious	none	⨁⨁◯◯ LOW	27	27	-	-	MD **9.55 higher** (4.08 higher to 15.02 higher) **Favors ablation**
Walking (at 3 months) - Ablation + PRP + HA vs. PRP + HA											
54 (1 RCT)	serious [a]	not serious	serious [c]	not serious	none	⨁⨁◯◯ LOW	27	27	-	-	MD **9.95 higher** (5.03 higher to 14.87 higher) **Favors ablation**
Stair climbing (at 3 months) - Ablation + PRP + HA vs. PRP + HA											
54 (1 RCT)	serious [a]	not serious	serious [c]	not serious	none	⨁⨁◯◯ LOW	27	27	-		MD **13.75 higher** (8.8 higher to 18.7 higher) **Favors ablation**
SAE (at 6 months) - Ablation vs. Intra-articular steroids											

Table 2. Ablation compared to intra-articular injections for OA Knee											
Certainty assessment							Summary of findings				
151 (1 RCT)	serious [b]	not serious	serious [c]	serious [d]	none	⨁◯◯◯ VERY LOW	8/75 (10.7%)	4/76 (5.3%)	**OR 0.47** (0.13 to 1.62)	107 per 1,000	**54 fewer per 1,000** (91 fewer to 55 more)

CI: Confidence interval; **MD:** Mean difference; **OR:** Odds ratio

Explanations

a No information on allocation concealment or blinding
b No blinding
c Intraarticular injection is not a usual care comparison
d Wide 95% CI that crosses line of no difference

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PICO 103: Lateral or medial wedged insole plus usual care compared to usual care for knee OA

Summary: This PICO question is addressed by 12 direct RCTs. The mean change values for most pain and function outcomes showed no significant between-group difference for lateral wedge insoles vs neutral insoles, with all results imprecise (Table 1). The results significantly favored lateral wedge insole treatment for VAS pain and Lequesne's index at 12 weeks. Medial wedged insoles had significantly more favorable

results than neutral insoles in WOMAC pain at 8 weeks and VAS pain on movement at 8 weeks (Table 3). The result for KOOS at 3 months showed no significant difference between lateral or medial wedged insoles and usual care (Table 3)

Quality of Evidence across outcomes: Low

Table 1. Lateral wedged insole compared to neutral insole for medial OA + usual care versus usual care for knee OA

Certainty assessment							Summary of findings				
№ of participants (studies) Follow-up	**Risk of bias**	**Inconsistency**	**Indirectness**	**Imprecision**	**Publication bias**	**Overall certainty of evidence**	**Number of patients**		**Relative effect (95% CI)**	**Anticipated absolute effects**	
							With neutral insole	**With Lateral wedged insole**		**Risk with neutral insole**	**Risk difference with Lateral wedged insole**
WOMAC pain, 12 months (lower scores indicate improvement)											
266 (2 RCTs)	not serious	serious [a]	not serious	serious [b]	none	⨁⨁◯◯ LOW	128	138	-	-	SMD **0.31 lower** (1.30 lower to 0.68 higher)
WOMAC pain, 24 months (lower scores indicate improvement)											
156 (1 RCT)	serious [d]	not serious	not serious	serious [b]	none	⨁⨁◯◯ LOW	74	82	-	-	SMD **0.14 higher** (0.17 lower to 0.46 higher)

Table 1. Lateral wedged insole compared to neutral insole for medial OA + usual care versus usual care for knee OA

Certainty assessment							Summary of findings				
WOMAC pain improved, 6 months (lower scores indicate improvement)											
156 (1 RCT)	serious [c,d]	not serious	not serious	serious [b]	none	⨁⨁◯◯ LOW	16/74 (21.6%)	16/82 (19.5%)	OR 0.88 (0.40 to 1.91)	216 per 1,000	**21 fewer per 1,000** (117 fewer to 129 more)
Pain on walking, 12 months (0-10, lower scores indicate improvement)											
200 (1 RCT)	not serious	not serious	not serious	not serious	none	⨁⨁⨁⨁ HIGH	97	103	-	-	MD **0.5 higher** (0.17 lower to 1.17 higher)
VAS pain, 12 weeks (lower scores indicate improvement)											
263 (3 RCTs)	serious [c,d]	not serious	not serious	not serious	none	⨁⨁⨁◯ MODERATE	130	133	-	-	SMD **0.90 lower** (1.64 lower to 0.15 lower) **Favors lateral wedge**
Lequesne's index, 12 weeks (lower scores indicate improvement)											

Table 1. Lateral wedged insole compared to neutral insole for medial OA + usual care versus usual care for knee OA

Certainty assessment							Summary of findings				
79 (1 RCT)	serious [d]	not serious	not serious	not serious	none	⨁⨁⨁◯ MODERATE	38	41	-	-	MD **2.34 lower** (4.37 lower to 0.31 lower) **Favors lateral wedge**
WOMAC function, 12 months (lower scores indicate improvement)											
266 (2 RCTs)	serious [c]	not serious	not serious	not serious	none	⨁⨁⨁◯ MODERATE	128	138	-	-	SMD **0.35 lower** (1.26 lower to 0.56 higher)
WOMAC function, 24 months (lower scores indicate improvement)											
156 (1 RCT)	serious [d]	not serious	not serious	not serious	none	⨁⨁⨁◯ MODERATE	74	82	-	-	SMD **0.18 higher** (0.13 lower to 0.50 higher)
WOMAC function improved, 6 months											

Table 1. Lateral wedged insole compared to neutral insole for medial OA + usual care versus usual care for knee OA

Certainty assessment							Summary of findings				
156 (1 RCT)	serious [c,d]	not serious	not serious	serious [b]	none	⨁⨁◯◯ LOW	10/74 (13.5%)	10/82 (12.2%)	OR 0.89 (0.35 to 2.27)	135 per 1,000	**13 fewer per 1,000** (83 fewer to 127 more)

CI: Confidence interval; **MD:** Mean difference; **OR:** Odds ratio

Explanations

a. High I-squared and Chi-squared values

b. Wide CI crossing significant effect and no-effect lines

c. The bias might be from not blinding assessor

d. Patients and personnel were not blinded

Table 2. Medial insole compared to Neutral insole for lateral OA + usual care versus usual care for knee OA

Certainty assessment							Summary of findings				
№ of participants (studies) Follow-up	**Risk of bias**	**Inconsistency**	**Indirectness**	**Imprecision**	**Publication bias**	**Overall certainty of evidence**	**Number of patients**		**Relative effect (95% CI)**	**Anticipated absolute effects**	
							With Neutral insole	**With Medial insole**		**Risk with Neutral insole**	**Risk difference with Medial insole**

Table 2. Medial insole compared to Neutral insole for lateral OA + usual care versus usual care for knee OA

Certainty assessment							Summary of findings				
WOMAC total score, 8 weeks (0-100, lower scores indicate improvement)											
30 (1 RCT)	serious [a]	not serious	not serious	serious [b]	none	⨁⨁◯◯ LOW	14	16	-	-	MD **15.5 lower** (24.24 lower to 6.76 lower) **Favors medial insole**
VAS pain on movement, 8 weeks (0-10, lower scores indicate improvement)											
30 (1 RCT)	serious [a]	not serious	not serious	serious [b]	none	⨁⨁◯◯ LOW	14	16	-	-	MD **3.4 lower** (5.29 lower to 1.51 lower) **Favors medial insole**

CI: Confidence interval; **MD:** Mean difference

Explanations

a. Non-blinded RCT

b. Small sample size

Table 3. Medial or lateral insole + usual care versus usual care compared to usual care for knee OA

Certainty assessment							Summary of findings				
№ of participants (studies) Follow-up	**Risk of bias**	**Inconsistency**	**Indirectness**	**Imprecision**	**Publication bias**	**Overall certainty of evidence**	**Number of patients**		**Relative effect (95% CI)**	**Anticipated absolute effects**	
							With control	**With Medial and lateral insole**		**Risk with control**	**Risk difference with Medial and lateral insole**
KOOS pain, 3 months (0-100, higher scores indicate improvement)											
33 (1 RCT)	serious [a]	not serious	not serious	serious [b]	none	⨁⨁◯◯ LOW	18	15	-	-	MD **5.6 higher** (5.13 lower to 16.33 higher)

CI: Confidence interval; **MD:** Mean difference

Explanations

a. Patients and personnel were not blinded

b. Wide CI crossing no-effect line

Table 4. RCT and systematic review data not suitable for RevMan

Author, year	Study type	Duration	Population Description	Treatment given to relevant population	Results
2886 Dessery 2016	Single-blinded RCT		Patients with knee OA	1) no orthoses; 2) customized foot orthosis made with arch support and without lateral inclination (neutral CFO); 3) 6° laterally wedged insole; 4) 10° laterally wedged insole	Knee pain ratings: No orthoses 23.0, Neutral CFO 21.8, with 6° CFO 20.4, with 10° CFO 24.2

5053 Campos 2015	single-blind RCT for 24 weeks	24 weeks	58 patients with knee OA	Lateral wedge insole group (W) n=29, Neutral group (N) n=29	WOMAC pain mean change: W -1.1, N -2.0 VAS change: W -6.2; N -10.1 Lequesne's index change: W -1.5; N -1
5063 Maillefert 2001	Non-blinded RCT	6-month	156 patients with medial knee osteoarthritis	laterally wedged insoles (LWI) and neutrally wedged insoles (NWI)	WOMAC pain change: LWI -0.7 (19.5%of patients with improvement); NWI -5.6 (21.6% of patients with improvement) WOMAC physical functioning change: +4.5, 12.2% with improvement); -2.7 (13.5% with improvement)
6718 Baker 2007	double-blind RCT	6 weeks	90 patients with medial knee osteoarthritis	lateral-wedge insole or a neutral insole for 6 weeks	The differential carryover was a 1.5-point difference in the WOMAC pain score (P=0.96). The mean difference between the 2 treatments across the time periods was 13.8 points (95% CI -3.9, 31.4) on the 500-point WOMAC pain scale. 11 of 86 subjects experienced minimal clinical improvement in the WOMAC pain score (>50 points) after both treatments. 21 patients achieved this level of improvement only with the wedged insole, but 19 patients achieved it only with the neutral insole (P=0.75). The lateral-wedge insole improved pain in patients with a K/L grade 4 by 21 points, compared with a 2-point improvement in those with a K/L grade of 4. Those with a BMI of 30 kg/m2 had a 29-point improvement in pain, compared with a 6-point improvement in those with a BMI>30 kg/m2 (P=0.06 for both).
1363 Sattari 2011	single-blinded RCT	9 months	60 patients with knee pain	Lateral wedge insoles (n=20) and controls (n=20)	VAS pain change: -3.7 vs -0.6
664 Duivenvoorden 2015	Cochrane review			1. Lateral wedge insole versus no insole 2. Lateral wedge insole versus neutral insole 3. Medial wedge insole versus neutral insole	**Lateral wedge insole versus no insole**: 1. Pain (VAS) MD (IV, Random, 95% CI) -1.60 [-2.31, -0.89] 2. Walking distance (km) MD 0.70 [0.52, 0.88] **Lateral wedge insole versus neutral insole**: 1. Pain at rest 12 months: -0.4 [-1.06, 0.26] 2. Pain on walking 12 months: MD 0.10 [-0.45, 0.65]; 3. WOMAC pain 12 months: 0.89 [-2.89, 4.67]; 24 months 2.80 [-6.12, 11.72]; 4. WOMAC function 12 months: 0.94 [-2.98, 4.87]; 24 months -0.40 [-9.47, 8.67]; 5. Pain VAS 6 months: -11.80 [-22.04, -1.

					6. 56]; 24 months: -2.0 [-13.34, 9.34] 7. Lequesne's index 6 months: -1.5 [-4.23, 1.23]; 24 months: -2.3 [-5.45, 0.85]. **Medial wedge insole versus neutral insole:** 1. VAS rest MD -0.40 [-2.16, 1.36] 2. VAS movement MD -2.2 [-4.04, -0.36] 3. VAS night MD -1.50 [-3.12, 0.12] 4. WOMAC MD -6.70 [-17.09, 3.69] 5. Lequesne MD -2.40 [-5.28, 0.48]

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PICO 104: Modified shoe + gait retraining + usual care vs. Usual care in patients with knee OA

Summary. This PICO was addressed by 5 RCTs [1-5]. The studies comparing modified shoes to conventional shoes show no significant difference in WOMAC pain, WOMAC function, and the 6 minute walk test, although for the latter outcome the finding was imprecise (Table 1. When comparing before and after WOMAC pain and function scores there was a significant difference with improved pain and function within each group (Table 2).

Quality of evidence across all critical outcomes: Low

Table 1. Modified shoe compared to conventional shoe for knee OA

Certainty assessment							Summary of findings				
№ of participants (studies) Follow-up	**Risk of bias**	**Inconsistency**	**Indirectness**	**Imprecision**	**Publication bias**	**Overall certainty of evidence**	**Number of patients**		**Relative effect (95% CI)**	**Anticipated absolute effects**	
							With conventional shoe	**With Modified shoe**		**Risk with conventional shoe**	**Risk difference with Modified shoe**
WOMAC Pain (change from baseline) (lower scores indicate improvement)											
279 (2 RCTs)	serious [a]	not serious	not serious	not serious	none	⨁⨁⨁◯ MODERATE	146	133	-	-	SMD **0.02 lower** (0.26 lower to 0.21 higher)

Table 1. Modified shoe compared to conventional shoe for knee OA											
Certainty assessment							Summary of findings				
WOMAC Function (change from baseline) (lower scores indicate improvement)											
279 (2 RCTs)	serious [a]	not serious	not serious	not serious	none	⨁⨁⨁◯ MODERATE	146	133	-	-	SMD **0** (0.23 lower to 0.24 higher)
6 minute walk test (m) (higher scores indicate improvement)											
56 (1 RCT)	serious [b]	not serious	not serious	serious [c]	none	⨁⨁◯◯ LOW	28	28	-	-	MD **11 higher** (9.81 lower to 31.81 higher)

CI: Confidence interval; **SMD:** Standardised mean difference; **MD:** Mean difference

Explanations

a. One study lacks allocation concealment and blinding

b. patients not blinded, no mention of allocation concealment

c. Wide 95% CI Crosses no effect line

Table 2. RCT data not suitable for effect size calculation or combining with other data

Ref ID, Author, year	Study type	Duration	Population Description	Treatment given to relevant population	Results
5189, Trombini-souza, 2015	RCT	6 Month	OA Knee Women 60-80 y/o	Modified shoe N=26 Conventional shoe N=24	**WOMAC pain score (change from baseline)** Modified shoe = -66.6% (p<0.001) Conventional shoe = -28% (p<0.001) **WOMAC function score (change from baseline)** Modified shoe = -63.2% (p<0.001) Conventional shoe = -19.4% (p<0.001)

773, Erhart, 2010	RCT	6 months	OA Knee At least 40 y/o	Variable stiffness shoe N=34 Constant stiffness shoe N=26	**WOMAC pain (change from baseline)** Modified shoe = -5.5 from baseline of 14.8 P=0.002 Control shoe = -3.1 from baseline of 16.1 P=0.16
2532, Erhart-Hledik, 2012	RCT	6 month	OA knee	Variable stiffness shoe N=32 Constant stiffness shoe N=23	**WOMAC pain (change from baseline)** Modified shoe = -4.7 from baseline of 15 P=0.002 Control shoe = -4.1 from baseline of 15.4 P=0.04

References

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PICO 105: Knee Brace compared to usual care for knee OA

Summary: This PICO question is addressed by 8 non-blinded RCTs[2-8,10], and 2 systematic reviews[1,9]. The results across all outcomes (WOMAC pain, KOOS pain, pain on stair climbing, and pain during six-minute walk) favored knee brace treatment over usual care. A literature search update in August 2018 identified one additional relevant RCT[11]; the findings of this study were consistent with the findings of the overall evidence base.

Quality of Evidence across outcomes: Moderate

Table 1. Knee brace compared to usual care for knee OA

Certainty assessment							Summary of findings				
№ of participants (studies) Follow-up	**Risk of bias**	**Inconsistency**	**Indirectness**	**Imprecision**	**Publication bias**	**Overall certainty of evidence**	**Number of patients**		**Relative effect (95% CI)**	**Anticipated absolute effects**	
							With usual care	**With Knee brace**		**Risk with usual care**	**Risk difference with Knee brace**
WOMAC pain, 6 months (0-500, lower scores indicate improvement)											
81 (1 RCT)	serious [c]	not serious	not serious	not serious	none	⨁⨁⨁◯ MODERATE	40	41	-	-	**MD 56.3** lower (88.58 lower to 24.02 lower) **Favors knee brace**
KOOS pain (0-100, higher scores indicate improvement)											
31 (1 RCT)	serious [a]	not serious	not serious	serious [b]	none	⨁⨁◯◯ LOW	15	16	-	-	**MD 8.25** higher (3.16 higher to 13.34 higher) **Favors knee brace**

Table 1. Knee brace compared to usual care for knee OA											
Certainty assessment							Summary of findings				
Pain after the stair-climbing test, 6 months (0-100, lower scores indicate improvement)											
81 (1 RCT)	serious [c]	not serious	not serious	not serious	none	⨁⨁⨁◯ MODERATE	40	41	-	-	**MD 21.49** lower (33.81 lower to 9.17 lower) **Favors knee brace**
Pain on the six-minute walking test, 6 months (0-100, lower scores indicate improvement)											
81 (1 RCT)	serious [c]	not serious	not serious	not serious	none	⨁⨁⨁◯ MODERATE	40	41	-	-	**MD 18.9** lower (29.74 lower to 8.06 lower) **Favors knee brace**

CI: Confidence interval; **MD:** Mean difference

Explanations

a. Allocation concealment and blinding of participants and personnel has not been performed

b. Small sample size

c. Blinding of participants and personnel has not been performed

Table 2. RCT and systematic review data not suitable for RevMan

Author, year	Study type	Duration	Population Description	Treatment given to relevant population	Results
603 Petersen 2016	SR of 24 articles		Patients with medial osteoarthritis (OA) of the knee	Unloader braces	Nine studies reported a decrease of pain in braced patients. One study demonstrated significant reductions in WOMAC pain score (20.4%) in the valgus knee brace group. In another study the scores from an analog pain scale decreased 48% with brace wear, and function with activities of daily living increased 79%. In another study, before brace wear, 78 % had pain with activities of daily living, but after the first evaluation, only 39 % continued to have such pain, and at the second evaluation, only 31 % were so affected.
662 Brouwer 2006	Non-blinded RCT for 12 months	12 months	117 patients with OA of the knee	Intervention group (n = 60) comprising conservative treatment with additional brace treatment and a control group (n = 57) comprising conservative treatment alone	VAS pain MD at 3 months: - 0.73 (-1.62;0.16) effect size 0.3 VAS pain MD at 6 months: - 0.58 (-1.48;0.32) effect size 0.3 VAS pain MD at 12 months: - 0.81 (-1.76;0.14), effect size 0.4 Overall VAS MD - 0.63 (-1.38;0.12), effect size 0.3
3997, Kapadia, 2016	Prospective RCT	3 month	OA knee	Pneumatic Brace N=24 Standard care N=12	**Walking speed** <u>Brace</u> Prespeed = 89.16 cm/sec (range: 51-128) Postspeed = 98.5 cm/sec (range: 54 – 157) P=0.0027 <u>Standard care</u> Prespeed = 92.5 cm/sec (range: 57-123) Postspeed = 95.5 cm/sec (range: 58 – 107) P=0.47
7981, Cherian, 2815	RCT pilot	3 month	OA knee	Knee brace N=9 Standard care N=9	**VAS (change 0-3 month)** Brace = 0.63 Standard treatment = -0.14 P = 0.44 **SF-36 physical (change 0-3 month)** Brace = 2.6 Standard treatment = 1.4 P = 0.689

					TUG test (change 0-3 month) Brace = -1 sec Standard treatment = --0.4 sec P = 0.614 **Timed stair climb (change 0-3 month)** Brace = -3 sec Standard treatment = -12 sec P = 0.24 **Chair rise (change 0-3 month)** Brace = -1.7 sec Standard treatment = -5.1 sec P = 0.141 **Two minute walk (change 0-3 month)** Brace = -21.6 feet Standard treatment = +41.8 feet P = 0.068
7395, Cherian, 2015	Prospective RCT	3 month	OA knee	Knee brace N=26 Matching control N=26	**VAS (change 0-3 month)** Brace = 1.9; p=0.0075 Standard treatment = -0.1; p=0.77 **SF-36 physical (change 0-3 month)** Brace = 2.5; p=0.31 Standard treatment = 6.3; p=0.25 **TUG test (change 0-3 month)** Brace = -2.4 sec; p=0.007 Standard treatment = --0.1 sec; p=0.096 **Timed stair climb (change 0-3 month)** Brace = -7.8 sec; p=0.0408 Standard treatment = -1.7 sec; p=0.065

					Chair rise (change 0-3 month) Brace = -1.4 sec; p=0.059 Standard treatment = -1.1 sec; p=0.23 **Two minute walk (change 0-3 month)** Brace = +43.3 feet; p=0.019 Standard treatment = -27 feet; p=0.24

References:

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PICO 106: PF brace + usual care compared to Usual care in knee OA

Summary. This PICO was addressed by 2 RCTs [1,2]. One study found a small but statistically significant improvement in KOOS pain and function for users of a PF brace compared to those who did not use a brace[1]. In contrast, the second study found no significant between-group difference in pain, function or side effects for use of an active PF brace versus an inactive PF brace (with realigning strap removed).

Quality of evidence across all critical outcomes: Low

PF Brace compared to No Brace for knee OA											
Certainty assessment							Summary of findings				
№ of participants (studies) Follow-up	Risk of bias	Inconsistency	Indirectness	Imprecision	Publication bias	Overall certainty of evidence	Number of Patients		Relative effect (95% CI)	Anticipated absolute effects	
							With No Brace	With Brace		Risk with No Brace	Risk difference with Brace
KOOS Pain (0-100, higher scores indicate improvement)											
126 (1 RCT)	serious [a]	not serious	not serious	serious [b]	none	⨁⨁◯◯ LOW	124	120	-	-	MD **5.70 higher** (0.68 higher to 10.72 higher) **Favors knee brace**
KOOS ADL (0-100, higher scores indicate improvement)											

PF Brace compared to No Brace for knee OA											
Certainty assessment							Summary of findings				
126 (1 RCT)	serious [a]	not serious	not serious	serious [b]	none	⨁⨁◯◯ LOW	63	63	-	-	MD **4.5 higher** (0.55 higher to 8.45 higher) **Favors knee brace**

CI: Confidence interval; **MD:** Mean difference

Explanations

a. Blinding of patients and providers not possible, blinding of outcome assessors possible but not reported
b. Single study with wide 95% CI.

Table 2. RCT data not suitable for RevMan

Author, year	Study type	Duration	Population Description	Treatment given to relevant population	Results
6751 Hunter 2011	Randomized crossover trial	6 weeks for each treatment period, with a 6 week washout period in-between	80 patients with symptomatic lateral patellofemoral OA	Realigning BioSkin Q brace for 6 weeks vs. Bioskin Q brace with realigning strap removed for 6 weeks (treatment order was randomized; all patients received both treatments sequentially)	VAS pain 0-10 (primary outcome): MD -0.68 (95% CI -6.20 to 4.84), p=0.8055 WOMAC pain 0-20: MD 0.11 (95% CI -0.66 to 0.88), p=0.7744 WOMAC function 0-68: MD -0.02 (95% CI -2.83 to 2.79), p=0.9878 Side effects were minor and did not differ significantly between groups.

References

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PICO 107: **Kinesiotaping compared to control for Knee OA**

Summary: The literature search identified six randomized controlled trials that addressed this PICO question (Anandkumar et al, Aydogdu et al, Cho et al, Cushnaghan et al, Hinman et al, Wageck et al).[1-6] The RCTs varied markedly in the design of the intervention and control. Interventions included U shaped, Y-shaped, horizontal, medial vertical, 3-layer tape applications, and controls included no-tension taping, horizontal taping across the quadriceps femoris, neutral taping, no taping. Study protocols also varied widely (five studies used a single-blind or non-blinded design, two used cross-over designs and three reported same-day outcome assessments). Pain by visual analog scale (VAS) was the most commonly reported pain outcome (Anandkumar et al, Aydogdu et al, Cho et al, Cushnaghan et al, Hinman et al). Three studies favored intervention (Cho et al, Cushnaghan et al, Hinman et al), and two studies reported no difference in VAS with kinesiotape application vs control (Aydogdu et al, Anandkumar et al). Additionally, two studies measured pressure pain threshold (Cho et al, Wageck et al), one favored intervention (Cho et al), and the other found no difference between intervention and control.

Function outcomes varied widely between studies, and included the WOMAC total score (Wageck et al), KOOS symptoms subscale (Aydogdu et al), and pain-free range of motion (Cho et al). All but one study reported no difference in function between intervention and control, however, Cho et al reported better pain-free range of motion in a single blind study of 46 knee OA patients with Y-shaped taping vs no-tension sham taping. Given wide heterogeneity of studies, the evidence for use of kinesiotaping for knee osteoarthritis remains unclear, as does the preferred tape application method.

A recent meta-analysis[7] including 10 RCTs reported significant benefits for therapeutic taping over control taping for pain and function improvement, but subgroup analyses suggested that the benefit was primarily associated with non-elastic leukotaping. None of the subgroup analyses showed statistically significant benefits for elastic kinesiotaping (Table 2). However, this was primarily due to one study with an effect size in the opposite direction to the effect size in other kinesiotaping studies.

A literature search update in August 2018 identified 2 additional relevant RCTs[8,9]. The findings of these studies did not alter the findings of the overall evidence base.

Quality of evidence across all critical outcomes: Low

Kinesiotape application to the knee compared to control for Knee OA									
Certainty assessment							Summary of findings		
№ of participants		Inconsistency	Indirectness	Imprecision	Publication bias	Overall certainty	Number of patients	Relative effect	Anticipated absolute effects

Kinesiotape application to the knee compared to control for Knee OA											
Certainty assessment							**Summary of findings**				
(studies) Follow-up	**Risk of bias**					**of evidence**	**With control**	**With Kinesiotape application to the knee**	**(95% CI)**	**Risk with control**	**Risk difference with Kinesiotape application to the knee**
Pain by VAS (cm) (0-10, lower scores indicate improvement)											
140 (3 RCTs)	serious [a]	serious [b]	not serious	not serious	none	⨁⨁◯◯ LOW	71	69	-	-	MD **1.33 lower** (1.65 lower to 1.01 lower) **Favors tape**
Pressure pain threshold											
118 (2 RCTs)	serious [a]	serious [c]	not serious	serious [d]	none	⨁◯◯◯ VERY LOW	59	59	-	-	MD **0.90 higher** (0.37 lower to 2.17 higher)
WOMAC total score (0-100, lower scores indicate improvement)											
72 (1 RCT)	serious [a]	not serious	not serious	not serious	none	⨁⨁⨁◯ MODERATE	36	36	-	-	MD **2 lower** (10.11 lower to 6.11 higher)
KOOS symptoms score (0-100, higher scores indicate improvement)											

Kinesiotape application to the knee compared to control for Knee OA											
Certainty assessment							**Summary of findings**				
54 (1 RCT)	serious [a]	not serious	not serious	serious [d]	none	⨁⨁◯◯ LOW	28	26	-	-	MD **2.91 lower** (9.92 lower to 4.1 higher)
Pain-free range of motion (higher scores indicate improvement)											
46 (1 RCT)	serious [a]	not serious	not serious	not serious	none	⨁⨁⨁◯ MODERATE	23	23	-	-	MD **19.4 higher** (13.45 higher to 25.35 higher) **Favors tape**

CI: Confidence interval; **MD:** Mean difference

Explanations

a. Participants not blinded

b. Different tape applications studied, two studies with null result, one favoring intervention

c. One study with null results, one favoring intervention

d. Wide confidence interval crossing no-effect line

Table 2. RCT or systematic review data not suitable for effect size calculation or combining with other data

Ref ID, Author, year	Study type	Duration	Population Description	Treatment given to relevant population	Results

Ref 5673 Ouyang 2018	Systematic review (10 RCTs)	30 minutes to 1 month across studies	10 RCTs including 359 patients with knee OA	Leukotaping (non-elastic) vs control in 5 studies Kinesiotaping (elastic) vs control in 5 studies	VAS 0-100 pain relief (9 studies) MD 12.8 mm (95% CI 6.66 to 18.89 mm); SMD 1.15 (95% CI 0.48 to 1.80), favors therapeutic taping. Kinesiotaping only (4 studies) MD 12.1 mm (95% CI -0.39 to 24.51 mm, p=0.06 Leukotaping only (5 studies) MD 11,6 mm (95% CI 8.22 to 15.07 mm), favors leukotaping Stepping and climbing stairs (4 studies) Leukotaping (2 studies): SMD 0.82 (95% CI 0.40 to 1.24), favors leukotaping. Kinesiotaping (2 studies): SMD 1.34 (95% CI -2.08 to 4.77, p=0.44 Walking (2 studies) SMD 0.77 (95% CI 0.34 to 1.20), favors therapeutic taping
Ref 7581 Cushnagh an 1994	single-blind cross-over RCT	4 days	14 Patients with knee OA	Horizontal taping medial and superior of the patella vs neutral taping, 4 days of daily application	Mean difference in pain at day 4 on a 10-point VAS, neutral tape application vs medial application: 1.55, 95%CI (0.24-2.86)
Ref 4354 Hinman 2003	Within-subject design, randomized to order of different tape applications	Same day	18 subjects with knee OA, mean age 66.9 yo	Two pieces of rigid tape applied a medial patellar glide and corrected lateral and AP tilt. Two further pieces of tape applied distal to the patella unloaded the infrapatellar fat pad, vs no taping, and no-tension taping in the same locatio	Mean difference in pain on pain when walking, 10-point VAS, no-tension tape application vs experimental application: 1.28, 95%CI (0.58–1.98)

References:

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PICO 108. Ultrasound-guided hyaluronic acid injection compared to anatomic/landmark-guided hyaluronic acid injection in patients with knee or hip OA

Summary. The literature searches did not identify any studies that addressed this question.

Quality of evidence across all critical outcomes: Very low

PICO 109. Ultrasound-guided corticosteroid injection compared to anatomic/landmark-guided corticosteroid injection in patients with knee or hip OA

Summary. The literature searches identified two RCTs that addressed this question in patients with knee OA. One RCT[1] directly compared ultrasound-guided CS injection to anatomic-guided CS injection in 92 patients with knee OA. It found significantly lower VAS pain scores in the ultrasound group compared to the anatomic group at 2 weeks post-injection, and significantly reduced pain during injection in the ultrasound group. At 6 months the effects of CS had worn off and VAS pain was equal in both groups (Table 1). The second RCT was indirect in both the patient population (more patients had RA than OA) and the intervention (arthrocentesis followed by CS injection). This trial also found greater VAS pain reduction in the ultrasound group at 2 weeks and significantly reduced pain during the procedure (Table 2). Our searches did not identify any studies comparing ultrasound-guided CS injection to anatomic-guided CS injection in patients with hip OA.

Quality of evidence across all critical outcomes: Low (for direct evidence for knee OA)

Table 1. US-guided CS injection versus Anatomic-guided CS Injection for Knee OA

Certainty assessment							Summary of findings				
№ of participants (studies) Follow-up	**Risk of bias**	**Inconsistency**	**Indirectness**	**Imprecision**	**Publication bias**	**Overall certainty of evidence**	**Number of patients**		**Relative effect (95% CI)**	**Anticipated absolute effects**	
							With anatomic-guided injection	**With US-guided injection**		**Risk with control**	**Risk difference with US-guided injection**
VAS pain score (0-10, lower scores indicate improvement) at 2 weeks											
92 (1 RCT)	serious [a]	not serious	not serious	serious [b]	none	⨁⨁◯◯ LOW	46	46	-	-	MD **1 lower** (1.86 lower to 0.14 lower)
VAS pain score (0-10, lower scores indicate improvement) at 6 months											
92 (1 RCT)	serious [a]	not serious	not serious	serious [b]	none	⨁⨁◯◯ LOW	46	46	-	-	MD **0** (1.13 lower to 1.13 higher)
VAS pain score (0-10, lower scores indicate improvement) during injection											
92 (1 RCT)	serious [a]	not serious	not serious	serious [b]	none	⨁⨁◯◯ LOW	46	46	-	-	MD **2.1 lower** (2.92 lower to 1.28 lower)

CI: Confidence interval; **MD:** Mean difference

Explanations

a. patients not blinded, randomization method and allocation concealment not reported

b. Single study with wide 95% CI

Table 2. US-guided Arthrocentesis plus CS injection versus Anatomic-guided Arthrocentesis plus CS Injection for Knee OA

Certainty assessment							Summary of findings				
№ of participants (studies) Follow-up	**Risk of bias**	**Inconsistency**	**Indirectness**	**Imprecision**	**Publication bias**	**Overall certainty of evidence**	**Number of patients**		**Relative effect (95% CI)**	**Anticipated absolute effects**	
							With anatomic-guided injection	**With US-guided injection**		**Risk with control**	**Risk difference with US-guided injection**
VAS pain score (0-10, lower scores indicate improvement) at 2 weeks											
64 (1 RCT)	serious [a]	not serious	serious [b]	serious [c]	none	⨁◯◯◯ VERY LOW	22	42	-	-	MD **1.3 lower** (2.46 lower to 0.14 lower)
VAS pain score (0-10, lower scores indicate improvement) during injection											
64 (1 RCT)	serious [a]	not serious	serious [b]	serious [c]	none	⨁◯◯◯ VERY LOW	22	42	-	-	MD **2.8 lower** (4.31 lower to 1.29 lower)

CI: Confidence interval; **MD:** Mean difference

Explanations

a. Patients not blinded, randomization method and allocation concealment not reported

b. Two-thirds of patients had RA, not OA, and arthrocentesis was used prior to CS injection.

c. Single study with wide 95% CI

References

1. Sibbitt WL Jr, Band PA, Kettwich LG, Chavez-Chiang NR, Delea SL, Bankhurst AD. A randomized controlled trial evaluating the cost-effectiveness of sonographic guidance for intra-articular injection of the osteoarthritic knee. J Clin Rheumatol. 2011;17(8):409-15.
2. Sibbitt WL Jr1, Kettwich LG, Band PA, Chavez-Chiang NR, DeLea SL, Haseler LJ, Bankhurst AD. Does ultrasound guidance improve the outcomes of arthrocentesis and corticosteroid injection of the knee? Scand J Rheumatol. 2012 Feb;41(1):66-72.

PICO 110: **Pulsed electrical stimulation compared to control for Knee OA**

Summary: The literature search identified four RCTs that addressed this PICO question (Fary et al, Gundog et al, Garland et al, Zizic et al)[1-4]. All RCTs provided direct evidence by comparing pulsed electrical therapy to sham interventions. Three of the four RCTs favored pulsed electrical stimulation over control for pain (Gundog et al, Garland et al, Zizic et al), and one favored control (Fary et al). Three of the four RCTs favored pulsed electrical stimulation over control for function (Gundog et al, Garland et al, Zizic et al), and one showed a null result (Fary et al). The study by Gundog et al. that showed the most precise effect on both pain and function favoring pulsed electrical stimulation was rather different from the rest of the studies. This was a single blinded study that evaluated interferential current therapy vs sham applied for 20 minutes per session 5 days a week for 3 weeks. All other studies were double-blind RCTs and evaluated pulsed electrical stimulation vs sham applied for 6-7 hrs a day for 4-26 weeks. Meta-analysis of 3 of these RCTs found no significant between-group difference for WOMAC pain and function, but the findings were inconclusive due to serious inconsistency and serious imprecision in summary effect estimates.

Quality of evidence across all critical outcomes: Very low

Pulsed electrical stimulation compared to control for Knee OA											
Certainty assessment							**Summary of findings**				
№ of participants (studies) Follow-up	**Risk of bias**	**Inconsistency**	**Indirectness**	**Imprecision**	**Publication bias**	**Overall certainty of evidence**	**Number of patients**		**Relative effect (95% CI)**	**Anticipated absolute effects**	
							With control	**With pulsed electrical stimulation**		**Risk with control**	**Risk difference with pulsed electrical stimulation**
WOMAC pain score (lower scores indicate improvement)											

Pulsed electrical stimulation compared to control for Knee OA											
Certainty assessment							Summary of findings				
158 (3 RCTs)	serious [a]	serious [b]	not serious	serious [c]	none	⨁◯◯◯ VERY LOW	70	88	-	-	SMD **1.02 lower** (2.47 lower to 0.44 higher)
WOMAC function score (lower scores indicate improvement)											
158 (3 RCTs)	serious [a]	serious [d]	not serious	serious [c]	none	⨁◯◯◯ VERY LOW	70	88	-	-	SMD **1.36 lower** (2.97 lower to 0.25 higher)

CI: Confidence interval; **MD:** Mean difference

Explanations

a. One of the three contributing trials was not blinded

b. Two studies (including one non-blinded) favor intervention, and one blinded study favors control

c. CIs cross the no effect line for both blinded studies

d. Two studies (including one non-blinded) favor intervention, and one blinded study has a null result

Table 2. RCT data not suitable for effect size calculation or combining with other data

Ref ID, Author, year	Study type	Duration	Population Description	Treatment given to relevant population	Results

7892 Zizic, 1995	double-blind RCT	4 weeks	78 patients with knee OA	Pulsed electrical stimulation vs sham, 6 hrs/day for 4 weeks	% difference in patient assessment of pain (not otherwise described): Intervention group: 31.3% (N = 38); Control group: 19.01% (N = 33), p 0.04 % difference in patient assessment of function (not otherwise described): Intervention group: 30.25% (N = 38); Control group: 19.42% (N = 33), p 0.045

References

1. Fary, R. E., et al. (2011). "The effectiveness of pulsed electrical stimulation in the management of osteoarthritis of the knee: results of a double-blind, randomized, placebo-controlled, repeated-measures trial." Arthritis Rheum 63(5): 1333-1342.
2. Garland, D., et al. (2007). "A 3-month, randomized, double-blind, placebo-controlled study to evaluate the safety and efficacy of a highly optimized, capacitively coupled, pulsed electrical stimulator in patients with osteoarthritis of the knee." Osteoarthritis Cartilage 15(6): 630-637.
3. Gundog, M., et al. (2012). "Interferential current therapy in patients with knee osteoarthritis: comparison of the effectiveness of different amplitude-modulated frequencies." Am J Phys Med Rehabil 91(2): 107-113.
4. Zizic, T. M., et al. (1995). "The treatment of osteoarthritis of the knee with pulsed electrical stimulation." J Rheumatol 22(9): 1757-1761.

Hand Osteoarthritis

PICO 1. Oral NSAIDs compared to no treatment in patients with hand OA

Summary. The literature searches identified one relevant double-blind RCT that addressed this question. The study compared lumiracoxib (200 or 400 mg daily) to placebo in patients with symptomatic hand OA. At 4 weeks, lumiricoxib (both dosages) showed significant benefit over placebo for improvement of VAS pain and AUSCAN pain. For AUSCAN function scores, only the 400 mg dose led to a significant improvement compared to placebo.

Quality of evidence across all critical outcomes: Moderate

NSAIDs (200 mg) compared to placebo for Hand OA for Hand OA											
Certainty assessment							**Summary of findings**				
№ of participants (studies) Follow-up	**Risk of bias**	**Inconsistency**	**Indirectness**	**Imprecision**	**Publication bias**	**Overall certainty of evidence**	**Study event rates (%)**		**Relative effect (95% CI)**	**Anticipated absolute effects**	
							With placebo for Hand OA	**With NSAIDs (200 mg)**		**Risk with placebo for Hand OA**	**Risk difference with NSAIDs (200 mg)**
VAS pain (0-100, change from baseline to 4 weeks)											
401 (1 RCT)	serious [a]	not serious	not serious	not serious	none	⨁⨁⨁◯ MODERATE	196	205	-	-	MD **8.7 lower** (12.93 lower to 4.47 lower)
AUSCAN pain (0-20, change from baseline to 4 weeks)											
401 (1 RCT)	serious [a]	not serious	not serious	not serious	none	⨁⨁⨁◯ MODERATE	196	205	-	-	MD **0.9 lower** (1.71 lower to 0.09 lower)

NSAIDs (200 mg) compared to placebo for Hand OA for Hand OA											
Certainty assessment							**Summary of findings**				
AUSCAN function (0-36, change from baseline to 4 weeks)											
401 (1 RCT)	serious [a]	not serious	not serious	not serious	none	⨁⨁⨁◯ MODERATE	196	205	-	-	MD **1.2 lower** (2.6 lower to 0.2 higher)

CI: Confidence interval; **MD:** Mean difference

Explanations

a. Randomization method and allocation concealment not reported

NSAIDs (400 mg) compared to placebo for Hand OA for Hand OA **Bibliography: . NSAIDs versus No Treatment for Hand OA. Cochrane Database of Systematic Reviews [Year], Issue [Issue].**											
Certainty assessment							**Summary of findings**				
Nº of participants (studies) Follow-up	**Risk of bias**	**Inconsistency**	**Indirectness**	**Imprecision**	**Publication bias**	**Overall certainty of evidence**	**Study event rates (%)**		**Relative effect (95% CI)**	**Anticipated absolute effects**	
							With placebo for Hand OA	**With NSAIDs (400 mg)**		**Risk with placebo for Hand OA**	**Risk difference with NSAIDs (400 mg)**
VAS pain (0-100, change from baseline to 4 weeks)											
389 (1 RCT)	serious [a]	not serious	not serious	not serious	none	⨁⨁⨁◯ MODERATE	196	193	-	-	MD **10.7 lower** (15.13 lower to 6.27 lower)
AUSCAN pain (0-20, change from baseline to 4 weeks)											

NSAIDs (400 mg) compared to placebo for Hand OA for Hand OA Bibliography: . NSAIDs versus No Treatment for Hand OA. Cochrane Database of Systematic Reviews [Year], Issue [Issue].											
Certainty assessment							Summary of findings				
389 (1 RCT)	serious [a]	not serious	not serious	not serious	none	⨁⨁⨁◯ MODERATE	196	193	-	-	MD **1.8 lower** (2.66 lower to 0.94 lower)
AUSCAN function (0-36, change from baseline to 4 weeks)											
389 (1 RCT)	serious [a]	not serious	not serious	not serious	none	⨁⨁⨁◯ MODERATE	196	193	-	-	MD **2.9 lower** (4.34 lower to 1.46 lower)

CI: Confidence interval; **MD:** Mean difference

Explanations

a. Randomization method and allocation concealment not reported

References

1. Grifka JK, Zacher J, Brown JP, Seriolo B, Lee A, Moore A, Gimona A. Efficacy and tolerability of lumiracoxib versus placebo in patients with osteoarthritis of the hand. Clin Exp Rheum. 2004;22:589-596.

PICO 2. Acetaminophen compared to no treatment in patients with hand OA

Summary. The literature searches did not identify any studies that addressed this question.

Quality of evidence across all critical outcomes: Very low

PICO 3. Bisphonates compared to no treatment in patients with hand OA

Summary. The literature searches did not identify any studies that addressed this question.

Quality of evidence across all critical outcomes: Very low

PICO 4. Glucosamine compared to no treatment in patients with hand OA

Summary. The literature searches did not identify any studies that addressed this question.

Quality of evidence across all critical outcomes: Very low

PICO 5: Chondroitin compared to no treatment for hand OA

Summary: One randomized trial compared chondroitin to no treatment (placebo) in 162 patients with hand OA.[1] At 6 months, this study found significantly lower scores in pain (VAS) and self-reported function (FIHOA) favoring chondroitin over no treatment, although the wide CIs include the possibility of a non-clinically significant difference between groups. Serious adverse event rates were similar in both groups, although the small number of events means the possibility of a between-group difference cannot be ruled out.

Overall quality of evidence for all critical outcomes: Low

Chondroitin compared to no treatment for hand OA											
Certainty assessment							Summary of findings				
№ of participants (studies) Follow-up	Risk of bias	Inconsistency	Indirectness	Imprecision	Publication bias	Overall certainty of evidence	Number of events		Relative effect (95% CI)	Anticipated absolute effects	
							With no treatment	With chondroitin		Risk with no treatment	Risk difference with chondroitin
Pain VAS (0-100, lower scores indicate improvement)											

Chondroitin compared to no treatment for hand OA											
Certainty assessment							**Summary of findings**				
162 (1 RCT)	serious [a]	not serious	not serious	serious [b]	none	⨁⨁◯◯ LOW	82	80	-	-	MD **8.7 lower** (16.41 lower to 0.99 lower) **Favors chondroitin**
FIHOA score (0 to 30, 30 worst possible score) (lower scores indicate improvement)											
162 (1 RCT)	serious [a]	not serious	not serious	serious [b]	none	⨁⨁◯◯ LOW	82	80	-	-	MD **2.2 lower** (3.76 lower to 0.64 lower) **Favors chondroitin**
Mean grip strength change from baseline to 6 months (performance based function) (higher scores indicate improvement)											
162 (1 RCT)	serious [a]	not serious	not serious	serious [b]	none	⨁⨁◯◯ LOW	82	80	-	-	MD **1.9 higher** (0.02 lower to 3.82 higher)
SAEs over 6 month trial											

Chondroitin compared to no treatment for hand OA											
Certainty assessment							Summary of findings				
162 (1 RCT)	serious [a]	not serious	not serious	serious [b]	none	⨁⨁◯◯ LOW	2/82 (2.4%)	2/80 (2.5%)	**OR 1.03** (0.14 to 7.46)	24 per 1,000	**1 more per 1,000** (21 fewer to 133 more)

CI: Confidence interval; **MD:** Mean difference; **OR:** Odds ratio

Explanations

[a] Differential drop-out, with nearly twice as many dropouts in the placebo group.
[b] Wide 95% CI that includes possibility of no effect or no clinically significant effect

References

1. Gabay C, Medinger-Sadowski C, Gascon D, Kolo F, Finckh A. Symptomatic effects of chondroitin 4 and chondroitin 6 sulfate on hand osteoarthritis: a randomized, double-blind, placebo-controlled clinical trial at a single center. Arthritis Rheum. 2011;63(11):3383-3391.

PICO 6. Glucosamine plus chondroitin compared to no treatment for hand OA

Summary. The literature searches did not identify any studies that addressed this question.

Quality of evidence across all critical outcomes: Very low

PICO 7. Non-tramadol opioids compared to no treatment for hand OA

Summary. The literature searches did not identify any studies that addressed this question.

Quality of evidence across all critical outcomes: Very low

PICO 8. Tramadol compared to no treatment in patients with hand OA

Summary. The literature searches did not identify any studies that addressed this question.

Quality of evidence across all critical outcomes: Very low

PICO 9. Duloxetine compared to no treatment in patients with hand OA

Summary. The literature searches identified one RCT[1] that compared Duloxetine (30 to 60 mg daily) to placebo in patients with hand OA. In the intention-to-treat analysis there were no significant between-group differences in AUSCAN pain or function or NRS pain at 13 weeks.

Quality of evidence across all critical outcomes: Low

Duloxetine compared to no treatment for Hand OA										
Certainty assessment							**Summary of findings**			
№ of participants (studies) Follow-up	**Risk of bias**	**Inconsistency**	**Indirectness**	**Imprecision**	**Publication bias**	**Overall certainty of evidence**	**Number of patients**		**Relative effect (95% CI)**	**Anticipated absolute effects**	
							With no treatment (placebo) for 13 wks	**With duloxetine for 13 weeks**		**Risk with no treatment (placebo) for 8 wks**	**Risk difference with diclofenac sodium gel 1% (Voltaren)**
AUSCAN pain index (0 no pain, 100 extreme pain) change from baseline to 8 wks (lower scores indicate improvement)											

Duloxetine compared to no treatment for Hand OA											
Certainty assessment							**Summary of findings**				
43 (1 RCT)	serious [a]	not serious	not serious	serious [b]	none	⨁⨁◯◯ LOW	22	21	-	The mean AUSCAN pain was **0**	MD **10.81 higher** (79.75 lower to 101.37 higher)
AUSCAN function index (0 very good, 100 very poor) change from baseline to 8 wks (lower scores indicate improvement)											
43 (1 RCT)	serious [a]	not serious	not serious	serious [b]	none	⨁⨁◯◯ LOW	22	21	-	The mean AUSCAN function was **0**	MD **34.5 lower** (195.82 lower to 126.82 higher)
NRS pain (0 to 10, lower scores indicate improvement)											
43 (1 RCT)	serious [a]	not serious	not serious	serious [b]	none	⨁⨁◯◯ LOW	22	21	-	The mean NRS pain was **0**	MD **1.4 lower** (3.15 lower to 0.35 higher)

CI: Confidence interval; **MD:** Mean difference

Explanations

a. Unclear description of allocation concealment, >20% attrition in treatment group

b. Wide 95% CI that overlaps line of no effect

References

1. Sofat N, Harrison A, Russell MD, Ayis S, Kiely PD, Baker EH, et al. The effect of pregabalin or duloxetine on arthritis pain: a clinical and mechanistic study in people with hand osteoarthritis. J Pain Res. 2017;10:2437-2449.

PICO 11: Topical NSAIDs compared to no treatment for hand OA

Summary: One randomized trial compared diclofenac sodium gel 1% (Voltaren) to no treatment (placebo) in 385 patients with hand OA.[1] This study found lower AUSCAN pain and function scores favoring diclofenac at 8 weeks, although only the function score change from baseline to 8 weeks was significantly improved compared to placebo. Although more patients in the diclofenac group experienced skin reactions, the 95% CI was wide and there was no significant between-group difference.

Overall quality of evidence for all critical outcomes: Low

Diclofenac sodium gel 1% (Voltaren) compared to no treatment (placebo) for 8 wks for hand OA											
Certainty assessment							**Summary of findings**				
№ of participants (studies) Follow-up	**Risk of bias**	**Inconsistency**	**Indirectness**	**Imprecision**	**Publication bias**	**Overall certainty of evidence**	**Number of patients**		**Relative effect (95% CI)**	**Anticipated absolute effects**	
							With no treatment (placebo) for 8 wks	**With diclofenac sodium gel 1% (Voltaren)**		**Risk with no treatment (placebo) for 8 wks**	**Risk difference with diclofenac sodium gel 1% (Voltaren)**
AUSCAN pain index (0 no pain, 100 extreme pain) change from baseline to 8 wks (lower scores indicate improvement)											

Diclofenac sodium gel 1% (Voltaren) compared to no treatment (placebo) for 8 wks for hand OA											
Certainty assessment							**Summary of findings**				
385 (1 RCT)	serious [a]	not serious	not serious	serious [b]	none	⨁⨁◯◯ LOW	187	198	-	-	MD **4.7 lower** (10.17 lower to 0.77 higher)
AUSCAN function index (0 very good, 100 very poor) change from baseline to 8 wks (lower scores indicate improvement)											
385 (1 RCT)	serious [a]	not serious	not serious	not serious	none	⨁⨁⨁◯ MODERATE	187	198	-	-	MD **7.3 lower** (12.86 lower to 1.74 higher)
skin reaction (application site reaction)											
385 (1 RCT)	serious [a]	not serious	not serious	serious [b]	none	⨁⨁◯◯ LOW	4/187 (2.1%)	9/198 (4.5%)	**OR 2.18** (0.66 to 7.20)	21 per 1,000	**24 more per 1,000** (7 fewer to 115 more)

CI: Confidence interval; **MD:** Mean difference; **OR:** Odds ratio

Explanations

a Randomization method and allocation concealment not reported.

b Wide 95% CI that overlaps with the line of no difference.

References

1. Altman RD, Dreiser RL, Fisher CL, Chase WF, Dreher DS, Zacher J. Diclofenac sodium gel in patients with primary hand osteoarthritis: a randomized, double-blind, placebo-controlled trial. J Rheumatol. 2009;36(9):1991-1999.

PICO 12. Topical capsaicin compared to no treatment in patients with hand OA

Summary. The literature searches did not identify any studies that addressed this question.

Quality of evidence across all critical outcomes: Very low

PICO 13. Iontophoresis compared to no treatment in patients with hand OA

Summary. The literature searches did not identify any studies that addressed this question.

Quality of evidence across all critical outcomes: Very low

PICO 14. Acetaminophen compared to oral NSAIDs in patients with hand OA

Summary. The literature searches did not identify any studies that addressed this question.

Quality of evidence across all critical outcomes: Very low

PICO 15. Glucosamine compared to oral NSAIDs in patients with hand OA

Summary. The literature searches did not identify any studies that addressed this question.

Quality of evidence across all critical outcomes: Very low

PICO 16. Chondroitin compared to oral NSAIDs in patients with hand OA

Summary. The literature searches did not identify any studies that addressed this question.

Quality of evidence across all critical outcomes: Very low

PICO 17. Glucosamine plus chondroitin compared to oral NSAIDs in patients with hand OA

Summary. The literature searches did not identify any studies that addressed this question.

Quality of evidence across all critical outcomes: Very low

PICO 18. Non-tramadol opioids compared to oral NSAIDs in patients with hand OA

Summary. The literature searches did not identify any studies that addressed this question.

Quality of evidence across all critical outcomes: Very low

PICO 19. Tramadol compared to oral NSAIDs in patients with hand OA

Summary. The literature searches did not identify any studies that addressed this question.

Quality of evidence across all critical outcomes: Very low

PICO 20. Duloxetine compared to oral NSAIDs in patients with hand OA

Summary. The literature searches did not identify any studies that addressed this question.

Quality of evidence across all critical outcomes: Very low

PICO 21. Anti-nerve growth factor compared to oral NSAIDs in patients with hand OA

Summary. The literature searches did not identify any studies that addressed this question.

Quality of evidence across all critical outcomes: Very low

PICO 22. Topical NSAIDs compared to oral NSAIDs in patients with hand OA

Summary. The literature searches did not identify any studies that addressed this question.

Quality of evidence across all critical outcomes: Very low

PICO 23. Topical capsaicin compared to oral NSAIDs in patients with hand OA

Summary. The literature searches did not identify any studies that addressed this question.

Quality of evidence across all critical outcomes: Very low

PICO 24. Iontophoresis compared to oral NSAIDs in patients with hand OA

Summary. The literature searches did not identify any studies that addressed this question.

Quality of evidence across all critical outcomes: Very low

PICO 25 Intra-articular corticosteroid vs oral NSAIDS for hand OA

Summary. Two double-blind RCTs indirectly addressed this comparison.[1,2] Both studies compared intra-articular corticosteroid vs intra-articular placebo (saline) injections in patients with hand OA. In one study[1] patients in both groups were allowed to take oral NSAIDs, while the other trial did not mention anything about NSAID use.[2] There were no significant differences between groups for pain (VAS), function (DASH), or grip strength, but the findings were imprecise. The combination of indirectness in the comparison and imprecision in the results means the strength of evidence for all outcomes was low.

Overall strength of evidence for all critical outcomes: Low

Ref ID, Author, year	Study type	Duration	Population Description	Treatment given to relevant population	Results

4300 Heyworth, 2008	Double-blind RCT	26 wks	40 patients with CMC joint OA See Revman for more details	Intra-articular steroid vs intra-articular placebo injection. Oral NSAIDS permitted throughout trial. See Revman for more details	Data reported in graph form, no SD or SE provided. There were no significant differences between groups for pain (VAS), function (DASH), or grip strength. **Grip strength** placebo (n=18) Baseline 39 26 wks 36 Steroid (n=22) Baseline 41 26 wks 38 **DASH (self-reported function)** placebo (n=18) Baseline 33 26 wks 22 Steroid (n=22) Baseline 41 26 wks 30 **Pinch strength key pinch** – no data presented **Pinch strength – tip pinch** no data presented **Pain (VAS)** placebo (n=18) Baseline 4.5 26 wks 3.95 Steroid (n=22) Baseline 4.8 26 wks 3.75
6633 Meenagh, 2004	Double-blind RCT	24 wks	40 patients with CMC joint OA See Revman for more details	Intra-articular steroid vs intra-articular placebo injection. No mention either way that patients could or could not use oral NSAIDS.	Followup data are reported as median change scores (interquartile range) compared to baseline. There was no significant between-group difference in pain (VAS). **Pain VAS** Placebo (n=20) Baseline median score 56 (50 to 78) 24 wks 14.0 (-12.5 to 16.9)

				See Revman for more details	Steroid (n=20) Baseline median score 52 (40 to 72) 24 wks 0.0 (-12.5 to 2.3)

References

1. Heyworth BE, Lee JH, Kim PD, Lipton CB, Strauch RJ, Rosenwasser MP. Hylan versus corticosteroid versus placebo for treatment of basal joint arthritis: a prospective, randomized, double-blinded clinical trial. J Hand Surg Am. 2008;33(1):40-48.
2. Meenagh GK, Patton J, Kynes C, Wright GD. A randomised controlled trial of intra-articular corticosteroid injection of the carpometacarpal joint of the thumb in osteoarthritis. Ann Rheum Dis. 2004;63(10):1260-1263.

PICO 26. Intra articular hyaluronic acid compared to oral NSAIDS for hand OA

Summary. Two RCTs indirectly addressed this question by comparing intra-articular hyaluronic acid to intra-articular saline in patients with hand OA.[1,2] All patients in one trial[1] had previously not responded to NSAIDs, and no mention was made regarding whether NSAID use was allowed during the trial. The other trial[2] allowed NSAID use. At 24 weeks follow-up in one trial,[1] VAS pain and functional status did not differ significantly between groups, but the 95% CI was too wide to rule out the possibility of a benefit from hyaluronic acid injection (Table 1). The other trial[2] did not report measures of dispersion and found no significant difference between groups in VAS pain, function (DASH) or grip strength at 26 weeks follow-up, but the findings were imprecise (Table 2).

Overall quality of evidence for all critical outcomes: Very low

Table 1. PICO 26 intra articular hyaluronic acid compared to oral NSAIDS for hand OA

Certainty assessment							Summary of findings		
№ of participants		**Inconsistency**	**Indirectness**	**Imprecision**	**Publication bias**	**Overall certainty**	**Number of patients**	**Relative effect**	**Anticipated absolute effects**

Table 1. PICO 26 intra articular hyaluronic acid compared to oral NSAIDS for hand OA											
Certainty assessment							Summary of findings				
(studies) Follow-up	**Risk of bias**					**of evidence**	**With intra-articular saline**	**With intra-articular hyaluronic acid**	**(95% CI)**	**Risk with oral NSAIDS**	**Risk difference with PICO 26 intra articular hyaluronic acid**
VAS pain at 24 wks followup, post scores only (0-100, lower scores indicate improvement)											
62 (1 RCT)	serious [a]	not serious	serious [b]	serious [c]	none	⨁◯◯◯ VERY LOW	31	31	-	-	MD **2.5 lower** (8.05 lower to 3.05 higher)
Dreiser functional index, 24 wks, post scores only (0-30, lower scores indicate improvement)											
62 (1 RCT)	serious [a]	not serious	serious [b]	serious [c]	none	⨁◯◯◯ VERY LOW	31	31	-	-	MD **4 lower** (8.12 lower to 0.12 higher)

CI: Confidence interval; **MD:** Mean difference

Explanations

a Allocation concealment and blinding of outcome assessor not reported, some outcomes not reported for both groups separately

b Control group received intra-articular saline, not reported whether any patients in either group received NSAIDs.

c. Wide 95% CI that crosses line of no effect

Table 2. RCT data not suitable for effect size calculation or combining with other data

Ref ID, Author, year	Study type	Duration	Population Description	Treatment given to relevant population	Results
4300 Heyworth, 2008	Double-blind RCT	26 wks	38 patients with CMC joint OA	Intra-articular hylan vs intra-articular placebo injection. Oral NSAIDS permitted throughout trial.	Data reported in graph form, no SD or SE provided. There was no significant difference between groups in pain, DASH, or grip strength. **Grip strength** placebo (n=18) Baseline 39 26 wks 36 Hylan (n=20) Baseline 42 26 wks 45 **DASH (self-reported function)** placebo (n=18) Baseline 33 26 wks 22 Hylan (n=20) Baseline 37 26 wks 26 **Pinch strength key pinch** – no data presented **Pinch strength – tip pinch** no data presented **Pain (VAS)** placebo (n=18) Baseline 4.5 26 wks 3.95 Hylan (n=20) Baseline 4.8 26 wks 3.3

References

1. Figen Ayhan F, Ustun N. The evaluation of efficacy and tolerability of Hylan G-F 20 in bilateral thumb base osteoarthritis: 6 months follow-up. Clin Rheumatol. 2009;28(5):535-541.
2. Heyworth BE, Lee JH, Kim PD, Lipton CB, Strauch RJ, Rosenwasser MP. Hylan versus corticosteroid versus placebo for treatment of basal joint arthritis: a prospective, randomized, double-blinded clinical trial. J Hand Surg Am. 2008;33(1):40-48.

PICO 27. Tramadol compared to non-tramadol opioids in patients with hand OA

Summary. The literature searches did not identify any studies that addressed this question.

Quality of evidence across all critical outcomes: Very low

PICO 28. Topical capsaicin compared to topical NSAIDs in patients with hand OA

Summary. The literature searches did not identify any studies that addressed this question.

Quality of evidence across all critical outcomes: Very low

PICO 29. Intra articular hyaluronic acid compared to intra-articular steroid for hand OA

Summary. Three RCTs compared intra-articular hyaluronic acid to intra-articular steroid in patients with hand OA.[1-3] At 6 months follow-up in one trial,[1] VAS pain was significantly lower in the steroid group compared to the HA group, despite the HA group receiving 3 injections (1 week apart) and the steroid group receiving only one injection (Table 1). The other two trials did not find a significant between group difference in pain at 6 months (Table 2). Functional outcomes (grip or pinch strength) did not differ significantly between groups for two studies,[1,2] but the findings were imprecise. The other trial[3] did not report measures of dispersion but found significant differences favoring HA grip strength and pinch strength at 6 months (Table 2).

Overall quality of evidence for all critical outcomes: Low

Intra-articular HA compared to intra-articular steroid for hand OA

Certainty assessment							Summary of findings				
№ of participants (studies) Follow-up	**Risk of bias**	**Inconsistency**	**Indirectness**	**Imprecision**	**Publication bias**	**Overall certainty of evidence**	**Number of patients**		**Relative effect (95% CI)**	**Anticipated absolute effects**	
							With intra-articular steroid	**With intra-articular HA**		**Risk with intra-articular steroid**	**Risk difference with intra-articular HA**
VAS pain at 6 months, post scores (0-10, lower scores indicate improvement)											
40 (1 RCT)	serious [a]	not serious	not serious	serious [b]	none	⨁⨁◯◯ LOW	20	20	-	-	MD **2.2 higher** (0.95 higher to 3.45 higher) **Favors steroid**
VAS pain at 12 months, post scores (0-10, lower scores indicate improvement)											
40 (1 RCT)	serious [a]	not serious	not serious	serious [b]	none	⨁⨁◯◯ LOW	20	20	-	-	MD **1.1 higher** (0.17 lower to 2.37 higher)
grip strength at 6 months, change score (higher scores indicate improvement)											
40 (1 RCT)	serious [a]	not serious	not serious	serious [b]	none	⨁⨁◯◯ LOW	20	20	-	-	MD **0.4 lower** (6.47 lower to 5.67 higher)

Intra-articular HA compared to intra-articular steroid for hand OA											
Certainty assessment							**Summary of findings**				
grip strength at 12 months, change scores (higher scores indicate improvement)											
40 (1 RCT)	serious [a]	not serious	not serious	serious [b]	none	⨁⨁◯◯ LOW	20	20	-	-	MD **1.2 higher** (5.38 lower to 7.78 higher)
pinch strength, 6 months change scores (higher scores indicate improvement)											
40 (1 RCT)	serious [a]	not serious	not serious	serious [b]	none	⨁⨁◯◯ LOW	20	20	-	-	MD **1 higher** (0.35 lower to 2.35 higher)
pinch strength at 12 months, change score (higher scores indicate improvement)											
40 (1 RCT)	serious [a]	not serious	not serious	serious [b]	none	⨁⨁◯◯ LOW	20	20	-	-	MD **0.8 higher** (0.51 lower to 2.11 higher)

CI: Confidence interval; **MD:** Mean difference

Explanations

a No blinding of patients or personnel, allocation concealment not reported

b Wide 95% CI, small number of patients

Table 2.

Ref ID, Author, year	Study type	Duration	Population Description	Treatment given to relevant population	Results
4300 Heyworth, 2008	Double-blind RCT	26 wks	42 patients with CMC joint OA	Hylan vs steroid	Data reported in graph form, no SD or SE provided. No significant differences between groups for pain (VAS), function (DASH), and grip strength. **Grip strength** Hylan (n=20) Baseline 42 26 wks 45 Steroid (n=22) Baseline 41 26 wks 38 **DASH (self-reported function)** Hylan (n=20) Baseline 37 26 wks 26 Steroid (n=22) Baseline 41 26 wks 30 **Pinch strength key pinch** – no data presented **Pinch strength – tip pinch** not all data for all time points reported but at 12 weeks hylan (3.3 kg F) and steroid (2.4 kg F). **Pain (VAS)** Hylan (n=20) Baseline 4.8 26 wks 3.3 Steroid (n=22) Baseline 4.8 26 wks 3.75
4688 Fuchs, 2006	Outcome observer blinded RCT	26 wks	56 patients with OA of the thumb CMC joint	Sodium hyaluronic acid (SH Ostenil mini) vs.	Data reported as medians for pain VAS SH Baseline: 65.5 (n=28) 26 week followup: 30.0 (n=25)

Ref ID, Author, year	Study type	Duration	Population Description	Treatment given to relevant population	Results
				triamcinolone acetate (TA Volon)	% reporting improvement 88% TA Baseline: 63.5 (n=28) 26 week followup: 45.5 (n=26) % reporting improvement 79.1% There was no statistically significant difference in % reporting improvement in pain, authors stated that non-inferiority was proven for this outcome. Lateral pinch power after 26 weeks Univariate Mann Whitney estimators and one-sided 97.5% CI for lateral pinch (key grip) strength: after 6 months of treatment moderate superiority of the SH-group was found (MW: 0.6331, lower bound CI: 0.5273, P-value: 0.0226). After 6 months 52.0% of the SH-group and 42.3% of the TA-group patients reported improvement. Pulp pinch power also using MW test: According to study author superiority of SH-group could be observed (week 26: MW: 0.6062, lower bound CI: 0.474, P-value: 0.1045). After 6 months 40.0% of the SH-group and 28.0% of the TA-group patients reported improvement.

References

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PICO 30. Hand exercise plus usual care compared to usual care for hand OA

Summary. The literature search identified 5 RCTs that addressed this comparison in patients with hand OA.[1-5] Three studies that measured pain improvement (AUSCAN score or VAS) found no significant between-group difference at 4 to 12 months follow-up for hand exercise versus usual care (Tables 1 and 2).[2-4] Two studies measuring self-reported function (FIHOA or AUSCAN scores} did not find a significant between-group difference at 3-4 months,[3,5] but one out of two studies found a significant difference (AUSCAN score) favoring hand exercise at 6 months (Tables 1 and 2).[5] Three out of four studies found no significant between-group difference in grip strength at 3-6 months (Tables 1 and 2), but imprecision in effect estimates renders this finding inconclusive. One study found no significant between-group difference in pinch strength (Tables 1).[2] Another study that measured pinch strength did not report whether the between-group difference was statistically significant.[3]

Quality of evidence across all critical outcomes: Low

Table 1. Hand exercise compared to usual care for hand OA

Certainty assessment							Summary of findings				
№ of participants (studies) Follow-up	**Risk of bias**	**Inconsistency**	**Indirectness**	**Imprecision**	**Publication bias**	**Overall certainty of evidence**	**Number of patients**		**Relative effect (95% CI)**	**Anticipated absolute effects**	
							With usual care	**With hand exercise**		**Risk with usual care**	**Risk difference with hand exercise**
AUSCAN pain mean difference (6 mo) (0-20, lower scores indicate improvement)											
257 (1 RCT)	serious [a]	not serious	serious [g]	not serious	none	⨁⨁◯◯ LOW	127	130	-	-	MD **0.4 lower** (1.37 lower to 0.57 higher)
AUSCAN pain mean difference (12 mo) (0-20, lower scores indicate improvement)											
257 (1 RCT)	serious [a]	not serious	serious [g]	not serious	none	⨁⨁◯◯ LOW	127	130	-	-	MD **0.8 lower** (1.73 lower to 0.13 higher)

Table 1. Hand exercise compared to usual care for hand OA

Certainty assessment							Summary of findings				
AUSCAN function mean difference (6 mo) (0-36, lower scores indicate improvement)											
257 (1 RCT)	serious [a]	not serious	serious [g]	not serious	none	⨁⨁◯◯ LOW	127	130	-	-	MD **1.2 lower** (3.08 lower to 0.68 higher)
FIHOA Mean change (3 mo) (0-30, lower scores indicate improvement)											
201 (2 RCTs)	serious [b]	not serious	serious [g]	serious [c]	none	⨁◯◯◯ VERY LOW	99	102	-	-	MD **2.27 lower** (5.4 lower to 0.87 higher)
FIHOA Mean change (6 mo) (0-30, lower scores indicate improvement)											
130 (1 RCT)	not serious	not serious	serious [g]	not serious	none	⨁⨁⨁◯ MODERATE	65	65	-	-	MD **0.6 lower** (0.81 lower to 0.39 lower) **Favors exercise**
Mean change R hand grip strength; Martin vigorimeter (3 mo) (higher scores indicate improvement)											
40 (1 RCT)	serious [d]	not serious	serious [g]	serious [c]	none	⨁◯◯◯ VERY LOW	20	20	-	-	MD **0.09 higher** (0.03 lower to 0.21 higher)
Mean change R hand max grip strength; Jaymar dynamom (3 mo) (higher scores indicate improvement)											

Table 1. Hand exercise compared to usual care for hand OA											
Certainty assessment							Summary of findings				
130 (1 RCT)	not serious	not serious	serious [g]	serious [c]	none	⨁⨁◯◯ LOW	65	65	-	-	MD **1.1 higher** (1.71 lower to 3.91 higher)
Mean change R hand max grip strength; Jaymar dynamom (6 mo) (higher scores indicate improvement)											
130 (1 RCT)	not serious	not serious	serious [g]	serious [c]	none	⨁⨁◯◯ LOW	65	65	-	-	MD **1 higher** (1.85 lower to 3.85 higher)
Mean change max grip strength R hand; Grippit electronic device (3 mo) (higher scores indicate improvement)											
71 (1 RCT)	serious [e]	not serious	serious [g]	not serious	none	⨁⨁◯◯ LOW	34	37	-	-	MD **51.2 higher** (24.9 higher to 77.5 higher) **Favors exercise**
Grip strength (6 mo) (higher scores indicate improvement)											
257 (1 RCT)	serious [a]	not serious	serious [g]	serious [c]	none	⨁◯◯◯ VERY LOW	127	130	-	-	MD **1.7 higher** (3.64 lower to 7.04 higher)
Pinch strength (6 mo) (higher scores indicate improvement)											

Table 1. Hand exercise compared to usual care for hand OA											
Certainty assessment							Summary of findings				
257 (1 RCT)	serious [a]	not serious	serious [g]	not serious	none	⨁⨁◯◯ LOW	127	130	-	-	MD **0.4 higher** (0.47 lower to 1.27 higher)
Pain/swelling all fingers (3 mo)											
130 (1 RCT)	not serious	not serious	serious [g]	very serious [f]	none	⨁◯◯◯ VERY LOW	0/65 (0.0%)	2/65 (3.1%)	**OR 5.16** (0.24 to 109.55)	0 per 1,000	**0 fewer per 1,000** (0 fewer to 0 fewer)

CI: Confidence interval; **MD:** Mean difference; **OR:** Odds ratio

Explanations

a. Baseline data not presented for all groups

b. Patients and providers not blinded in one study

c. Wide 95% CI that overlaps line of no effect

d. Patients not blinded, randomization method and allocation concealment not reported

e. Patients and providers not blinded

f. Very wide 95% CI based on very low number of events

g. Indirectness due to heterogeneity in the patient populations (mixed different types of hand OA)

Table 2. RCT data not suitable for effect size calculation or combining with other data

Ref ID, Author, year	Study type	Duration	Population Description	Treatment given to relevant population	Results
7205 Dziedzic, 2015	RCT (4-groups)	Primary outcome at 6 months; 3, 6, 12 months	257 participants 50 years of age or older with hand OA	4 treatment groups: (1) joint protection; (2) hand exercises; (3) joint protection and hand exercises combined; (4) no joint protection or hand exercises.	Note: AUSCAN pain, 6 months: (Adjusted mean difference) 0.06 (-0.85 to 0.97); direction of effect differs with raw calculations Adverse events: No adverse events related to interventions were reported.
3715 Rogers, 2009	Randomized controlled crossover trial	16 weeks	76 patients aged 50 or over with radiographic OA in at least one hand joint (n=46 completed the full 48-week follow up)	Hand exercise program vs. placebo (sham therapeutic hand cream application)	**AUSCAN Physical Function score (16 weeks)** Exercise group: 476 at baseline vs. 460 at follow-up; difference = -16 Sham group: 473 at baseline vs. 433 at follow-up; difference = -40 ($p<0.05$) **AUSCAN Pain score (16 weeks)** Exercise: group: 225 at baseline vs. 190 at follow-up; difference = -35 ($p<0.05$) Sham group: 230 at baseline vs. 190 at follow-up; difference = -40 ($p<0.05$) **Max grip strength (16 weeks)** Exercise group: Right: 42.53 at baseline vs.44.5 at follow-up; difference = 1.98 ($p<0.05$) Left: 38.35 at baseline vs.40.88 at follow-up; difference = 2.53 ($p<0.05$) Sham group: Right: 43.28 at baseline vs.43.78 at follow-up; difference = 0.50 Left: 39.70 at baseline vs.39.40 at follow-up; difference = 0.30 **Max key pinch strength (16 weeks)** Exercise group: Right: 10.88 at baseline vs.11.78 at follow-up; difference = 0.90 ($p<0.05$)

Ref ID, Author, year	Study type	Duration	Population Description	Treatment given to relevant population	Results
					Left: 9.44 at baseline vs.10.68 at follow-up; difference = 1.24 (p<0.05) Sham group: Right: 11.05 at baseline vs.11.01 at follow-up; difference = 0.04 Left: 9.49 at baseline vs.9.51 at follow-up; difference = 0.03
4930 Stamm, 2002	RCT	3 months	40 patients with hand OA	Joint protection and home hand exercise instruction vs. controls (information about hand OA)	VAS for pain: n.s. difference between groups (data not shown)
2330 Hennig, 2015 5082 Osteras, 2014 3715 Rogers, 2009 4930 Stamm, 2002	RCTs	variable		Hand exercise vs. control or sham	**Grip Strength summary data: % change** % chng L % chng R 2330 Hennig con -7.8 -6.1 exer 21.2 26.9 5082 Osteras con -1.8 -1.3 (3mo) exer 6.2 3.5 (3mo) con -5.3 -6.7 (6mo) exer -4.8 -2.6 (6mo) 3715 Rogers sham -0.8 1.2 exer 6.6 4.6 4930 Stamm con 5.7 5.6 exer 25.0 27.9

References

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2. Dziedzic K, Nicholls E, Hill S, Hammond A, Handy J, Thomas E, et al. Self-management approaches for osteoarthritis in the hand: a 2x2 factorial randomised trial. Ann Rheum Dis. 2015;74(1):108-118.
3. Rogers MW, Wilder FV. Exercise and hand osteoarthritis symptomatology: a controlled crossover trial. J Hand Ther. 2009;22(1):10-17; discussion 19-20; quiz 18.
4. Stamm TA, Machold KP, Smolen JS, Fischer S, Redlich K, Graninger W, et al. Joint protection and home hand exercises improve hand function in patients with hand osteoarthritis: a randomized controlled trial. Arthritis Rheum. 2002;47(1):44-49.
5. Osteras N, Hagen KB, Grotle M, Sand-Svartrud AL, Mowinckel P, Kjeken I. Limited effects of exercises in people with hand osteoarthritis: results from a randomized controlled trial. Osteoarthritis Cartilage. 2014;22(9):1224-1233.

PICO 31. Paraffin/usual care compared to usual care for hand OA

Summary. Two RCTs with 107 patients addressed this comparison.[1,2] In one trial[1], treatment duration was 3 weeks with a follow-up of 12 weeks. At 12 weeks, a significant between-group difference favoring paraffin over usual care for improved AUSCAN pain, but the finding was imprecise due to the small sample size and wide 95% CI. No significant between-group difference was found for AUSCAN function, but imprecision due to the wide 95% CI means that a significant difference favoring paraffin could not be ruled out (Table 1). Grip strength was significantly higher at 12 weeks in the paraffin group, while pinch strength did not show a significant between-group difference (Table 2). The second trial[2] had a treatment duration of 2 weeks with a 6-week follow-up. At 2 and 6 weeks, paraffin plus home exercise showed significantly greater benefit compared to home exercise alone for VAS pain, AUSCAN, HAQ, hand grip strength, and pinch strength.

Overall quality of evidence for all critical outcomes: Low

PICO 31 paraffin/UC compared to UC for hand OA											
Certainty assessment							Summary of findings				
№ of participants (studies) Follow-up	Risk of bias	Inconsistency	Indirectness	Imprecision	Publication bias	Overall certainty of evidence	Number of patients		Relative effect (95% CI)	Anticipated absolute effects	
							With UC	With paraffin/UC		Risk with UC	Risk difference with paraffin/UC

PICO 31 paraffin/UC compared to UC for hand OA											
Certainty assessment							**Summary of findings**				
AUSCAN pain at 12 wks (0-20, lower scores indicate improvement)											
46 (1 RCT)	serious [a]	not serious	not serious	serious [b]	none	⨁⨁◯◯ LOW	22	24	-	-	MD **3.05 lower** (5.67 lower to 0.43 lower) **Favors paraffin**
AUSCAN function at 12 wks (0-36, lower scores indicate improvement)											
46 (1 RCT)	serious [a]	not serious	not serious	serious [b]	none	⨁⨁◯◯ LOW	22	24	-	-	MD **4.02 lower** (8.53 lower to 0.49 higher)

CI: Confidence interval; **MD:** Mean difference

Explanations

a. Patients not blinded

b. Small study with wide 95% CI

Table 2. RCT data not suitable for effect size calculation or combining with other data

Ref ID, Author, year	Study type	Duration	Population Description	Treatment given to relevant population	Results
Refid 3435 Dilek, 2013	RCT	12 weeks	56 patients with hand OA , 46 included in final analysis	Paraffin bath/UC vs UC	All data are reported as median (25% to 75%) **Pain at rest VAS (0 to 10 cm scale, higher worse)** Paraffin group (24) Baseline 5.00 (4.00 to 5.00)

Ref ID, Author, year	Study type	Duration	Population Description	Treatment given to relevant population	Results
					3 wk. (end of treatment) 2.00 (0.00 to 4.00) 12 wk. (end of study) 0.00 (0.00 to 3.00) Control (22) Baseline 4.00 (3.00 to 8.00) 3 wk. (end of treatment) 4.00 (3.00 to 5.00) 12 wk. (end of study) 5.00 (1.00 to 6.00) **Pain during ADL VAS (0 to 10 cm scale, higher worse)** Paraffin group (24) Baseline 7.00 (7.00 to 9.00) 3 wk. (end of treatment) 5.00 (3.00 to 6.00) 12 wk. (end of study) 5.00 (3.00 to 6.50) Control (22) Baseline 8.00 (6.00 to 8.00) 3 wk. (end of treatment) 7.00 (5.00 to 8.00) 12 wk. (end of study) 7.00 (5.00 to 8.00) **Grip strength (JAMAR dynamometer) right (dominant hand in all cases) hand** Paraffin group (24) Baseline 18.00 (14.66 to 24.66) 3 wk. (end of treatment) 18.00 (15.33 to 22.66) 12 wk. (end of study) 20.00 (14.66 to 23.33) Control (22) Baseline 16.66 (11.33 to 22.66) 3 wk. (end of treatment) 16.00 (12.60 to 20.66) 12 wk. (end of study) 13.33 (10.00 to 18.66) **Grip strength (JAMAR dynamometer) left hand** Paraffin group (24) Baseline 18.00 (14.00 to 21.33) 3 wk. (end of treatment) 17.33 (15.00 to 22.00) 12 wk. (end of study) 18.00 (14.66 to 22.00) Control (22) Baseline 15.33 (12.66 to 21.00) 3 wk. (end of treatment) 16.66 (12.00 to 20.66)

Ref ID, Author, year	Study type	Duration	Population Description	Treatment given to relevant population	Results
					12 wk. (end of study) 12.00 (9.33 to 18.00) **Pinch strength (kg) right hand chuck pinch** Paraffin group (24) Baseline 4.33 (3.50 to 5.50) 3 wk. (end of treatment) 4.50 (3.66 to 6.00) 12 wk. (end of study) 5.33 (3.33 to 6.33) Control (22) Baseline 5.16 (3.83 to 6.33) 3 wk. (end of treatment) 4.33 (3.00 to 5.83) 12 wk. (end of study) 3.66 (2.66 to 5.33) The authors also reported data for lateral pinch (p value significant) and pulp to pulp pinch (p value not significant) **Pinch strength (kg) left hand chuck pinch** Paraffin group (24) Baseline 4.66 (3.33 to 6.00) 3 wk. (end of treatment) 4.33 (3.83 to 5.50) 12 wk. (end of study) 4.83 (3.50 to 6.16) Control (22) Baseline 4.83 (3.50 to 5.16) 3 wk. (end of treatment) 4.50 (3.00 to 5.66) 12 wk. (end of study) 3.66 (2.60 to 5.00) The authors also reported data for lateral pinch (p value significant) and pulp to pulp pinch (p value not significant)
9152 Aksoy and Altan 2018	RCT	6 weeks	61 patients with hand OA	Paraffin therapy + home-based exercise vs home-based exercise alone	**VAS pain** Median at 6 weeks: -3 vs. -0.6, p<0.001, favors paraffin **AUSCAN** Median at 6 weeks: -4 vs. -1, p<0.001, favors paraffin **HAQ** Median at 6 weeks: -0.45 vs. 0.00, p<0.001, favors paraffin **Hand grip strength (kg)** Median at 6 weeks: 1.96 vs. 0.45, p=0.026, favors paraffin **Pinch strength (kg)** Median at 6 weeks: 1.09 vs. 0.21, p=0.012, favors paraffin

References

1. Dilek B, Gozum M, Sahin E, Baydar M, Ergor G, El O, et al. Efficacy of paraffin bath therapy in hand osteoarthritis: a single-blinded randomized controlled trial. Arch Phys Med Rehabil. 2013;94(4):642-649.
2. Aksoy M, Altan L. Short-term efficacy of paraffin therapy and home-based exercise programs in the treatment of symptomatic hand osteoarthritis. Turk J Phys Med Rehab 2018;64(2):108-113

PICO 32. Therapeutic heat/usual care compared to usual care for hand OA

Summary. One RCT addressed this comparison for 90 patients with hand OA. Stange-Rezende et al.[1] randomized patients to heat therapy using infrared radiation in a tiled stove room, three times a week for three weeks, plus usual care versus usual care as the control. VAS pain did not show a significant between-group difference in improvement, while AUSCAN pain showed a significant improvement favoring heat therapy over usual care. AUSCAN function and grip strength did not show significant between-group differences.

Quality of evidence for all critical outcomes: Low

PICO 32 therapeutic heat/UC compared to UC for hand OA											
Certainty assessment							Summary of findings				
№ of participants (studies) Follow-up	Risk of bias	Inconsistency	Indirectness	Imprecision	Publication bias	Overall certainty of evidence	Study event rates (%)		Relative effect (95% CI)	Anticipated absolute effects	
							With UC	With therapeutic heat/UC		Risk with UC	Risk difference with therapeutic heat/UC
pain in hands VAS, change score (0-100, lower scores indicate improvement)											
90 (1 RCT)	serious [a]	not serious	serious	serious [b]	none	⨁◯◯◯ VERY LOW	45	45	-	-	MD **1.7 lower** (9.31 lower to 5.91 higher)

PICO 32 therapeutic heat/UC compared to UC for hand OA											
Certainty assessment							**Summary of findings**				
AUSCAN pain, change score, (0-20, higher scores indicate improvement)											
90 (1 RCT)	serious [a]	not serious	not serious	serious [b]	none	⨁⨁◯◯ LOW	45	45	-	-	MD **0.95 higher** (0 to 1.9 higher) **Favors heat**
AUSCAN function, change score (0-36, higher scores indicate improvement)											
90 (1 RCT)	serious [a]	not serious	not serious	serious [b]	none	⨁⨁◯◯ LOW	45	45	-	-	MD **0.76 lower** (2.32 lower to 0.8 higher)
grip strength, change score, higher scores indicate improvement											
90 (1 RCT)	serious [a]	not serious	not serious	not serious	none	⨁⨁⨁◯ MODERATE	45	45	-	-	MD **0** (0.04 lower to 0.04 higher)

CI: Confidence interval; **MD:** Mean difference

Explanations

a. Patients not blinded, randomization method and allocation concealment not reported

b. Wide 95% CI that overlaps line of no effect

c. Unique intervention probably not reproducible in clinical practice

References

1. Stange-Rezende L, Stamm TA, Schiffert T, Sahinbegovic E, Gaiger A, Smolen J, et al. Clinical study on the effect of infrared radiation of a tiled stove on patients with hand osteoarthritis. Scand J Rheumatol. 2006;35(6):476-480.

PICO 33. Therapeutic cooling plus usual care compared to usual care in patients with hand OA

Summary. The literature searches did not identify any studies that addressed this question.

Quality of evidence across all critical outcomes: Very low

PICO 34. Patient education plus usual care compared to usual care for hand OA

Summary. Two RCTs addressed this comparison in patients with hand OA.[1,2] One small low-quality RCT[1] found a significant reduction in hand pain during activity favoring education at the end of 10 weeks, but no significant difference in pain at rest or grip strength (Table 1). Imprecision in the effect estimates means that a between-group difference could not be ruled out. The remaining study[2] found no significant between-group difference in GAT scores at 6 months, but the finding is imprecise (Table 2). The high risk of bias and serious imprecision in this evidence base means that the quality of evidence is very low.

Quality of evidence across all critical outcomes: Very low

Table 1. PICO 34 patient education and UC compared to UC for hand OA

Certainty assessment							Summary of findings				
№ of participants (studies) Follow-up	Risk of bias	Inconsistency	Indirectness	Imprecision	Publication bias	Overall certainty of evidence	Number of patients		Relative effect (95% CI)	Anticipated absolute effects	
							With UC for hand OA	With patient education and UC		Risk with UC for hand OA	Risk difference with patient education and UC
VAS pain at rest at the end of the treatment period, change score (lower scores indicate improvement)											

Table 1. PICO 34 patient education and UC compared to UC for hand OA											
Certainty assessment							Summary of findings				
30 (1 RCT)	very serious [a]	not serious	not serious	serious [b]	none	⨁◯◯◯ VERY LOW	11	19	-	-	MD **1.77 lower** (4.83 lower to 1.29 higher)
VAS hand pain during activity at the end of the treatment period, change score (lower scores indicate improvement)											
30 (1 RCT)	very serious [a]	not serious	not serious	serious [b]	none	⨁◯◯◯ VERY LOW	11	19	-	-	MD **3.29 lower** (5.3 lower to 1.28 lower) **Favors education**
grip strength at the end of treatment for the right hand, change score (higher scores indicate improvement)											
30 (1 RCT)	very serious [a]	not serious	not serious	serious [b]	none	⨁◯◯◯ VERY LOW	11	19	-	-	MD **0.85 higher** (3.22 lower to 4.92 higher)
grip strength at the end of treatment for the left hand, change score (higher scores indicate improvement)											

Table 1. PICO 34 patient education and UC compared to UC for hand OA											
Certainty assessment							**Summary of findings**				
30 (1 RCT)	very serious [a]	not serious	not serious	serious [b]	none	⨁◯◯◯ VERY LOW	11	19	-	-	MD **3.69 higher** (0.37 lower to 7.75 higher)

CI: Confidence interval; **MD:** Mean difference

Explanations

a. No blinding of patients, providers or outcome assessors, randomization method and allocation concealment not reported

b. Small study with wide 95% CI

Table 2. RCT data not suitable for effect size calculation or combining with other data

Ref ID, Author, year	Study type	Duration	Population Description	Treatment given to relevant population	Results
2221 Hansson, 2010	Single-blind RCT	6 months	114 patients with knee, hip or hand OA	Education/UC vs UC	Baseline data reported as mean and SD but 6 month followup data is reported as mean change, no SD provided. All patients had all tests so some without hand OA took this test too. Reported as ITT. **GAT (high scores correspond to decreased hand function)** Education/UC (n=61) Baseline 22.87 (SD 10.09) 6 month mean change -1.52 UC (n=53) Baseline 24.67 (SD 7.83) 6-month mean change -1.69

References

1. Garfinkel MS, Schumacher HR, Jr., Husain A, Levy M, Reshetar RA. Evaluation of a yoga based regimen for treatment of osteoarthritis of the hands. J Rheumatol. 1994;21(12):2341-2343.

2. Hansson EE, Jonsson-Lundgren M, Ronnheden AM, Sorensson E, Bjarnung A, Dahlberg LE. Effect of an education programme for patients with osteoarthritis in primary care--a randomized controlled trial. BMC Musculoskelet Disord. 2010;11:244.

PICO 35. Occupational therapy (OT)/hand therapy plus UC compared to UC for hand OA

Summary. The literature search identified four RCTs that addressed this comparison.[1-4] One study found a significant between-group difference in VAS pain favoring OT at 2 to 3 months, but a second study found no between-group difference.[1,4] Two studies measuring pain using AUSCAN did not find a significant difference at 3 months.[1,2] However, the same two studies did find a significant between-group difference in AUSCAN function favoring OT at 3 months. None of the studies found a significant between-group difference in COPM performance, pinch strength or grip strength, but these findings were inconclusive due to wide 95% CIs around the summary effect estimates.

Quality of evidence across all critical outcomes: Low

PICO 35 OT/hand therapy plus UC compared to UC for hand OA											
Certainty assessment							Summary of findings				
№ of participants (studies) Follow-up	Risk of bias	Inconsistency	Indirectness	Imprecision	Publication bias	Overall certainty of evidence	Number of patients		Relative effect (95% CI)	Anticipated absolute effects	
							With UC	With OT/hand therapy plus UC		Risk with UC	Risk difference with OT/hand therapy plus UC
pain VAS at 2 to 3 month followup (lower scores indicate improvement)											
130 (2 RCTs)	serious [a]	not serious	not serious	serious	none	⨁⨁◯◯ LOW	65	65	-	-	SMD **5.63 lower** (16.5 lower to 5.24 higher)
AUSCAN pain at 3 months (0-20, lower scores indicate improvement)											

PICO 35 OT/hand therapy plus UC compared to UC for hand OA											
Certainty assessment							Summary of findings				
216 (2 RCTs)	serious [b]	not serious	not serious	not serious	none	⨁⨁⨁◯ MODERATE	107	109	-	-	MD **0.12 lower** (0.52 lower to 0.28 higher)
AUSCAN function at 3 months (0-36, lower scores indicate improvement)											
216 (2 RCTs)	serious [b]	not serious	not serious	not serious	none	⨁⨁⨁◯ MODERATE	107	109	-	-	MD **0.49 lower** (0.84 lower to 0.15 lower) **Favors OT**
tip pinch strength at 2 months, post scores (higher scores indicate improvement)											
60 (1 RCT)	not serious	not serious	not serious	not serious	none	⨁⨁⨁⨁ HIGH	30	30	-	-	MD **0** (0.1 lower to 0.1 higher)
COPM performance/activity at 3 months											
217 (2 RCTs)	serious [b]	not serious	not serious	serious [c]	none	⨁⨁◯◯ LOW	107	110	-	-	MD **1 higher** (1.65 lower to 3.64 higher)
grip strength at 2 to 3 months											
206 (2 RCTs)	serious [b]	not serious	not serious	serious [c]	none	⨁⨁◯◯ LOW	102	104	-	-	MD **0.4 lower** (2.9 lower to 2.09 higher)

CI: Confidence interval; **COPM**: Canadian occupational performance measure; **MD:** Mean difference

Explanations

a. Patients and providers not blinded in one study

b. Patients and providers not blinded in both studies

c. Wide 95% CI that overlaps line of no effect

References

1. Kjeken I, Darre S, Smedslund G, Hagen KB, Nossum R. Effect of assistive technology in hand osteoarthritis: a randomised controlled trial. Ann Rheum Dis. 2011;70(8):1447-1452.
2. Stukstette MJ, Dekker J, den Broeder AA, Westeneng JM, Bijlsma JW, van den Ende CH. No evidence for the effectiveness of a multidisciplinary group based treatment program in patients with osteoarthritis of hands on the short term; results of a randomized controlled trial. Osteoarthritis Cartilage. 2013;21(7):901-910.
3. Villafane JH, Silva GB, Fernandez-Carnero J. Effect of thumb joint mobilization on pressure pain threshold in elderly patients with thumb carpometacarpal osteoarthritis. J Manipulative Physiol Ther. 2012;35(2):110-120.
4. Villafane JH, Cleland JA, Fernandez-de-Las-Penas C. The effectiveness of a manual therapy and exercise protocol in patients with thumb carpometacarpal osteoarthritis: a randomized controlled trial. J Orthop Sports Phys Ther. 2013;43(4):204-213.

PICO 36. Acupuncture plus usual care compared to usual care in patients with hand OA

Summary. The literature searches did not identify any studies that addressed this question.

Quality of evidence across all critical outcomes: Very low

PICO 37. Digital orthosis plus usual care compared to usual care in patients with hand OA

Summary. The literature searches did not identify any studies that addressed this question.

Quality of evidence across all critical outcomes: Very low

PICO 38. Glove plus usual care compared to usual care in patients with hand OA

Summary. The literature searches identified one systematic review that evaluated 4 randomized crossover studies that indirectly addressed this question. The studies compared compression gloves to placebo gloves. The evidence is indirect because the majority of the 74 patients had RA; only 5 patients had hand OA. For these 5 patients, no significant between-group differences were found for nocturnal pain, stiffness, overall arthritis/health assessment, or grip strength (numbers not reported).

Quality of evidence across all critical outcomes: Very low

Table 1. SR data not suitable for effect size calculation or combining with other data

Ref ID, Author, year	Study type	Duration	Population Description	Treatment given to relevant population	Results
2835 Hammond 2016	Systematic review of 4 randomized crossover studies	Range 2 to 8 weeks across studies	Most patients had RA; only 5 patients had hand OA	Compression gloves vs. placebo gloves	For hand OA patients (n=5): No significant between-group differences were found for nocturnal pain, stiffness, overall arthritis/health assessment, or grip strength (numbers not reported).

References

1. Hammond A, Jones V, Prior Y. The effects of compression gloves on hand symptoms and hand function in rheumatoid arthritis and hand osteoarthritis: a systematic review. Clin Rehab. 2016;30(3):213-224.

PICO 39. Strengthening exercises compared to stretching/ROM exercises in patients with hand OA

Summary. The literature searches did not identify any studies that addressed this question.

Quality of evidence across all critical outcomes: Very low

PICO 40. HCQ plus NSAIDs plus usual care compared to oral NSAIDs for symptomatic erosive hand OA

Summary. The literature searches identified two double-blind multicenter RCTs[1,2] that indirectly addressed this question. HCQ (200 to 400 mg daily) showed no significant benefit over placebo for any pain and function outcomes at 6 to 12 months of follow-up. Serious adverse events did not differ significantly between HCQ and placebo. Because HCQ showed no benefit over placebo, and NSAIDs are known to be effective for pain relief, we did not downgrade the quality of the evidence for indirectness.

Quality of evidence across all critical outcomes: Moderate

HCQ compared to placebo for Hand OA for Hand OA
Bibliography: . HCQ versus No Treatment for Hand OA. Cochrane Database of Systematic Reviews [Year], Issue [Issue].

Certainty assessment							Summary of findings				
№ of participants (studies) Follow-up	**Risk of bias**	**Inconsistency**	**Indirectness**	**Imprecision**	**Publication bias**	**Overall certainty of evidence**	**Study event rates (%)**		**Relative effect (95% CI)**	**Anticipated absolute effects**	
							With placebo for Hand OA	**With HCQ**		**Risk with placebo for Hand OA**	**Risk difference with HCQ**
VAS or NRS (6 months)											
428 (2 RCTs)	not serious	not serious	not serious	serious [a]	none	⨁⨁⨁◯ MODERATE	217	211	-	-	SMD **0.02 lower** (0.21 lower to 0.17 higher)
VAS pain at 12 months											
232 (1 RCT)	not serious	not serious	not serious	serious [a]	none	⨁⨁⨁◯ MODERATE	119	113	-	-	SMD **0.04 lower** (0.3 lower to 0.22 higher)
AUSCAN pain at 6 months											
232 (1 RCT)	not serious	not serious	not serious	serious [a]	none	⨁⨁⨁◯ MODERATE	119	113	-	-	MD **0.15 higher** (1 lower to 1.3 higher)
AUSCAN pain at 12 months											

HCQ compared to placebo for Hand OA for Hand OA

Bibliography: . HCQ versus No Treatment for Hand OA. Cochrane Database of Systematic Reviews [Year], Issue [Issue].

Certainty assessment							Summary of findings				
230 (1 RCT)	not serious	not serious	not serious	serious [a]	none	⨁⨁⨁◯ MODERATE	117	113	-	-	MD **0.54 higher** (0.63 lower to 1.71 higher)
AUSCAN function at 6 months											
230 (1 RCT)	not serious	not serious	not serious	serious [a]	none	⨁⨁⨁◯ MODERATE	118	112	-	-	MD **0.32 higher** (1.69 lower to 2.33 higher)
AUSCAN function at 12 months											
230 (1 RCT)	not serious	not serious	not serious	serious [a]	none	⨁⨁⨁◯ MODERATE	118	112	-	-	MD **0.98 higher** (1.06 lower to 3.02 higher)
AUSCAN total score at 6 months											
196 (1 RCT)	not serious	not serious	not serious	serious [a]	none	⨁⨁⨁◯ MODERATE	98	98	-	-	MD **1.9 lower** (6.93 lower to 3.13 higher)
Grip strength at 12 months (right hand)											

HCQ compared to placebo for Hand OA for Hand OA Bibliography: . HCQ versus No Treatment for Hand OA. Cochrane Database of Systematic Reviews [Year], Issue [Issue].											
Certainty assessment							Summary of findings				
208 (1 RCT)	not serious	not serious	not serious	serious [a]	none	⨁⨁⨁◯ MODERATE	103	105	-	-	MD **0.95 lower** (3.28 lower to 1.38 higher)
Serious adverse events											
232 (1 RCT)	not serious	not serious	not serious	serious [a]	none	⨁⨁⨁◯ MODERATE	8/119 (6.7%)	7/113 (6.2%)	**OR 0.92** (0.32 to 2.62)	67 per 1,000	**5 fewer per 1,000** (45 fewer to 92 more)

CI: Confidence interval; **SMD:** Standardised mean difference; **MD:** Mean difference; **OR:** Odds ratio

Explanations

a. Wide 95% CI that overlaps with line of no effect

References

1. Kingsbury SR, Tharmanathan P, Keding A, Ronaldson SJ, Grainger A, Wakefield RJ, et al. Hydroxychloroquine effectiveness in reducing symptoms of hand osteoarthritis Ann Int Med. 2018;168:385-395.
2. Lee W, Ruijgrok L, Boxma-de Klerk B, Kok MR, Kloppenburg M, Gerards A, et al. Efficacy of hydroxychloroquine in hand osteoarthritis: a randomized, double-blind, placebo-controlled trial. Arth Care Res. 2018;70:1320-1325.

PICO 41. TNF/NSAID/UC compared to placebo plus oral NSAID for symptomatic erosive hand OA

Summary. Three RCTs indirectly address this question in 222 patients with erosive hand OA.[1-3] In one trial, patients were randomized to receive adalimumab 40 mg for two subcutaneous injections at a 15 day interval or placebo. Another trial was a randomized crossover trial where the order of treatment (adalimumab 40 mg or placebo) was randomized; all patients received the same treatments in different order for a 12 week

duration for each treatment. The third trial randomized patients to receive adalimumab 40 mg or placebo subcutaneously every 2 weeks for 52 weeks. All patients were considered refractory to NSAIDs, and although NSAIDs were allowed less than half of the patients in each group were using NSAIDs at baseline. In all trials there were no significant between-group differences for VAS pain, AUSCAN pain or function, FIHOA, Cochin score, or serious adverse events. However, for serious adverse events the findings were imprecise due to few events and a wide 95% CI around the effect sizes, meaning the possibility of a difference between groups in serious AEs could not be ruled out.

Quality of evidence across all critical outcomes: Moderate

TNF/NSAID/UC compared to placebo plus oral NSAID for erosive hand OA											
Certainty assessment							**Summary of findings**				
№ of participants (studies) Follow-up	**Risk of bias**	**Inconsistency**	**Indirectness**	**Imprecision**	**Publication bias**	**Overall certainty of evidence**	**Number of patients**		**Relative effect (95% CI)**	**Anticipated absolute effects**	
							With placebo plus oral NSAID	**With TNF/ NSAID/UC**		**Risk with placebo plus oral NSAID**	**Risk difference with TNF/NSAID/UC**
pain VAS at 12 to 26 wks, mean change from baseline score (0-100, lower scores indicate improvement)											
156 (2 RCTs)	not serious	not serious	serious [a]	not serious	none	⨁⨁⨁◯ MODERATE	76	80	-	-	MD **1.95 lower** (9.83 lower to 5.93 higher)
AUSCAN pain at 12 wks, mean change from baseline (0-500, lower scores indicate improvement)											
81 (1 RCT)	not serious	not serious	serious [a]	not serious	none	⨁⨁⨁◯ MODERATE	40	41	-	-	**MD 16 lower** (67.08 lower to 35.08 higher)
AUSCAN function at 12 wks, mean change from baseline (0-900, lower scores indicate improvement)											

TNF/NSAID/UC compared to placebo plus oral NSAID for erosive hand OA											
Certainty assessment							Summary of findings				
81 (1 RCT)	not serious	not serious	serious [a]	not serious	none	⨁⨁⨁◯ MODERATE	40	41	-	-	**MD 16.30 lower** (95.22 lower to 62.62 higher)
AUSCAN pain at 52 wks, mean change from baseline (0-50, lower scores indicate improvement)											
60 (1 RCT)	not serious	not serious	serious [a]	serious [b]	none	⨁⨁◯◯ LOW	30	30	-	-	**MD 3.7 lower** (9.55 lower to 2.55 higher)
AUSCAN function at 52 wks, mean change from baseline (0-90, lower scores indicate improvement)											
60 (1 RCT)	not serious	not serious	serious [a]	serious [b]	none	⨁⨁◯◯ LOW	30	30	-	-	**MD 0.8 higher** (8.41 lower to 10.01 higher)
FIHOA (0 to 30) at 26 wks, change score from baseline (lower scores indicate improvement)											
77 (1 RCT)	not serious	not serious	serious [a]	not serious	none	⨁⨁⨁◯ MODERATE	37	40	-	-	MD **0** (2.77 lower to 2.77 higher)
Cochin score at 26 wks, change from baseline (0-90, lower scores indicate improvement)											
77 (1 RCT)	not serious	not serious	serious [a]	not serious	none	⨁⨁⨁◯ MODERATE	37	40	-	-	MD **0.4 higher** (6.94 lower to 7.74 higher)
SAEs											

TNF/NSAID/UC compared to placebo plus oral NSAID for erosive hand OA											
Certainty assessment							Summary of findings				
162 (2 RCTs)	not serious	not serious	serious [a]	serious [b]	none	⨁⨁◯◯ LOW	2/79 (2.5%)	4/83 (4.8%)	**OR 2.13** (0.46 to 9.92)	25 per 1,000	**26 more per 1,000** (13 fewer to 192 more)

CI: Confidence interval; **MD:** Mean difference; **OR:** Odds ratio

Explanations

a. NSAIDs were allowed but not assigned as part of treatment; not all patients in each group used NSAIDs (less than half were using NSAIDs at baseline).

b. Wide 95% CI that overlaps line of no effect

References

1. Chevalier X, Ravaud P, Maheu E, Baron G, Rialland A, Vergnaud P, et al. Adalimumab in patients with hand osteoarthritis refractory to analgesics and NSAIDs: a randomised, multicentre, double-blind, placebo-controlled trial. Ann Rheum Dis. 2015;74(9):1697-1705.
2. Aitken D, Laslett LL, Pan F, Haugen IK, Otahal P, Bellamy N et al. A randomised double-blind placebo-controlled crossover trial of HUMira (adalimumab) for erosive hand OsteoaRthritis - the HUMOR trial. Osteoarth Cart 2018;26: 880-887.
3. Verbruggen G, Wittoek R, Vander Cruyssen B, Elewaut D. Tumour necrosis factor blockade for the treatment of erosive osteoarthritis of the interphalangeal finger joints: a double blind, randomised trial on structure modification. Ann Rheum Dis 2012;71:891-898.

PICO 42. Methotrexate plus NSAIDs plus usual care compared to oral NSAIDs for symptomatic erosive hand OA

Summary. The literature searches did not identify any studies that addressed this question.

Quality of evidence across all critical outcomes: Very low

PICO 43. Interleukin-1 inhibitors plus NSAIDs plus usual care compared to oral NSAIDs

Summary. The literature searches did not identify any studies that addressed this question.

Quality of evidence across all critical outcomes: Very low

PICO 44. Intra-articular corticosteroids compared to usual care for 1st CMC OA

Summary. The literature searches did not identify any studies that addressed this question.

Quality of evidence across all critical outcomes: Very low

PICO 45. Iontophoresis plus usual care compared to intra-articular corticosteroids for 1st CMC OA

Summary. The literature searches did not identify any studies that addressed this question.

Quality of evidence across all critical outcomes: Very low

PICO 46. Rigid hand splint/UC compared to UC for 1st CMC (hand OA)

Summary. Two RCTs addressed this comparison in 48 patients with OA in the first CMC joint.[1,2] Neither study found a significant between-group difference in any pain or function outcomes (see table below). However, the small sample size and wide 95% CIs around effect sizes resulted in serious imprecision, meaning that the possibility of a between-group difference cannot be ruled out.

When all splint studies were combined (including those from PICO 47 and 51), splints showed a significant benefit in VAS pain reduction over usual care at 4 to 12 weeks follow-up (4 RCTs) and 12 months follow-up (1 RCT). Significant differences favoring splints over usual care were also observed for DASH scores and pinch strength at 4 to 12 weeks follow-up.

Quality of evidence across all critical outcomes: Low

Rigid hand splint/UC compared to UC for 1st CMC (hand OA)											
Certainty assessment							**Summary of findings**				
№ of participants (studies) Follow-up	**Risk of bias**	**Inconsistency**	**Indirectness**	**Imprecision**	**Publication bias**	**Overall certainty of evidence**	**Number of patients**		**Relative effect (95% CI)**	**Anticipated absolute effects**	
							With UC	**With rigid hand splint/UC**		**Risk with UC**	**Risk difference with rigid hand splint/UC**
pain VAS (4 to 12 wks) (0-10, lower scores indicate improvement)											
212 (4 RCTs)	serious [a]	not serious	not serious	not serious	none	⨁⨁⨁◯ MODERATE	97	115	-	-	MD **2.04 lower** (3.63 lower to 0.45 lower) **Favors splint**
Pain VAS, mean change from baseline to 12 month followup (0-100, lower scores indicate improvement)											

Rigid hand splint/UC compared to UC for 1st CMC (hand OA)											
Certainty assessment							Summary of findings				
97 (1 RCT)	serious [a]	not serious	not serious	not serious	none	⨁⨁⨁◯ MODERATE	45	52	-	-	MD **14.3 lower** (23.6 lower to 5 lower) **Favors splint**
pain on MHQ change from baseline to 4 wks (0-100, lower scores indicate improvement)											
25 (1 RCT)	serious [a]	not serious	not serious	serious [b]	none	⨁⨁◯◯ LOW	9	16	-	-	MD **2.01 lower** (18.85 lower to 14.83 higher)
function on MHQ change from baseline to 4 wks (0-100, lower scores indicate improvement)											
25 (1 RCT)	serious [a]	not serious	not serious	serious [b]	none	⨁⨁◯◯ LOW	9	16	-	-	MD **12.44 higher** (2.15 lower to 27.03 higher)
DASH post treatment scores at 4 to 12 wks (0-100, lower scores indicate improvement)											
86 (2 RCTs)	serious [a]	not serious	not serious	not serious	none	⨁⨁⨁◯ MODERATE	42	44	-	-	MD **7.45 lower** (12.40 lower to 2.50 lower) **Favors splint**
grip strength at 4 to 12 wks post treatment scores (higher scores indicate improvement)											
23 (1 RCT)	serious [a]	not serious	not serious	serious [b]	none	⨁⨁◯◯ LOW	11	12	-	-	MD **0.7 higher** (1.05 lower to 2.45 higher)

Rigid hand splint/UC compared to UC for 1st CMC (hand OA)											
Certainty assessment							Summary of findings				
pinch strength post treatment scores at 4 to 12 wks (higher scores indicate improvement)											
148 (2 RCTs)	serious [a]	not serious	not serious	not serious	none	⨁⨁⨁◯ MODERATE	68	80	-	-	MD **1.96 higher** (1.56 higher to 2.36 higher) **Favors splint**
pinch strength, mean change baseline to 12 months (higher scores indicate improvement)											
96 (1 RCT)	serious [a]	not serious	not serious	serious [c]	none	⨁⨁◯◯ LOW	46	50	-	-	MD **9 higher** (11.53 lower to 29.53 higher)

CI: Confidence interval; **MD:** Mean difference

Explanations

a. No blinding in one trial, patients not blinded in second trial, unclear if any blinding or allocation concealment in second trial

b. Small study with wide 95% CI

References

1. Bani MA, Arazpour M, Kashani RV, Mousavi ME, Hutchins SW. Comparison of custom-made and prefabricated neoprene splinting in patients with the first carpometacarpal joint osteoarthritis. Disabil Rehabil Assist Technol. 2013;8(3):232-237.
2. Arazpour M, Soflaei M, Ahmadi Bani M, Madani SP, Sattari M, Biglarian A, et al. The effect of thumb splinting on thenar muscles atrophy, pain, and function in subjects with thumb carpometacarpal joint osteoarthritis. Prosthet Orthot Int. 2017;41(4):379-386.

3. Rannou F, Dimet J, Boutron I, Baron G, Fayad F, Mace Y, et al. Splint for base-of-thumb osteoarthritis: a randomized trial. Ann Intern Med. 2009;150(10):661-669.
4. Gomes Carreira AC, Jones A, Natour J. Assessment of the effectiveness of a functional splint for osteoarthritis of the trapeziometacarpal joint on the dominant hand: a randomized controlled study. J Rehabil Med. 2010;42(5):469-474.

PICO 47. Neoprene hand-base spica/UC compared to UC for 1st CMC (hand OA)

Summary. Two RCTs addressed this comparison in 124 patients with OA of the 1st CMC joint.[1,2] One study found significantly greater improvement in VAS pain favoring the neoprene splint at one month follow-up, while the other did not find a significant between-group difference. The study that reported longer-term follow-up also found significant improvement favoring the neoprene splint at 12 months.[2] Both studies also found significant improvement in pinch strength favoring the splint over usual care at one month. The study with longer follow-up did not find a between-group difference in pinch strength at 12 months.[2] One study found an increase in DASH score favoring the splint at one month (the authors described this as an improvement) and found no significant between-group difference in grip strength at one month.[1] The non-significant findings were all imprecise due to wide 95% CIs around the effect sizes, which means the findings were inconclusive for those outcomes.

Quality of evidence across all critical outcomes: Low

PICO 47 Neoprene hand-base spica/UC compared to UC for 1st CMC (hand OA)											
Certainty assessment							Summary of findings				
Nº of participants (studies) Follow-up	Risk of bias	Inconsistency	Indirectness	Imprecision	Publication bias	Overall certainty of evidence	Number of patients		Relative effect (95% CI)	Anticipated absolute effects	
							With UC	With splint/UC		Risk with UC	Risk difference with splint/UC
Pain VAS, mean change from baseline to 12 month followup (0-100, lower scores indicate improvement)											

PICO 47 Neoprene hand-base spica/UC compared to UC for 1st CMC (hand OA)											
Certainty assessment							Summary of findings				
97 (1 RCT)	serious [a]	not serious	not serious	not serious	none	⨁⨁⨁◯ MODERATE	45	52	-	-	MD **14.3 lower** (23.6 lower to 5 lower) **Favors splint**
pain VAS 1 month followup (0-100, lower scores indicate improvement)											
124 (2 RCTs)	serious [a]	not serious	not serious	serious [b]	none	⨁⨁◯◯ LOW	57	67	-	-	MD **15.32 lower** (47.26 lower to 16.62 higher)
DASH at 1 month (post scores only) (0-100, lower scores indicate improvement)											
23 (1 RCT)	serious [a]	not serious	not serious	serious [b]	none	⨁⨁◯◯ LOW	11	12	-	-	MD **9.8 higher** (2.03 higher to 17.57 higher) **Favors splint**
pinch strength, 1 month (higher scores indicate improvement)											
125 (2 RCTs)	serious [a]	not serious	not serious	not serious	none	⨁⨁⨁◯ MODERATE	57	68	-	-	MD **2.1 higher** (1.63 higher to 2.57 higher) **Favors splint**
pinch strength, mean change baseline to 12 months (higher scores indicate improvement)											

PICO 47 Neoprene hand-base spica/UC compared to UC for 1st CMC (hand OA)											
Certainty assessment							Summary of findings				
96 (1 RCT)	serious [a]	not serious	not serious	serious [c]	none	⨁⨁◯◯ LOW	46	50	-	-	MD **9 higher** (11.53 lower to 29.53 higher)
grip strength (post treatment scores) at 1 month followup (higher scores indicate improvement)											
23 (1 RCT)	serious [a]	not serious	not serious	serious [b]	none	⨁⨁◯◯ LOW	11	12	-	-	MD **0.8 higher** (0.46 lower to 2.06 higher)

CI: Confidence interval; **MD:** Mean difference

Explanations

a. Patients not blinded in either study, no blinding in one study

b. Small study with wide 95% CI

c. Wide 95% CI that overlaps line of no effect

References

1. Bani MA, Arazpour M, Kashani RV, Mousavi ME, Hutchins SW. Comparison of custom-made and prefabricated neoprene splinting in patients with the first carpometacarpal joint osteoarthritis. Disabil Rehabil Assist Technol. 2013;8(3):232-237.
2. Rannou F, Dimet J, Boutron I, Baron G, Fayad F, Mace Y, et al. Splint for base-of-thumb osteoarthritis: a randomized trial. Ann Intern Med. 2009;150(10):661-669.

PICO 48. Glove plus usual care compared to usual care for 1st CMC (hand OA)

Summary. The literature searches did not identify any studies that addressed this question.

Quality of evidence across all critical outcomes: Very low

PICO 49. Kinesiotape plus usual care compared to usual care for 1st CMC (hand OA)

Summary. The literature searches did not identify any studies that addressed this question.

Quality of evidence across all critical outcomes: Very low

PICO 50. Orthosis plus usual care compared to kinesiotape for 1st CMC (hand OA)

Summary. The literature searches did not identify any studies that addressed this question.

Quality of evidence across all critical outcomes: Very low

PICO 51. Rigid cock-up splint/UC compared to UC for symptomatic wrist OA

Summary. One RCT compared a functional thermoplastic splint plus usual care against usual care in 40 patients with OA of the TMC joint.[1] At 90 days follow-up, this study found significantly lower VAS pain favoring the splint over usual care. Measures of function (DASH, grip strength, and pinch strength) did not differ significantly between groups, but serious imprecision in the effect estimates means that the possibility of a between-group difference could not be ruled out.

Quality of evidence across all critical outcomes: Low

Functional splint/UC compared to UC for Symptomatic wrist OA											
Certainty assessment							Summary of findings				
№ of participants (studies) Follow-up	Risk of bias	Inconsistency	Indirectness	Imprecision	Publication bias	Overall certainty of evidence	Number of patients		Relative effect (95% CI)	Anticipated absolute effects	
							With UC	With functional splint/UC		Risk with UC	Risk difference with functional splint/UC

Functional splint/UC compared to UC for Symptomatic wrist OA											
Certainty assessment							Summary of findings				
Pain VAS (0 to 10 cm, 0 no pain) average for past week without splint at 90 days followup (lower scores indicate improvement)											
40 (1 RCT)	serious [a]	not serious	not serious	not serious	none	⨁⨁⨁◯ MODERATE	20	20	-	-	MD **2.3 lower** (3.6 lower to 1 lower) **Favors splint**
DASH at 90 day followup (0-100, function/symptoms/social) (lower scores indicate improvement)											
40 (1 RCT)	serious [a]	not serious	not serious	serious [b]	none	⨁⨁◯◯ LOW	20	20	-	-	MD **6.7 lower** (16.48 lower to 3.08 higher)
grip strength w/o splint at 90 day followup (higher scores indicate improvement)											
40 (1 RCT)	serious [a]	not serious	not serious	serious [b]	none	⨁⨁◯◯ LOW	20	20	-	-	MD **0.8 higher** (3.07 lower to 4.67 higher)
pinch strength 90 day followup for key pinch w/o splint (higher scores indicate improvement)											
40 (1 RCT)	serious [a]	not serious	not serious	serious [b]	none	⨁⨁◯◯ LOW	20	20	-	-	MD **0.2 higher** (0.86 lower to 1.26 higher)
pinch strength without splint at 90 day followup, tip pinch (higher scores indicate improvement)											

Functional splint/UC compared to UC for Symptomatic wrist OA											
Certainty assessment							**Summary of findings**				
40 (1 RCT)	serious [a]	not serious	not serious	serious [b]	none	⨁⨁◯◯ LOW	20	20	-	-	MD **0.1 higher** (0.58 lower to 0.78 higher)

CI: Confidence interval; **MD:** Mean difference

Explanations

a. Patients and providers not blinded

b. Wide 95% CI that overlaps line of no effect

References

1. Gomes Carreira AC, Jones A, Natour J. Assessment of the effectiveness of a functional splint for osteoarthritis of the trapeziometacarpal joint on the dominant hand: a randomized controlled study. J Rehabil Med. 2010;42(5):469-474.

PICO 52. Neoprene cock-up splint/UC compared to UC for symptomatic wrist OA

Summary. The literature searches did not identify any studies that addressed this question.

Quality of evidence across all critical outcomes: Very low