

Draft Comparative Effectiveness Review

Number XXX

Treatment of Primary and Secondary Osteoarthritis of the Knee: An Update Review

Prepared for:

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Preface

The Agency for Healthcare Research and Quality (AHRQ), through its Evidence-based Practice Centers (EPCs), sponsors the development of systematic reviews to assist public- and private-sector organizations in their efforts to improve the quality of health care in the United States. These reviews provide comprehensive, science-based information on common, costly medical conditions, and new health care technologies and strategies.

Systematic reviews are the building blocks underlying evidence-based practice; they focus attention on the strength and limits of evidence from research studies about the effectiveness and safety of a clinical intervention. In the context of developing recommendations for practice, systematic reviews can help clarify whether assertions about the value of the intervention are based on strong evidence from clinical studies. For more information about AHRQ EPC systematic reviews, see www.effectivehealthcare.ahrq.gov/reference/purpose.cfm

AHRQ expects that these systematic reviews will be helpful to health plans, providers, purchasers, government programs, and the health care system as a whole. Transparency and stakeholder input are essential to the Effective Health Care Program. Please visit the Web site (www.effectivehealthcare.ahrq.gov) to see draft research questions and reports or to join an e-mail list to learn about new program products and opportunities for input.

We welcome comments on this systematic review. They may be sent by mail to the Task Order Officer named below at: Agency for Healthcare Research and Quality, 5600 Fishers Lane, Rockville, MD 20857, or by email to epc@ahrq.hhs.gov.

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Technical Expert Panel

In designing the study questions and methodology at the outset of this report, the EPC consulted several technical and content experts. Broad expertise and perspectives were sought. Divergent and conflicted opinions are common and perceived as healthy scientific discourse that results in a thoughtful, relevant systematic review. Therefore, in the end, study questions, design, methodologic approaches, and/or conclusions do not necessarily represent the views of individual technical and content experts.

Technical Experts must disclose any financial conflicts of interest greater than \$10,000 and any other relevant business or professional conflicts of interest. Because of their unique clinical or content expertise, individuals with potential conflicts may be retained. The TOO and the EPC work to balance, manage, or mitigate any potential conflicts of interest identified.

The list of Technical Experts who participated in developing this report follows:

[To be added in the Final Report]

Peer Reviewers

Prior to publication of the final evidence report, EPCs sought input from independent Peer Reviewers without financial conflicts of interest. However, the conclusions and synthesis of the scientific literature presented in this report does not necessarily represent the views of individual reviewers.

Peer Reviewers must disclose any financial conflicts of interest greater than \$10,000 and any other relevant business or professional conflicts of interest. Because of their unique clinical or content expertise, individuals with potential non-financial conflicts may be retained. The TOO and the EPC work to balance, manage, or mitigate any potential non-financial conflicts of interest identified.

The list of Peer Reviewers follows:

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Treatment of Primary and Secondary Osteoarthritis of the Knee: An Update Review

Structured Abstract

Objectives. To assess the evidence for the efficacy and safety of the following interventions for improving clinical outcomes in adults with osteoarthritis of the knee: cell-based therapies; glucosamine, chondroitin, or glucosamine plus chondroitin; strength-training, agility, or aerobic exercise (land- or water-based); balneotherapy, mud bath therapy; electrical stimulation techniques (including transcutaneous electrical stimulation [TENS], neuromuscular electrical stimulation [NMES], and pulsed electromagnetic field therapy [PEMF]); whole body vibration; heat, infrared or ultrasound; braces, orthoses, or specially designed shoes; weight loss diets; and home-based therapy or self-management.

Data Sources. PubMed, EMBASE, the Cochrane Collection, Web of Science, and the Physiotherapy Evidence Database (PEDRO) from 2006 to the present; and ClinicalTrials.gov and the proceedings from the 2015 American College of Rheumatology annual meetings.

Review Methods. We included randomized controlled trials (RCTs) conducted in adults 18 years or over diagnosed with OA of the knee, comparing any of the interventions of interest to placebo (sham) or any other intervention of interest, that reported a clinical outcome (including pain, function, and quality of life). We also included single-arm and prospective observational studies that analyzed the effects of weight loss in individuals with OA of the knee on a clinical outcome. Standard methods were used for data abstraction and analysis, assessment of study quality, and assessment of the quality of the evidence, according to the AHRQ EPC Methods Guide.

Results. Evidence was insufficient to draw conclusions about the effectiveness of most interventions, largely due to heterogeneous and poor quality study design, which limited the number of studies that met inclusion criteria and could be pooled. Only weight loss (dieting with or without exercise) (on short to long-term pain and function), TENS (on the short-term outcome of pain), and self-management (on medium-term pain and function) were supported by a moderate or low-to-moderate level of evidence. A beneficial effect of intraarticular injections of platelet-rich plasma on medium-term pain compared with saline, glucosamine-chondroitin (on medium-term pain and function), strength training (on total WOMAC score), agility training (on short-term pain), and whole-body vibration (on medium-term function) were supported by a low level of evidence. Low SoE was also found for a lack of effect of manual therapy. No consistent serious adverse effects were reported for any intervention; minor gastrointestinal effects were observed for low calorie weight loss diets. Almost no studies conducted subgroup analysis to assess the participant characteristics associated with better outcomes, and few studies systematically compared interventions head-to-head. Additional limitations included lack of blinding and sham controls in studies of physical interventions and the potentially limited applicability of study results to patients seen in non-academic health care settings.

Conclusions. Among the interventions assessed for efficacy and safety in this review, the strongest evidence supports a combination of weight loss with exercise as well as self-

management programs to decrease pain and improve function in individuals with OA of the knee. Larger randomized controlled trials are needed, with more attention to appropriate comparison groups and longer duration, to assess newer therapies and to determine which types of physical modalities are most effective.

Contents

Executive Summary	ES-1
Background and Objectives	ES-1
Scope and Key Questions	ES-2
Methods.....	ES-4
Results.....	ES-6
Findings.....	ES-7
Discussion.....	ES-18
Introduction.....	1
Background and Objectives	1
Scope and Key Questions	3
Organization of This Report	7
Methods.....	8
Criteria for Inclusion/Exclusion of Studies in the Review	8
Results.....	12
Discussion.....	61
Summary of Key Findings and SoE.....	61
Summary of Findings in Relationship to what is Already Known	62
Applicability	64
Limitations of the Evidence Base	65
Conclusions.....	69
References	74
Abbreviations / Acronyms.....	84

Tables

Table A. Summary strength of evidence.....	ES-26
Table 1. PICOTs for the Review.....	3
Table 2. Summary strength of evidence	70

Figures

Figure A. Analytic Framework for Osteoarthritis of the Knee.....	ES-4
Figure B. Literature flow diagram	ES-6
Figure 1. Analytic Framework for Osteoarthritis of the Knee.....	7
Figure 2. Literature flow diagram.....	13
Figure 3. Forest Plot for Short-term effects of Strength Training on WOMAC Pain	24
Figure 4. Forest Plot for Short-term effects of Strength Training on WOMAC Function	25
Figure 5. Forest Plot for Short-term effects of TENS on WOMAC Pain.....	38
Figure 6. Forest Plot for Medium-term effects of Whole Body Vibration on WOMAC Pain	41
Figure 7. Forest Plot for Medium-term effects of Whole Body Vibration on WOMAC Function	42
Figure 8. Forest Plot for Medium-term effects of Whole Body Vibration on 6-minute Walk Distance.....	43
Figure 9. Forest Plot for Short-term effects of Orthotics on WOMAC Total.....	45
Figure 10. Forest Plot for Medium-term effects of Orthotics on WOMAC Pain	46
Figure 11. Forest Plot for Short-term effects of Massage or Acupressure on WOMAC Pain	50

Appendixes

Appendix A: Search Strategy

Appendix B: List of Excluded Studies

Appendix C: Evidence Table

Appendix D: Data abstraction forms

Appendix E: Strength of Evidence Table

Appendix F: Quality of Included Studies

Appendix G: Policies, Guidelines, Coverage, Stakeholder Information on Interventions of Interest

Appendix H. Adverse Events

Appendix I. MCID cutoffs

Executive Summary

Background and Objectives

Osteoarthritis (OA) of the knee is a highly prevalent condition among adults, characterized by the progressive destruction of the articular cartilage that lines the knee joints, the subchondral bone surfaces, and synovium, accompanied by pain, immobility, and reduction in function and the ability to complete activities of daily living (ADL). Two types of OA of the knee are recognized: the more prevalent primary OA of the knee is considered to be a natural consequence of aging, whereas secondary OA of the knee can be caused by trauma, inactivity, overweight, or a disease process such as rheumatoid arthritis. No evidence suggests that the two types are treated differently or respond differently to treatments.¹ The clinical diagnosis of OA of the knee is typically based on presentation, including insidious onset of weight-bearing knee pain that is exacerbated by use of the joint and relieved by rest, and that tends to worsen over the course of the day. Radiographic evidence of OA may precede symptomatic OA but may not correlate with symptom severity. Radiologic severity can be estimated and expressed using the Kellgren and Lawrence (K-L) criteria. However, a number of versions of the criteria exist: At low cutoff scores, correlation with symptoms is poor,² whereas at higher cutoff scores, agreement tends to be higher. The primary impact of these different versions of the criteria may be the challenge that they create in trying to assess, compare, and pool the findings of research studies.² Some longitudinal studies have even used different criteria at different time points within the same study. Because of the variation in scores for radiographic finding under various versions of the criteria (especially for individuals with less-advanced disease), stratification is important. Some evidence suggests that among individuals with knee pain, MRI demonstrates physical signs of osteoarthritic changes in the knee before they are visible radiographically.³ However, the sensitivity and specificity of MRI in diagnosis and monitoring of progression have not yet been definitively demonstrated and are not used in routine clinical practice.

The goals of treatment for OA of the knee include relief of pain and inflammation, slowing of progression, and improvement in or maintenance of mobility, function (including activities of daily living [ADLs]), and health-related quality of life (HRQoL). Although numerous treatment strategies have been implemented, from the least intense (analgesics) to the most (knee replacement [TKR] surgery), it has remained unclear which treatments or combinations of treatments are most effective for which populations. Whereas the efficacy of TKR for improving pain and function has been demonstrated, not all patients are candidates for this surgery. In addition, TKR may not be a permanent solution, as surgery may need to be repeated within two decades. Thus, effective treatments need to be identified that can relieve pain and improve function to delay or avert surgery.

Treatment options for OA of the knee include analgesics, disease modifying agents and cell-based therapies that aim to halt or reverse joint damage, physical modalities aimed at restoring or improving function, and others. Information on the FDA status, indications, and warnings for the treatments included in this review is included in Appendix G.

Numerous recent evidence-based treatment guidelines have been issued, including the 2012 American College of Rheumatology Guidelines⁴ and the 2013 American Academy of Orthopedic Surgeons guidelines for the treatment of OA of the knee. These guidelines are not in total

agreement about the recommended treatments: For example the 2012 American College of Rheumatology (ACR) Guidelines conditionally recommend HA, while the American Academy of Orthopaedic Surgeons (AAOS) guidelines recommend against its use to treat patients with symptomatic conditions.⁵

Scope and Key Questions

Scope of the Review

Systematic reviews have been conducted on many of the modalities used to treat OA of the knee, including four reviews by AHRQ Evidence-based Practice Centers since 2007.^{1, 6-8} Uncertainty continues to surround the use of all treatments intended as disease-modifying agents (including intra-articular hyaluronic acid [HA] and glucosamine and chondroitin), acupuncture, physical therapy, exercise, braces and orthotics, and arthroscopic lavage, as well as the comparative efficacy and safety of oral, topical, and intraarticular analgesics and anti-inflammatories.

This review is part of a continuous update review process that aims to repeatedly assess the need to update—and then to update if needed—a systematic review that was conducted in 2007¹ that assessed the efficacy and safety of HA, glucosamine and/or chondroitin, and arthroscopic surgery. Prior to preparing this review, we conducted an updating surveillance assessment that comprised an environmental scan and consultation with a technical expert panel (TEP) to assess the currency of the conclusions of the 2007 review.⁹ A document that summarized the findings of this bifurcated process was posted for public review.¹⁰

The TEP for the surveillance process uniformly advised us that the conclusions of the 2007 report for intraarticular HA, oral glucosamine chondroitin, and arthroscopic surgery remained current and did not need updating. Instead, they recommended reviewing cell-based therapies, physical modalities, SNRIs, topical agents, weight loss, and acupuncture. The TEP for the current review concurred with the suggestions of the TEP for the surveillance report and also requested inclusion of home-based and self-management therapies.

The environmental scan supported the TEP's suggestion that the topics of intra-articular HA and arthroscopic surgery did not need updating. However, we identified at least one large recent trial on glucosamine-chondroitin that prompted us to want to update the review on this topic.

A 2012 SR by another EPC reviewed the effects of the physical modalities.⁷ We made the decision that as part of this review, we would also update the findings of that review.

Topics not included in this report (e.g., HA and intraarticular corticosteroids, SNRIs, topical agents, and acupuncture) will be re-assessed for the need to update (or to conduct a new review) in a later surveillance period.

The treatment modalities selected for inclusion in this review reflect a combination of the findings of the environmental scan, the TEP for the Surveillance process, the public comments, and the TEP for this review.

The included topics (interventions) for the current report are listed in the PICOTs outline (Table 1 in the main report).

The protocol has been published on the AHRQ Effective Healthcare website (<http://effectivehealthcare.ahrq.gov/index.cfm/search-for-guides-reviews-and-reports/?pageaction=displayproduct&productid=2247>).

Key Questions

Based on the findings of the environmental scan, TEP assessments, and public comments, the Key Questions from the 2007 report were revised as follows.

Key Question 1a: What is the clinical effectiveness of cell-based therapies, oral glucosamine and/or chondroitin, physical treatment modalities, weight loss, , or home-based and self-management therapies in patients with primary or secondary OA of the knee, compared with appropriate placebo/sham controls or compared with other active interventions? Key Question 1b: How do the outcomes of each intervention differ by the following population and study characteristics: sex, disease subtype (lateral, patellofemoral), severity (stage/baseline pain and functional status), weight status (body mass index), baseline fitness (activity level), comorbidities, prior or concurrent treatments (including self-initiated therapies), and treatment duration or intensity?

Key Question 2a: What harms are associated with each intervention in patients with primary or secondary OA of the knee?

Key Question 2b: How do the harms associated with each intervention differ by the following population or study characteristics: sex, disease subtype (lateral tibiofemoral, patellofemoral), severity (stage/baseline pain and functional status), weight status (body mass index), baseline fitness (activity level), comorbidities, prior or concurrent treatments (including self-initiated therapies), and treatment duration or intensity?

Analytic Framework

The review was guided by the analytic framework shown in Figure A.

Figure A. Analytic Framework for Osteoarthritis of the Knee

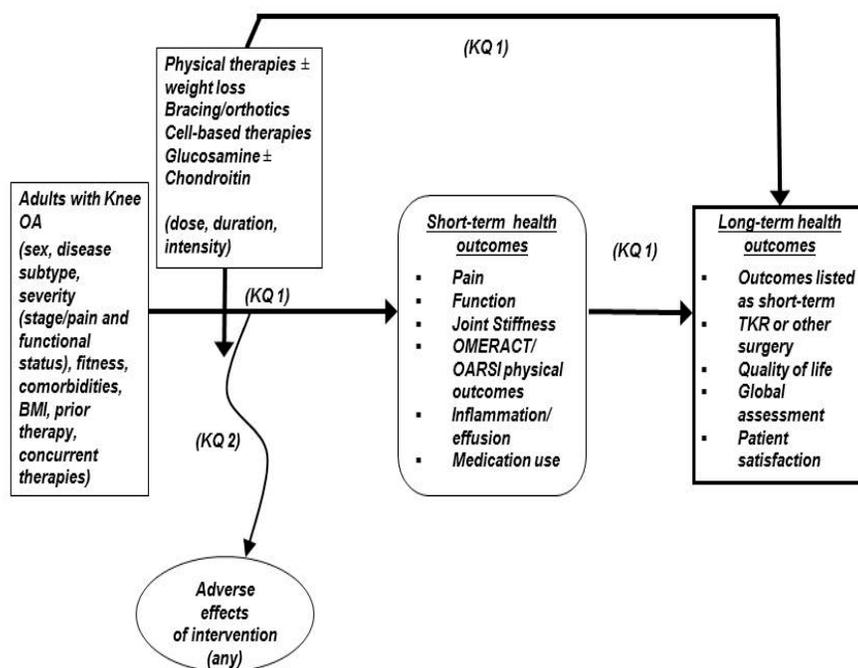


Figure notes: KQ = Key Question; OA = Osteoarthritis; TKR = Total Knee Replacement;

Methods

The methods used to conduct the systematic review portion of this continuous update are based on the EPC Methods Guide.⁹ Systematic searches of electronic databases were designed and conducted to identify English language studies and those with an English–language abstract that enrolled participants with a confirmed diagnosis of osteoarthritis of the knee. Searches were supplemented by references identified by TEP members and content experts, who hand-searched recent relevant conference proceedings. The inclusion/exclusion criteria by target population, interventions, outcomes, comparators, setting, and study duration are shown in Table 1. We limited included studies for assessment of efficacy to randomized controlled trials, with the exception of studies that assessed the effects of weight loss, for which we also included single-arm trials and prospective cohort studies. We included prospective observational studies and case reports that reported on adverse events associated with use of the interventions of interest for the treatment of OA of the knee. Conference proceedings and letters that reported sufficient information to enable assessment of risk of bias and that reported unique data were included. Relevant systematic reviews were also considered for inclusion.

The searches commenced with the year 2006, one year prior to the latest search dates of the original review of glucosamine and chondroitin that we are updating.⁷ However, because we are also updating topics covered in an EPC review on physical modalities for the treatment of pain in

patients with OA of the knee that was conducted in 2012,¹¹ we did not re-review studies included in (or actively excluded from) that review unless the study included a treatment group of interest that the original review did not evaluate.

In addition, relevant stakeholders, including manufacturers of over-the-counter and prescription medications and medical devices used to treat OA of the knee were contacted by the Scientific Resource Center for scientific information packets that contain any unpublished information on the efficacy and/or safety of their products when used specifically to treat OA of the knee; no information was obtained from manufacturers. A notice was also placed in the Federal Register requesting any relevant information on the use of dietary supplements containing glucosamine or chondroitin to treat OA of the knee.

Pairs of experienced literature reviewers screened titles identified by literature searches using pre-specified criteria, without reconciliation of decisions. Abstracts of those titles selected for inclusion by one or both reviewers were dually screened using prespecified criteria, with disagreements reconciled by the project leaders, if necessary. Full text articles or other documents were obtained for included abstracts. DistillerSR™ software was used for screening, abstraction, reconciliation, and tracking. Any references that were suggested by members of the TEP, peer reviewers, or public reviewers were obtained and underwent the same screening and abstraction process. Reference lists from recent systematic reviews on the topics of interest were also screened for relevant articles that had not appeared in the search output.

We will also conduct an update search during peer review and include any relevant studies from the update search in the final report. Study-level details and data were dually abstracted by reviewers, who also rated the quality of studies.

Outcome data were stratified by length of time from baseline. Short-term outcomes were 4 to 12 weeks, medium-term outcomes were 12 to 26 weeks, and long-term outcomes were longer than 26 weeks. If a study reported outcomes at more than one short-, medium-, or long-term time period, we abstracted the longer one(s).

If three or more studies reported the same outcome measure for the same intervention during the same follow-up time period, we pooled the outcomes using the Hartung Knapp method for random effects meta-analysis.¹² Because some studies did not report the scales used for outcome measures and because it was not always possible to determine the scales from the data, we report pooled outcomes as standardized mean differences; we did not pool studies that used different tools to measure a similar outcome (e.g., VAS and WOMAC pain measures), as two tools used in the same study on the same participant population sometimes resulted in different outcomes. The findings of meta-analyses are reported quantitatively with forest plots. All studies for which results are included in the report are described qualitatively (narratively) by the type of intervention and the duration of followup. Descriptions of studies of similar interventions were grouped by outcome measures when feasible.

We also assessed whether significant standardized mean differences of pooled outcomes met a pre-specified minimum clinically important difference (MCID). If studies reported whether their outcomes met a MCID or reported on the percent of participants who achieved a response, we noted that in the narrative descriptions. We rated the strength of evidence (SoE) of each intervention-outcome-followup time based on the AHRQ Methods Guide. Domains include study limitations (study design, ROB, overall methodological quality), consistency of the direction of effect sizes across studies, precision of the estimate (including number of studies), directness of the relationship between outcomes measured and the outcomes of interest, and magnitude of the effect size.

For outcomes for which no pooling was possible, we estimated a rating based on qualitative assessment of the individual studies that met the inclusion criteria. Consistency was assessed as the direction of the reported effect across studies (or within studies if a single RCT used multiple tools to measure the same outcome), precision was assessed in terms of the similarity in effect sizes, the average variance, and the numbers of studies. Directness was assessed as it would be for pooled outcomes. Lack of pooling automatically decreased the SoE grade by one unit.

Based on these domains, we rated the SoE for each comparison of interest as high, moderate, low, or insufficient (if no or too few studies were identified that addressed the outcome). We rated applicability of participant populations and interventions separately, as described below.

Peer Review and Public Commentary

To be added in the Final Report

Results

We identified 90 studies that met inclusion criteria for assessing the efficacy of interventions for treating OA and 45 studies that reported on AEs. Our literature flow diagram (Figure B) displays our screening results. Appendix D contains our data abstraction tools that were used for abstracting the data of the 90 included studies. This section presents the key points for each treatment modality and the strength of the evidence for conclusions.

Figure B. Literature flow diagram

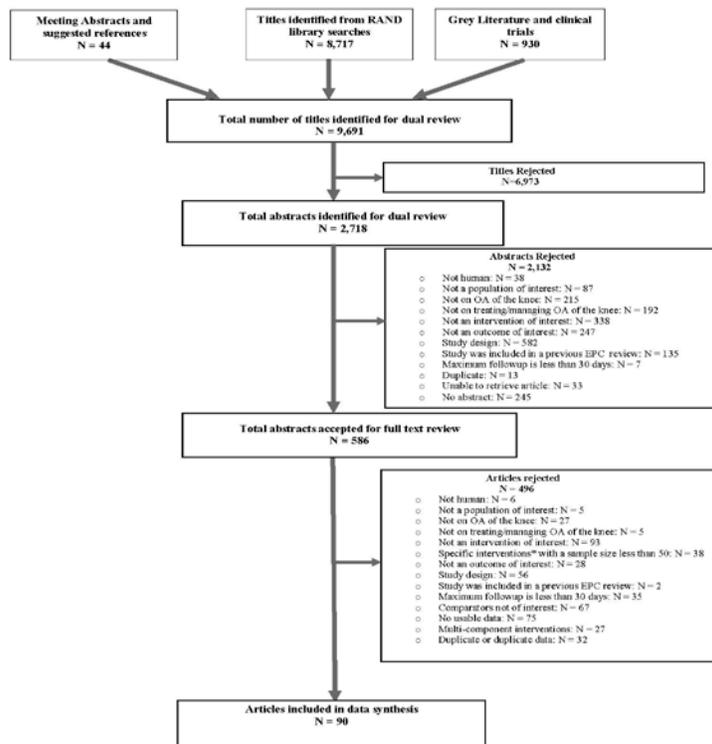


Figure notes: *Interventions with a sample size less than 50 participants: Glucosamine, TENS, Aerobic exercise, and Strength Training

Findings

The conclusions and SoE are summarized in Table A.

Key Question 1a: What is the clinical effectiveness of cell-based therapies, oral glucosamine and/or chondroitin, physical treatment modalities, weight loss, or home-based and self-management therapies in patients with primary or secondary OA of the knee, compared with appropriate placebo/sham controls or compared with other active interventions?

Key Question 1b: How do the outcomes of each intervention differ by the following population and study characteristics: sex, disease subtype (lateral, patellofemoral), severity (stage/baseline pain and functional status), weight status (body mass index), baseline fitness (activity level), comorbidities, prior or concurrent treatments (including self-initiated therapies), and treatment duration or intensity?

Cell-based Therapies

Four RCTs were identified that assessed short-term (4-12 weeks) and medium-term (12-26 weeks) effects of platelet-rich plasma (PRP) on pain and function.¹³⁻¹⁶ We identified no RCTs on other cell-based therapies. These therapies were not reviewed in previous EPC SRs.

Key Points

- It is unclear whether PRP or other cell-based therapies have any benefit for patients with OA of the knee, as we identified only four small studies on PRP that met inclusion criteria, and results were inconsistent among them.
- Studies showed a low strength of evidence for a beneficial effect of PRP on medium-term pain but not on function or other outcomes. Evidence was insufficient for outcomes at shorter or longer times.
 - Four RCTs, two saline-controlled and two compared with analgesic or treatment as usual, showed statistically significant medium-term (6 months) beneficial effects of PRP on pain (total n=321; average RoB: moderate). Among two RCTs that assessed medium-term effects on function, one showed greater improvement from baseline in the PRP group than in the control group, whereas the other showed equal improvement in both groups

Glucosamine with or without Chondroitin or Chondroitin Alone

Seven studies that assessed the effects of glucosamine,¹⁷⁻¹⁹ chondroitin,^{17, 18, 20, 21} or the combination met inclusion criteria.^{17, 18, 22, 23} No studies addressed short-term outcomes of glucosamine combined with chondroitin, and no studies addressed short- or medium-term effects of glucosamine alone.

Key Points

- Whether glucosamine, chondroitin, or the combination of glucosamine plus chondroitin have any consistent benefit for patients with knee OA remains unclear. One large non-

inferiority trial showed no difference in benefit between glucosamine-chondroitin and NSAIDs, whereas two placebo-controlled trials show no benefit. Benefits of glucosamine alone and chondroitin alone are also inconsistent across time-points and trials.

- **Glucosamine + chondroitin:** Three RCTs assessed medium and long-term effects. Glucosamine-chondroitin exerted medium-term effects on pain, function, and stiffness, based on two RCTs (low strength of evidence [SoE]). No long-term effects on any outcomes were seen, based on three RCTs (low SoE).
 - The MOVES Trial (n= 603; low RoB) showed statistically significant beneficial medium-term effects on pain, function, stiffness, OMERACT-OARSI outcomes, global assessment of well-being and HRQoL, equivalent to analgesic; this trial did not include a placebo group. A smaller open trial (n=117, high RoB) also showed significant beneficial effects on pain, function, and stiffness.
 - The MOVES Trial, GAIT Trial (n=1,583; low RoB) and LEGS Trial (n=605; low RoB) showed no significant long-term effects of glucosamine + chondroitin on pain or function compared with placebo.
- **Glucosamine:** No RCTs met inclusion criteria for short- or medium-term outcomes. No long-term effects of glucosamine alone were observed on pain, function, or other outcomes (insufficient evidence).
 - The LEGS Trial and the GAIT Trial showed no significant beneficial effects at 1 or 2 years on pain or function compared with the effects of placebo; a third RCT (n=190, unclear RoB) showed a smaller worsening of pain and function at 3 years.
 - A long-term followup of two RCTs (n=275; low RoB) showed a significant decrease in the risk of undergoing TKR in individuals who took glucosamine sulfate for a minimum of 12 months.
- **Chondroitin:** Chondroitin alone had beneficial short-term effects on pain and function compared with placebo, based on one RCT (low strength of evidence). Chondroitin alone showed significant medium-term benefit for pain (low strength of evidence) but not function (insufficient evidence), based on two RCTs. Chondroitin alone showed no long-term effect on pain, based on three large RCTs (moderate strength of evidence) and no long-term effects on function (low strength of evidence)
 - One large, multisite placebo-controlled RCT of chondroitin sulfate showed a significant beneficial short-term effect on pain and function (n=352; low RoB) administered as one or two daily doses.
 - Two large, multi-site placebo-controlled RCTs showed a significant beneficial medium-term effect on pain (total n=974; low RoB) but the STOPP trial showed no benefit for function.
- No studies were identified that compared glucosamine sulfate with glucosamine hydrochloride.
- No studies analyzed the time course of effects of glucosamine and/or chondroitin, but studies that examined effects at multiple time points showed that the maximum effects are achieved at 3 to 6 months.

Strength or Resistance Training

Eight studies that assessed strength or resistance training met inclusion criteria.²⁴⁻³¹

Key Points

- Although it is unclear whether strength and resistance training have a statistically significant beneficial effect on patients with OA of the knee, pooled analysis of five RCTs supports a possible clinical benefit on pain and function, and individual study findings suggest significant benefit on total WOMAC scores.
- Strength and resistance training had no statistically significant beneficial effect on short-term pain (low strength of evidence)
 - Pooled analysis of 5 RCTs (n=270; moderate RoB) that compared strength training with a control group (education or other exercise) showed no statistically significant effect on pain (random effects pooled estimate -0.40, 95% CI -1.22, 0.42).
- Strength and resistance training had no statistically significant beneficial effect on short-term function (low strength of evidence).
 - Pooled analysis of 5 RCTs (n=270, moderate RoB) that compared strength training with a control group showed no significant effect on WOMAC function (random effects pooled estimate -0.34, 95% CI -0.95, 0.28).
- Strength and resistance training showed mixed effects on other short-term function measures based on two RCTs (insufficient evidence).
- Strength and resistance training had a beneficial short-term effect on WOMAC total scores based on three RCTs (low SoE).
 - Two RCTs (total n=96, moderate RoB) comparing strength training to an education only control showed a benefit; one RCT (n=30; moderate RoB) showed a greater benefit for strength training on an uneven surface than for strength training on an even surface.
- Strength and resistance training showed no beneficial effect on medium-term pain, based on two RCTs (insufficient evidence).
- Strength and resistance training showed no consistent beneficial effects on medium-term function, based on two RCTs (insufficient evidence).
- Strength and resistance training had no benefit on medium-term WOMAC stiffness scores based on one RCT (insufficient evidence).
- Strength and resistance training showed a benefit for long-term pain and function at 32 weeks but only a benefit for function at 52 weeks, based on one RCT (insufficient evidence). The number of studies that assessed outcomes of interest at multiple follow up times was insufficient to assess trends in response to these interventions.
- No studies assessed the effects of any factors such as sex, obesity, or disease severity on outcomes of strength and resistance training.

Agility Training

Seven RCTs that assessed the effects of agility training met inclusion criteria. ²⁹³²³³³⁴³⁵³⁶³⁷

Key Points

- It is unclear whether agility training alone has any benefit for patients with knee OA. Identified studies showed inconsistent effects across time points and outcomes.

- Agility training showed a significant beneficial effect on short-term pain compared with passive controls, based on two RCTs and no difference from strength training in one RCT ((n=217, moderate RoB) (Low SoE).
- Agility training showed no consistent benefit on short-term function, based on three RCTs (insufficient evidence). Agility training showed no consistent benefit on medium-term pain, based on two RCTs (insufficient evidence).
- Agility training showed no long-term differences in pain or function compared with other standard training programs but improvements from baseline were sustained over the long-term. One RCT showed that improvements in both pain and function exceeded the MCID for agility training with or without strength training (insufficient evidence).

Aerobic Exercise

One RCT that assessed the effects of aerobic exercise met inclusion criteria.³⁸ No studies assessed short- or medium-term effects.

Key Points

- Based on one trial, it is unclear whether aerobic exercise alone has any beneficial effect on patients with knee OA.
- Aerobic exercise showed no significant long-term effects on pain, function, total WOMAC, quality of life, based on one RCT (insufficient evidence).³⁸

General Exercise Therapy

Three exercise interventions that combined exercise modalities and did not fit predefined categories were identified.³⁹⁻⁴¹ No studies assessed effects on short-term outcomes.

Key Points

- It is unclear whether general exercise programs have benefit for patients with knee OA, as the number of studies was limited, and studies were heterogeneous.
- General exercise improved medium-term pain and function compared with no exercise, based on one RCT (n=180; low RoB) (insufficient evidence).
- General exercise had inconsistent benefit for long-term outcomes, based on two RCTs (insufficient evidence).
 - One RCT showed no beneficial effect on pain, function, or physical quality of life among patients in a weight-loss program vs. no exercise (n=192; low RoB)
 - One RCT showed that a longer program had greater benefits for long-term pain and WOMAC total scores than a shorter program (n=75; moderate RoB).

Tai chi

Two RCTs that met inclusion criteria assessed the effects of tai chi compared with resistance training or no activity.^{27, 42}

Key Points

- It is unclear whether tai chi has any benefit for patients with OA for the knee, as we identified only two small RCTs (total n=86), and results were inconsistent across time points and outcomes.

- Tai chi had no significant beneficial short-term effect on pain, based on two RCTs (insufficient evidence)
- Tai chi showed inconsistent effects on short-term function, based on two RCTs.
 - An RCT that compared tai chi with resistance training and treatment as usual showed comparable effects on short-term function for tai chi and treatment as usual and no improvement compared with strength training (n=31; high RoB).
 - An RCT that compared tai chi with education showed a significant beneficial effect on function (MD -5.54, 95% CI -9.72, -1.36) (n=55; low RoB)
- Tai chi showed significant benefit for medium-term pain (MD -1.58, 95% CI -2.76, -0.40) and function (MD -5.52, 95% CI -9.70, -1.34) compared with education, based on one RCT (n=55, high RoB).

Yoga

One RCT that met inclusion criteria assessed the short-term effects of yoga.⁴³

Key Points

- It is unclear whether yoga has any benefit for patients with OA of the knee, as we identified only one small RCT (n=36).
- Yoga showed a beneficial short-term effect on pain and function, based on one RCT, compared with a wait-list control (n=36; moderate RoB) (insufficient evidence).

Manual Therapy (Including massage and acupuncture)

Eight RCTs that assessed effects of manual therapy (including massage, self-massage, and acupuncture) met inclusion criteria.⁴⁴⁴⁵⁴⁶⁴⁷⁴⁸⁴⁹⁵⁰⁴⁰

Key Points

- It is unclear whether manual therapies have any benefit for patients with knee OA. Across eight RCTs, benefits were inconsistent across time points and outcomes. Pooled analysis showed no statistically significant effect, although a clinically important effect could not be ruled out, due to the wide 95% confidence intervals.
- Manual therapy showed no consistent beneficial short-term effects on pain, based on six RCTs and a pooled analysis of three RCTs.
 - A random-effects meta-analysis of three trials (n=244; moderate-high RoB) showed no statistically significant effect of manual therapy (administered by a therapist or by patients themselves) on short-term WOMAC pain (SMD -0.57, 95% CI -1.60, 0.45) (low strength of evidence).
- Manual therapy showed inconsistent effects on short-term function, based on three RCTs. (low strength of evidence).
- Manual therapy showed inconsistent effects on medium-term pain, function, and other outcomes, based on four RCTs (insufficient evidence).
- Manual therapy had a significant beneficial effect on long-term pain when combined with exercise, compared with exercise alone, based on 12-month follow-up of a three-month intervention (n=75; moderate RoB) (insufficient evidence).

Balneotherapy and Mud Treatment

Four RCTs that met inclusion criteria assessed the effects of balneotherapy, mud baths or topical mud.⁵¹⁻⁵⁴ No studies of balneotherapy assessed short- or long-term outcomes.

Key Points

- It is unclear whether balneotherapy or mud baths show significant short-term benefit for patients with knee OA, based on the small number of RCTs we identified.
- Balneotherapy showed a significant beneficial effect on medium-term pain, based on two single-blind studies (n=60, 77; moderate RoB) (insufficient evidence).
 - One RCT (n=60) reported a significant improvement in VAS pain (0-100 scale, MD -42.50, 95% CI -53.67, -31.33) and WOMAC pain (MD -25.70, 95% CI -34.06, -17.34)
 - One RCT (n=77) reported a significant improvement in VAS pain (0-100 scale, MD -16.00, 95% CI -26.68, -5.32) but no difference in WOMAC pain
- Balneotherapy showed a significant beneficial effect on medium-term function, based on two single-blind studies (n=60, 77; moderate RoB) (insufficient evidence).
 - One RCT reported a significant improvement in WOMAC function scores (out of 170 possible points, MD -37.47, 95% CI -46.61, -28.33)
 - One RCT reported a significant improvement in WOMAC function scores (out of 100 possible points, MD -8.10, 95% CI -15.82, -0.38).
- Topical mud showed no beneficial short-term effects on pain or function but a beneficial effect on stiffness, based on one RCT (n=50; high RoB) (insufficient evidence)
- Mud bath therapy showed a significant beneficial medium-term effect on pain and stiffness compared with a control condition, based on one RCT (n=103; moderate RoB) (insufficient evidence).
- Mud bath therapy showed no consistent sustained long-term effects on pain, function, or quality of life, based on one RCT (insufficient evidence).

Heat, Infrared, and Therapeutic Ultrasound

One RCT that assessed the effects of heat,⁵⁵ one that assessed the effects of infrared,⁵⁶ and two that assessed the effects of pulsed and continuous U/S on outcomes of interest met inclusion criteria.^{57, 58} Only short-term effects were reported for heat and infrared, and no medium-term effects were reported for any of the interventions.

Key Points

- Heat treatment showed beneficial effects on short-term pain and function compared with pharmacotherapy alone, based on one RCT (n=46; unclear RoB) (insufficient evidence).
- Infrared treatment showed no beneficial effect on short-term pain compared with a sham control, based on one RCT (n=72; low RoB) (insufficient evidence).
- Ultrasound (U/S) showed inconsistent effects on short-term and long-term pain, based on two RCTs (insufficient evidence).
 - Continuous or pulsed U/S combined with exercise had a beneficial effect on short-term pain but comparable to that of exercise alone and no significant effect (n=30; unclear RoB).
 - Continuous and pulsed U/S showed no long-term beneficial effects on pain compared with a sham control (n=60; moderate RoB).

TENS and NMES

Three RCTs that compared the effects of TENS with those of sham-TENS⁵⁹⁻⁶¹ and five RCTs that assessed the effects of NMES met inclusion criteria.^{26, 62-65} No studies were identified that assessed long-term outcomes.

Key Points

- TENS appears to have a small clinically important short-term beneficial effect on pain in patients with knee OA; however effects on function and longer-term effects are inconsistent.
- TENS showed a small but significant beneficial short-term effect on pain compared with sham controls, based on a pooled analysis of three RCTs (moderate strength of evidence).
 - A random effects pooled estimate showed a small beneficial effect of treatment on pain compared with a sham control that met our prespecified minimum clinically important difference of -0.37 (pooled effect size -0.38 , 95% CI $-0.6, -0.14$) (n=343; RoB low-moderate)
- TENS showed no beneficial short-term effect on function or stiffness and no beneficial medium-term effects (low strength of evidence).
- NMES combined with exercise showed inconsistent short-term effects on pain compared with exercise alone, based on three RCTs (insufficient evidence).
 - Two RCTs reported a beneficial effect of NMES plus exercise compared with exercise alone on short-term pain (n=100, 63; low and moderate RoB)
 - One RCT reported no difference between NMES plus exercise and exercise alone (n=100, low RoB).
- NMES alone showed no beneficial short-term effect on pain compared with a sham control (n=41; high RoB).
- NMES had inconsistent effects on medium-term pain and function, based on two and three RCTs, respectively.

Pulsed electromagnetic field (PEMF)

Two RCTs that assessed short-term effects of PEMF on pain met inclusion criteria.^{66, 67} No RCTs were identified that assessed medium- or long-term outcomes of PEMF.

Key Points

- It is unclear whether PEMF has any beneficial effect on patients with knee OA, as we identified only two small RCTs.
- PEMF had inconsistent short-term effects on pain.
 - Among two RCTs that assessed short-term effects on pain, one reported a beneficial effect compared with a sham control group (n=34, low RoB) and the other (n=40; moderate RoB) reported no difference.^{66, 67}

Whole-Body Vibration (WBV)

Six RCTs that met the inclusion criteria assessed the effects of WBV on outcomes of interest.⁶⁸⁻⁷³ No studies that assessed long-term effects were identified.

Key Points

- It is unclear whether WBV has any beneficial effect on patients with knee OA, as pooled analysis showed inconsistent significant and clinically important effects on pain and function,
- WBV-based exercise demonstrated inconsistent short-term beneficial effects on pain compared with exercise performed on a stable surface, based on two RCTs (one unclear and one low RoB) (insufficient evidence).
- WBV showed no short-term effects on function or total WOMAC scores in one trial each (insufficient evidence).
- WBV-based exercise showed no significant beneficial medium-term effects on pain, based on four pooled RCTs (n=193; moderate-low RoB) (SMD -0.20, 95% CI -1.12, 0.71) (low strength of evidence).
- WBV-based exercise showed a small but statistically significant medium-term beneficial effect on WOMAC function, based on four pooled RCTs (n=193; moderate-low RoB) (SMD -0.26, 95% CI -0.45, -0.06) (low strength of evidence) that did not meet the prespecified MCID of -0.37.
- WBV-based exercise showed no beneficial effect on distance walked in the 6-minute walk, based on four pooled RCTs (SMD -28.16, 95% CI -75.45, 19.13) (low strength of evidence).

Braces and Orthoses

Three RCTs on braces,⁷⁴⁻⁷⁶ eight RCTs on orthoses,⁷⁶⁻⁸³ four RCTs on footwear,⁸⁴⁻⁸⁷ and one RCT on cane use⁸⁸ met the inclusion criteria. No RCTs on short-term effects of footwear were identified.

Key Points

- It is unclear whether knee braces or orthoses have a beneficial effect on patients with knee OA, as only a small number of RCTs on braces were identified, and studies of orthoses showed inconsistent effects across time points and outcomes.
- Custom knee braces had statistically significant beneficial effects on short-term (one RCT), medium-term (one RCT), and long-term (one RCT) measurements of pain compared to usual care, based on two RCTs (insufficient evidence). Custom orthoses had no consistent beneficial short-term effects on pain (based on four RCTs) or function (based on three RCTs).
- Orthoses showed no beneficial effect on short-term WOMAC total scores, based on pooled analysis of three RCTs.
 - A random-effects meta-analysis of the three trials showed no statistically significant short-term effect of orthotic use on WOMAC total scores (SMD -0.37, 95% CI -1.26, 0.53).
- Orthoses showed no statistically significant beneficial effects on medium-term WOMAC pain, based on pooled analysis of three RCTs.
 - A random-effects meta-analysis of three trials (n=131; unclear, moderate, and low RoB) showed no statistically significant effect (SMD -0.4, 95% CI -1.35, 0.56) (low strength of evidence).

- Orthoses showed no consistent beneficial effects on medium-term function, based on four RCTs (insufficient evidence).
- Orthoses showed no consistent beneficial effects on long-term pain or function, based on two RCTs (insufficient evidence).
- Two types of custom shoe demonstrated inconsistent effects on medium-term pain, based on two RCTs and a beneficial effect on function, based on one RCT (insufficient evidence).
- Custom shoes had no long-term beneficial effects on pain, based on one RCT (insufficient evidence).
- Cane use had a significant short-term beneficial effect on pain, physical function, and quality of life but not WOMAC total scores, based on one trial (insufficient evidence).

Weight Loss

Five RCTs⁸⁹⁻⁹³ and five single-arm trials (reported in six publications)⁹⁴⁻⁹⁹ that assessed the effects of weight loss on OA met inclusion criteria.

Key Points

- Dieting, with or without exercise had a beneficial effect on short-term pain and function, based on one RCT (n=45, RoB unclear) and one single-arm trial, but benefit was not proportional to weight loss (dose-response effects were not established) (insufficient evidence).
 - The RCT showed a significant beneficial effect for diet alone and diet plus exercise on pain (VAS 1-10 cm: MD -2.10, 95% CI -3.32, -0.88; MD -4.56, 95% CI -5.82, -3.30, respectively)
 - The RCT also showed a significant beneficial effect for diet alone and diet plus exercise on WOMAC function (diet only: MD -2.34, 95% CI -3.71, -0.97; exercise+diet: MD -4.01, 95% CI -5.56, -2.46)
- Weight loss had a significant beneficial effect on medium-term pain, based on two RCTs and four single-arm trials. One single-arm trial assessed and reported a dose-response effect between weight and outcomes of interest (moderate-level evidence).
 - One RCT (n=87, RoB moderate) showed a significant beneficial medium-term effect on WOMAC pain with weight loss (MD -2.00, 95% CI -3.25, -0.75).
 - A second RCT that compared the effects of behavioral weight management and behavioral weight management plus pain coping skills training with those of standard care found that the combined treatment group, the only group that lost significantly more weight than the standard care group, showed a significant beneficial effect on medium-term WOMAC pain (MD -10.80, 95% CI -15.77, -5.83).
- Weight loss had a significant beneficial effect on medium-term function, based on the same two RCTs and three single-arm trials (low-level evidence)
- Weight loss had a significant long-term beneficial effect on pain based on three RCTs and one single-arm trial (low level of evidence) but inconsistent effects on function and quality of life, based on two RCTs (inconsistent evidence).

Home-based and Self-Management Interventions

Four RCTs that met inclusion criteria assessed the effects of home-based exercise programs or self-management programs.^{29, 31, 93, 100}

Key Points

- A home-based exercise program and a self-management plus exercise program showed significant beneficial short-term effects on pain, based on two RCTs (low-moderate RoB) (low-level evidence).
 - One RCT that compared three different home-based exercise programs with a passive sham-treatment group (n=44, RoB moderate) found significant beneficial effects on WOMAC pain scores for all three exercise groups compared with the control (Strength training alone: MD -3.75, 95% CI -6.39, -1.11; agility training alone: MD -3.13, 95% CI -5.86, -0.40; strength+agility training: MD -3.00, 95% CI -5.45, -0.55).
 - An RCT that compared a knee OA self-management program to a wait list control (n=146, RoB low) reported a significant beneficial effect on WOMAC pain scores (MD -1.50, 95% CI -2.33, -0.67) and VAS pain scores (0-10cm MD -2.54, 95% CI -1.66, -3.41), and the likelihood of achieving a minimum clinically important improvement (MCII) was significantly greater in the self-management group (RR 0.20, 95% CI 0.08, 0.49)
- A home-based and self-management program showed inconsistent effects on short-term function (insufficient evidence).
 - The self-management program showed increased proportions of participants achieving minimum clinically important improvements (MCII) in short-term function and quality of life.
- Self-management and PCST plus strength training showed beneficial but inconsistent medium-term effects on pain, based on three RCTs (low SoE).
 - A weight-loss program that employed PCST showed medium-term improvements in weight loss and pain in the group that received combined PCST and behavioral weight management (BWM) skills training, compared with standard care (n=232; moderate RoB).
 - The 8-week OAK self-management program no longer showed beneficial effects on pain at 6 months (n=146; low RoB)
 - A combined PCST and strength training program had a beneficial effect on VAS walking pain but not on VAS pain at rest or WOMAC pain (n=222; low RoB)
- Self-management programs had significant beneficial effects on medium-term function compared with control conditions, based on three RCTs (moderate-level evidence).
 - A weight-loss program that employed PCST showed medium-term improvements in function in the group that received combined PCST and behavioral weight management (BWM) skills training, compared with standard care (n=232; moderate RoB)
 - The 8-week OAK self-management program showed continuing beneficial effects on function at 6 months (n=146; low RoB)

- A combined PCST and strength training program had a beneficial effect on WOMAC function compared with strength training alone (n=222; low RoB)
- Self-management programs had inconsistent medium-term effects on WOMAC total and quality of life, based on two RCTs (insufficient evidence).
- Self-management plus strength training had no beneficial effect on long-term pain or WOMAC function, based on one RCT (insufficient evidence).

Key Question 2a: What harms are associated with each intervention in patients with primary or secondary OA of the knee?

Key Question 2b: How do the harms associated with each intervention differ by the following population or study characteristics: sex, disease subtype (lateral tibiofemoral, patellofemoral), severity (stage/baseline pain and functional status), weight status (body mass index), baseline fitness (activity level), comorbidities, prior or concurrent treatments (including self-initiated therapies), and treatment duration or intensity?

Key Findings and SoE for Key Question 2a-b

- Of 45 studies that described some assessment of adverse events, fourteen studies reported on serious adverse events (SAEs). Most reported only whether any SAEs were identified. SAEs were extremely rarely reported and not limited to active treatment groups. AEs are shown by study in Appendix H.
- No studies assessed differences in adverse events by characteristics of subpopulations.

Discussion

The purpose of this report was to update the findings of a 2007 EPC SR on the effects of supplements containing glucosamine with or without chondroitin, the findings of a 2012 EPC SR on the effects of interventions within the physical therapy scope of practice, and several newer interventions (cell-based therapies) on clinical outcomes in patients with knee OA. The population of interest for this review consists of patients with a documented diagnosis of OA of the knee.

Summary of Findings in Relationship to what is Already Known

Platelet-rich Plasma. The current review identified beneficial short-term effects of PRP. Several 2015 SRs reviewed the effects of PRP, however all prior reviews included studies comparing PRP to hyaluronic acid or corticosteroid injections. We included only studies that compared PRP to saline injections to control for any placebo effect. Thus, we identified too few studies to pool.

Glucosamine with or without Chondroitin. The 2007 SR found no significant benefit for glucosamine, glucosamine plus chondroitin, or chondroitin alone, compared with placebo, based on the large (n=1,583) GAIT trial.

New RCTs identified for this review provided conflicting evidence for effects of supplemental glucosamine, chondroitin, or the combination. A large non-inferiority trial found comparable short- and medium-term effects for glucosamine plus chondroitin compared with NSAIDs, but no long-term effects of either. This trial did not include a placebo control. The 2008 post hoc analysis conducted by the authors of the GAIT trial found that when participants were stratified by baseline pain, those with moderate to severe pain demonstrated a trend toward improvement from glucosamine plus chondroitin (proportion experiencing 20 percent or greater improvement in pain).¹⁰¹ The effect was moderated by the large placebo response. No new trials assessed short- or medium-term effects of glucosamine sulfate alone; three RCTs found no consistent long-term effects on outcomes of interest. Chondroitin showed evidence of short- and medium-term effects but no long-term effects, in three new trials and a long-term followup of the GAIT trial. The analysis also found that the effect of chondroitin on swelling was seen predominantly in those with less-advanced disease.

Strength and Resistance Training. The 2012 SR found low-level evidence that “strengthening exercise” decreased pain and improved several other outcomes among individuals with OA of the knee, but no evidence for improvement in function was supported. That review did not describe their criteria for categorizing an intervention as a strengthening exercise intervention; therefore we have not attempted to pool studies identified for this report with theirs.

The current review did not identify sufficient evidence to strengthen the findings of the 2012 review on beneficial effects of strength and resistance training on pain and function. However, we identified moderate evidence for a significant beneficial effect on total WOMAC score. This finding seems at odds with the finding of no significant effect on pain and function, two of the three components of the total score. One explanation for this apparent discrepancy may be the larger number of studies that assessed total WOMAC scores, compared with the number of studies that assessed pain and function.

Agility Training. The current report identified evidence from five RCTs that strengthened the findings of the 2012 report on beneficial effects of agility training on long-term pain,¹¹ as well as providing evidence on short-term benefits for pain and function and long-term function. The current report did not identify evidence to augment the findings of the 2012 report on aerobic exercise, tai chi, or yoga.

Manual Therapy. For the current review, we found low-strength evidence for a lack of beneficial effect of manual therapy on short-term pain, based on three pooled RCTs, but no consistent effects on medium-term pain, function, or other outcomes, likely due to wide variation among the interventions. The 2012 SR reported a low strength of evidence for an effect of massage on function based on two pooled studies (6-13 weeks) and reported improvements in disability and other outcomes based on three unpooled studies.

WBV. The current review identified a significant beneficial effect of WBV on medium-term function but not on medium-term pain, based on pooled analysis of three RCTs (low-strength evidence). Insufficient evidence was found for short- and long-term effects. The 2012 SR did not consider WBV as an intervention, and no other recent high-quality SRs assessed the effects of WBV on pain or function.

TENS and NMES. The current review found a beneficial short-term effect of TENS on pain, based on a MA of three RCTs (moderate-level evidence), but no consistent effects on function and no medium- or long-term effects.

The 2012 SR identified a beneficial effect of electrical stimulation, (including TENS and NMES) on short-term pain, based on meta-analysis of seven RCTs, but no other significant effects of electrical stimulation.¹¹

Braces and Orthoses, Shoes, and Cane Use. The 2012 SR identified low-level evidence for an effect of orthoses on function.¹¹ That review did not identify studies on cane use, braces, or shoes.

The current review found no beneficial effects of orthoses on pain or function in pooled analyses. A 2015 Cochrane update review assessed the efficacy of orthoses (including one type of shoe, a custom variable-stiffness shoe) and knee braces.¹⁰² That review included only one RCT that was published since the 2012 SR (included in the current review) and, in agreement with the current review, concluded that braces and orthoses had no consistent effects on pain or function.

Other Physical Modalities. The current report did not identify evidence of sufficient strength to augment or contradict the findings of the 2012 SR on tai chi, yoga, ultrasound, PEMF, heat, balneotherapy or mud therapy.¹¹

Weight Loss. The 2012 SR did not consider the effects of weight loss, and no other systematic reviews were identified that assessed the effects of weight loss on the outcomes of interest for this review.

The current review identified low-moderate evidence from RCTs and single-arm trials supporting a beneficial of weight loss on medium-term pain and function and a low level of evidence supporting a beneficial effect of weight loss on long-term pain. Dose-response effects between weight loss and effect sizes were inconsistent across studies.

Home-based and self-management interventions. The 2012 SR included a number of studies that assessed the effects of home-based or self-management interventions but did not assess these interventions as a category. Two 2015 SRs reviewed the effects of home exercise programs¹⁰³ and self-management interventions¹⁰⁴ for the treatment of OA of the knee or knee conditions in general. These SRs reported positive effects of home exercise programs and self-

management programs with exercise on pain and function but noted the heterogeneity of interventions and challenges in study design. Most RCTs of exercise interventions included in the current report expected participants to perform exercises at home, but the studies we analyzed in this category explicitly assessed home-based or self-management programs. These programs showed beneficial effects on medium-term pain and function (low- and moderate-level evidence, respectively).

Adverse Events. Approximately half of the studies included in the current review reported having assessed AEs. Of the 13 RCTs that mentioned SAEs, most reported no SAEs or SAEs that could not be attributed to the intervention. Of note, AEs associated with glucosamine and chondroitin did not differ between groups in the placebo-controlled or non-inferiority trials. WBV was not associated with any AEs. PRP was associated with pain and stiffness that increased with the number of injections.

Limitations of the Evidence Base

Limitations Due to Study Quality. The results of the RoB assessments for each study appear in Table F1 in Appendix F of the report. In the Results section of the full report, we have provided summary RoB scores for each study. The most prevalent limit to study quality was participant blinding: Only 33 of 85 RCTs reported an attempt to blind participants appropriately, using sham injections, placebo pills, sham applications of a treatment such as TENS, or in the case of exercise interventions, a control condition that could be considered an intervention itself. Many RCTs of physical interventions reported that participants were not or could not be blinded. Although outcome assessors were often reported to have been blinded in these studies, many of the outcomes of interest to this report were self-assessed (such as pain and WOMAC function). This lack of blinding significantly limits conclusions we can draw from the literature and is further discussed below in regard to comparators.

Another quality issue is the large number of RCTs for which adequate concealment of allocation could not be ascertained: 46 of 85. The inability to ascertain allocation concealment might sometimes be attributed to word limitations in publications, but is still a concern.

A third quality concern is the finding that 41 studies did not indicate use of intent-to-treat analysis; since participants who are not experiencing benefit from treatment are more likely to drop out before study completion, per protocol analysis could artificially inflate apparent effects.

Fourth, 31 RCTs indicated evidence of incomplete adherence. This figure is actually deceptively low, as most interventions involving exercise require that participants work out on their own on days when they are not being supervised. Most studies did not attempt to monitor offsite compliance, and no studies assessed the effect of such compliance or adherence on outcomes.

Finally, although most studies demonstrated that participants were similar at baseline, some similarities were not routinely considered, such as weight status, or disease stage or severity, and almost no studies stratified outcomes by any baseline characteristics.

Additional Limitations. The applicability of the findings of many of the studies to community settings may be limited by their having been conducted in an academic setting and enrolling highly motivated participants. For this reason, we attempted to assess the effects of home-based interventions; however, these interventions are limited in number, and also tend to be highly supervised. Related to this concern, compliance or adherence was almost never reported.

The applicability of studies of the dietary supplements, glucosamine and chondroitin, may be limited as they either did not report sources, did not ensure purity and concentration of active ingredients, or used forms and preparations that are not available commercially. Likewise, the studies of PRP each prepared their material using proprietary processes, although at least one publication described the process.

Another intervention-related limitation concerns the fact that many studies employed (or failed to prevent) multicomponent interventions. We purposely excluded studies whose multicomponent intervention design precluded assessment of the effect of a single component of interest. However, studies of physical modality interventions often implemented or focused on one type of activity added to a regimen of other activities (with the control group receiving the “other activities” only). In addition, many of the studies permitted continued use of analgesics or other treatments, preventing attribution of improvement to a specific intervention (or blunting the potential effects of an intervention). This problem is discussed further below.

Duration of interventions and followup was a concern. We limited inclusion to studies with a minimum followup of four weeks, because OA of the knee is a chronic, progressive condition. This decision had several implications; for example, no studies of taping met inclusion criteria, as the follow-up time was usually brief. Also, we did not consider the duration of an intervention as an inclusion criterion (as interventions such as PRP injection have no duration). Thus, the interval between the end of an intervention and outcome assessment, especially medium- or long-term followup, differed across studies. In categorizing studies by the length of followup times for potential pooling, we did not consider the duration of the intervention, itself. This limitation could explain a lack of significant medium- and long-term effects, as few, if any, of the interventions included in this report are thought to have disease-modifying effects that last beyond the intervention.

Another major challenge concerns the choice of study comparators. Contributing to this challenge is the self-reported, subjective nature of pain as an outcome. The placebo effect observed in large placebo-controlled RCTs of glucosamine with or without chondroitin diminished the effect of the active intervention. At the same time, a recent trial comparing glucosamine plus chondroitin to an NSAID found comparable beneficial effects of both. For the current report, we excluded studies that used only comparators of unclear efficacy (e.g., HA as a comparator for PRP) to make it possible to discern the magnitude of the placebo effect. We also excluded studies that used a participant’s less-painful knee as the comparator. However, the selection of appropriate comparators is a concern, particularly for studies of physical modalities such as strength training. Many of the studies we included employed usual care as a control; however, as described above, usual care often included a physical therapy program (usually some combination of strength and agility exercises and manipulation). Therefore, the failure to see a difference in outcomes between an intervention and a usual care control group might be attributable to there simply being a limit to the improvement that might be possible over that from standard physical therapy (especially over the often short duration of a study, and without major effort being expended by participants to work out on their own on days they do not attend the study classes). This conclusion is particularly likely, given that most studies that reported no differences in outcomes between interventions and active controls did report significant improvements from baseline. It is unclear what the most appropriate control is for studies of physical modalities or even studies of weight loss that include exercise: the findings of studies that compared diet alone to exercise and to diet plus exercise were difficult to interpret because exercise might have the same beneficial effects as weight loss, and whether they are synergistic

or one actually masks the other could not be determined. That some studies used only active comparators while others used only inactive comparators also limited the numbers of studies that could be pooled or even compared.

A number of outcomes of interest were not reported in the included studies or were reported only sporadically. Risk for undergoing TKR was a prespecified outcome of interest in only one RCT. Many factors that cannot be accounted for influence the decision to undergo TKR. Thus, TKR has not proven to be a useful outcome for assessing the effectiveness of interventions.

We ideally hoped to assess the clinical as well as the statistical significance of any beneficial findings. To do so, we would assess whether statistically significant outcomes met a prespecified minimum clinically important difference (MCID). However, we encountered several major challenges in trying to do so. First, some publications failed to include the numerical scales used with their assessment tools. As a result, it was impossible to assess the potential clinical significance of their findings. Second, published MCIDs depend on the disease severity of the participants; the included studies varied widely in the disease severity of included participants, and some did not report it. Nevertheless, a wide variety of MCIDs have been derived and applied in reviews of similar patient populations (see Appendix I for a summary of published values). We selected and applied one set of values that has been applied in a number of similar reviews¹⁰⁵ to the small number of statistically significant outcomes for which we had pooled standardized mean differences or for which we were able to identify the numerical measurement scales. But, thirdly, it is important to note that MCIDs are derived by translating patients' responses on a scale of multiple items (e.g., the full WOMAC scale contains 24 items), each item graded using numerical rating scales of 4-100 points, to their response to a smaller, subjective set of anchoring questions; thus, their validity continues to be debated.

Finally, because of the heterogeneity among studies with regard to interventions, comparators, outcome measures, durations of treatment and followup, and even reporting of the scales used for some outcome measures, few studies could be pooled. Although, we describe each study narratively in the report, the inability to pool results limits our confidence in the strength of evidence.

Future Research Recommendations

In general, future studies need to enroll sufficient numbers of participants to enable prespecified subgroup analysis according to important participant characteristics and to enable assessment of both statistical and clinical improvement. Studies also need to employ designs that permit assessing the effects of specific interventions and to consider including both active (sham) and passive comparison groups to enable participant blinding. Isolation of the interventions being assessed needs to be accomplished both by careful design of the interventions themselves and by prohibiting participants from using alternative modes of therapy. In addition, many interventions need to be conducted for longer durations and mechanisms need to be developed to better measure compliance. Reported outcomes need to include the percent of participants who experience improvement as well as an estimate of whether the effect size achieves a MCID.

Recent OARSI guidelines on design of clinical trials for knee OA therapies include 25 recommendations. Among them are clear definition (of and rational for) inclusion/exclusion criteria; assessment and reporting of disease severity; ensuring randomization, blinding (to the extent possible), and similarity of important characteristics at baseline; use of validated outcome measures and steps to minimize bias in patient-reported outcomes.¹⁰⁶ Recommendations specific to particular interventions are described below.

Cell-based Therapies: Based on our finding of a significant effect of PRP in a small number of small, high RoB studies, and the number of studies that did not meet inclusion criteria because they compared PRP only to HA, we believe a large, saline-controlled trial is needed. Although corticosteroids could provide an additional comparator for non-inferiority, the immediate adverse effects of intraarticular injection of corticosteroids would be impossible to mask. Residual benefits that remain after the intervention is discontinued (and the effect of follow up treatment) also need to be assessed.

In addition, no studies of stem-cell therapy or other cell-based therapies met inclusion criteria. A large multisite commercial clinic that was contacted for trial results did not respond to the request. Clinicaltrials.gov lists several registered trials of stem-cell treatments for OA of the knee, which should be monitored for published findings. We also identified four published studies of gene therapies (using autologous chondrocytes genetically modified to deliver a growth factor and designed to be injected intraarticularly), which to date, have been tested only in Phase II trials.¹⁰⁷⁻¹¹⁰

Glucosamine with or without chondroitin: The 2016 MOVES Trial found significant beneficial medium-term effects on pain, function, stiffness, and quality of life for a prescription form of glucosamine hydrochloride plus chondroitin that were comparable with those of a Cox-2 inhibitor in a large patient population with severe pain. The rate of AEs was relatively small and similar across groups (individuals with cardiovascular conditions were excluded). Thus far, longer-term outcomes have not been reported but would need to be considered in formulating guidelines regarding the use of a prescription grade form of the supplement, especially in light of the findings of the LEGS Trial that glucosamine, chondroitin, and the combination had no beneficial effects at 1 and 2 years compared with placebo. In addition, a head-to-head trial similar to MOVES should be conducted using a combination of glucosamine sulfate and chondroitin, as some evidence has suggested glucosamine sulfate is more effective than glucosamine hydrochloride.

Physical modalities: The studies on strength, agility, and aerobic training that met inclusion criteria usually combined the training modality that was being tested with additional exercises, for example, a strength training intervention would include aerobic exercise as a warm-up and would sometimes include a brief session of exercises aimed at improving agility or gait as well. This design matches the physical therapy regimens in current use and probably makes sense as a therapeutic regimen, but it requires that studies that aim to test a specific modality are carefully designed to ensure that the results can be attributed to the intervention being tested. Other SRs have also noted the difficulty in drawing conclusions regarding the clinical utility of various physical modalities.

The efficacy of individually tailored multicomponent interventions also needs to be assessed but traditional clinical trial methods may not be well-suited to assess such interventions, because testing custom interventions essentially requires that patients serve as their own controls. A number of the trials included in our review modified interventions based on an assessment of individual participant deficits but only one assessed the effects of doing so and found no differences from participants who received a non-tailored therapy.

No studies of aquatherapy, and few studies of yoga or tai chi, met inclusion criteria. Larger trials of these modalities alone compared with both active comparators (to mask the intervention of interest) and waiting list (or other passive) comparators are needed, as they can easily be undertaken by sedentary individuals with no prior training.

OARSI recently published guidelines for the design and conduct of clinical trials of rehabilitation interventions, which include the physical modalities.^{106, 111} Recommendations are similar to those of the OARSI guidelines for assessing interventions for OA of the knee.¹⁰⁶ Emphasis is on participant blinding when possible; assessor blinding; use of both sham (active) and passive comparators; description of baseline severity (with clinical measures, if desired); prespecification of adverse events for assessment; use of valid outcome measures with a benchmark, if possible; and assessment of the percent of participants who achieve improvement. Comparative effectiveness trials are advocated for testing novel treatments against those with established effectiveness or when blinding is not otherwise possible. Caution is suggested in applying published MCIDs, as they have been shown to differ by population and other factors.¹¹²

Weight Loss: This review showed beneficial effects of weight loss interventions on pain and function. Future studies need to clarify the roles of exercise and self-efficacy education in the observed effect to assess whether exercise and/or self-efficacy have their own effects, independent of caloric restriction and weight loss or if these co-interventions assist with weight loss and weight maintenance.

The OARSI recently released guidelines on design and conduct of diet and exercise interventions for OA.¹¹¹ Most of the recommendations were similar to those provided for rehabilitation and for OA of the knee interventions in general, in copublications. However, they also provided several additional noteworthy recommendations. These include the need to determine in Phase 1 trials whether high-intensity strength training, aimed at increasing quadriceps muscle strength, is safe in older adults with knee OA. Also recommended is allowing monitored use of rescue medication (analgesics), as weight loss trials tend to be longer in duration than other studies.

Home-based therapies: Our results, based on only a small number of studies, suggest home-based therapies with periodic supervision show beneficial effects on pain and function. This model has the advantage of requiring few clinic visits but the disadvantages of lack of monitoring of compliance and correct form when performing activities. The 2016 SR of home-based therapies by Anwer and colleagues also cites the issue of difficulty assessing compliance with home-based interventions.¹⁰³ Future research studies of home-based exercise could easily employ any one of a number of fitness monitoring devices to assess adherence and could use applications like Skype to periodically monitor performance.

Adverse effects: Future studies need to prespecify AEs of concern. Researchers need to actively and systematically collect information on adverse effects of interventions at defined intervals, particularly for cell-based therapies and intensive exercise programs.

Conclusions

Among the interventions assessed for efficacy and safety for the management of OA of the knee in this review, several show moderate evidence for beneficial effects on pain or function, including weight loss and home-based and self-management programs, and TENS (for pain only). Interventions that show low or moderate evidence for beneficial effects on short- or medium-term pain or function include platelet-rich plasma, glucosamine-chondroitin, strength training, agility training, whole body vibration (on function but not pain). Insufficient evidence was found for other interventions and for additional outcomes, such as stiffness, swelling, quality of life, avoidance of knee replacement, for any outcome.

Larger randomized controlled trials are needed, with more attention to appropriate comparison groups and longer duration, to assess newer therapies and to determine which types of physical modalities are most effective.

Table A. Summary strength of evidence

Intervention/Outcome	Number, design of studies (and participants if pooling)	Findings (strength of evidence)
KQ 1 Platelet-rich plasma		
Short-term outcomes	2 RCTs	Beneficial effect on pain vs. placebo in one RCT; no difference vs. analgesic in one RCT Beneficial effect on function vs. placebo; Beneficial effect on WOMAC total vs. placebo (Insufficient evidence)
Medium-term pain	4 RCTs	Beneficial effects of single and multiple injections vs. placebo and analgesic (Low strength of evidence [SoE])
Medium-term other outcomes	2 RCTs	Beneficial effect on WOMAC function vs. placebo in one RCT; no difference vs. analgesic in one RCT Beneficial effect on WOMAC total vs. placebo (Insufficient evidence)
Long-term outcomes	0 RCTs	(Insufficient evidence)
Glucosamine with or without chondroitin		
<i>Glucosamine plus chondroitin</i>		
Short-term outcomes	0 RCTs	(Insufficient evidence)
Medium-term outcomes	2 RCTs	Beneficial effect on WOMAC pain, function, and stiffness vs. analgesic and placebo (Low SoE)
Long-term outcomes	3 RCTs	No consistent beneficial effect on pain, function, QoL (Low SoE)
<i>Glucosamine</i>		
Short-term outcomes	0 RCTs	(Insufficient evidence)
Medium-term outcomes	0 RCTs	(Insufficient evidence)
Long-term outcomes	3 RCTs and post-hoc analysis	No consistent beneficial effect vs. analgesic or placebo on pain or function at 1-2 years in 3 RCTs but a post hoc analysis of 2 RCTs showed decreased risk for TKR (Low SoE)
<i>Chondroitin-sulfate</i>		
Short-term outcomes	1 RCT	Beneficial effect on pain and function vs. placebo (Low SoE)
Medium-term pain	2 RCTs	Beneficial effect on pain vs. placebo (Low SoE)
Medium-term function	2 RCTs	No beneficial effect on function (vs. placebo) (insufficient evidence)
Long-term pain	3 RCTs	No beneficial effect on pain (moderate SoE)
Long-term function	3 RCTs	No beneficial effect on function (Low SoE)
Strength/resistance Training		
Short-term pain	5 RCTs	No significant beneficial effect vs. educational, other exercise, or no intervention (Low SoE)
Short-term function	5 RCTs	No significant beneficial effect vs. educational, other exercise, or no intervention (Low SoE)
Short-term WOMAC total	3 RCTs	Significant beneficial effect on WOMAC total (Low SoE)
Short-term quality of life	2 RCTs	Significant beneficial effect on quality of life (insufficient evidence)
Medium-term outcomes	2 RCTs	No significant beneficial effect on pain, function, quality of life (insufficient evidence)
Long-term outcomes	1 RCT	Significant beneficial effects in pain and function (insufficient evidence)
Agility Training		
Short-term pain	3 RCTs	Beneficial effect on pain vs. placebo and not different from strength training (Low SoE)
Short-term function	3 RCTs	No consistent beneficial effect on function vs. placebo (insufficient evidence)

Intervention/Outcome	Number, design of studies (and participants if pooling)	Findings (strength of evidence)
Medium-term pain	2 RCTs	No consistent beneficial effect vs. placebo (insufficient evidence)
Long-term outcomes	2 RCTs	No consistent beneficial effect on long-term pain or function (insufficient evidence)
Aerobic Exercise		
Short-term outcomes	0 RCTs	(insufficient evidence)
Medium-term outcomes	0 RCTs	(Insufficient evidence)
Long-term	1 RCT	No beneficial effect on pain or function vs. educational control (insufficient evidence)
Exercise, not specified		
Medium-term outcomes	1 RCT	Exercise had a beneficial effect on pain and function compared with no exercise (insufficient evidence)
Long-term outcomes	2 RCTs	Exercise had inconsistent effects on pain, function, and quality of life compared with no exercise or less exercise (insufficient evidence)
Tai Chi		
Short-term outcomes	2 RCTs	No consistent beneficial effect on pain and inconsistent beneficial effects on function vs. strength training and passive controls (insufficient evidence)
Medium-term outcomes	1 RCT	Significant beneficial effect on pain and function vs. education (insufficient evidence)
Yoga		
Short-term pain	1 RCT	Significant beneficial effect on pain and function vs. wait list control (insufficient evidence)
Manual Therapy		
Short-term pain	3 pooled RCTs, 3 unpooled	No significant beneficial effect of manual therapy on pain (Low SoE)
Short-term function	3 RCTs	No beneficial effect on function (insufficient evidence)
Medium-term outcomes	4 RCTs	No consistent beneficial effects on pain, function or other outcomes (insufficient evidence)
Long-term outcomes	1 RCT	Significant beneficial effect on pain when combined with exercise compared with exercise alone (insufficient evidence)
Balneotherapy and Mud Therapy		
<i>Balneotherapy</i>		
Medium-term pain	2 RCTs	Inconsistent beneficial effect on pain (insufficient evidence)
Medium-term function	2 RCTs	Significant beneficial effect on function, and quality of life, but not stiffness (insufficient evidence)
<i>Topical Mud therapy</i>		
Short-term outcomes	1 RCT	No beneficial effect on pain or function but beneficial effect on stiffness vs. placebo (insufficient evidence)
<i>Mud bath therapy</i>		
Medium-term outcomes	1 RCT	Significant beneficial effect on pain and stiffness vs. usual care (insufficient evidence)
Long-term outcomes	1 RCT	No significant beneficial effects on pain, function, or stiffness (insufficient evidence)
Heat, Infrared, Ultrasound		
Short-term pain	3 RCTs	Heat showed a beneficial effect on pain, comparable to analgesics; infrared showed no beneficial effect on pain vs. placebo; ultrasound plus exercise had a beneficial effect that was comparable with exercise alone (insufficient evidence)

Intervention/Outcome	Number, design of studies (and participants if pooling)	Findings (strength of evidence)
Short-term function	2 RCTs	Heat showed a beneficial effect on function, comparable to analgesics; ultrasound showed no benefit for function, vs. exercise (insufficient evidence)
Long-term outcomes	1 RCT	Continuous and pulsed ultrasound showed no long-term benefit for pain or function vs. sham ultrasound. (in sufficient evidence)
Pulsed Electromagnetic Field		
Short-term outcomes	2 RCTs	Inconsistent effect on pain (insufficient evidence)
Transcutaneous Electrical Nerve Stimulation (TENS)		
Short-term pain	3 RCTs	Significant beneficial effect on pain, exceeding MCID (moderate SoE)
Short-term function	2 RCTs	No beneficial effect on function (Low SoE)
Medium-term outcomes	2 RCTs	No beneficial effect on medium-term outcomes (Low SoE)
Neuromuscular Electrical Stimulation (NMES)		
Short-term	4 RCTs	Inconsistent effects of NMES alone or combined with exercise on short-term pain (insufficient evidence)
Medium-term outcomes	2 RCTs	No beneficial effects of NMES on pain or function (insufficient evidence)
Whole-body Vibration(WBV)		
Short-term outcomes	2 RCTs	Inconsistent effects of WBV-based exercise on pain and function (insufficient evidence)
Medium-term pain	4 RCTs, pooled	No significant beneficial effect on WOMAC pain (low strength of evidence)
Medium-term function	4 RCTs, pooled	Significant beneficial effect on WOMAC function that does not meet an MCID (low strength of evidence) No significant beneficial effect on the 6-minute walk (low strength of evidence)
Braces and Orthoses		
<i>Braces</i>		
Short-term pain	1 RCT	Beneficial effect on VAS pain (insufficient evidence)
Medium-term pain	1 RCT	Beneficial effect on pain (insufficient evidence)
Long-term pain	1 RCT	Beneficial effect on pain (insufficient evidence)
<i>Orthoses</i>		
Short-term pain	4 RCTs	Inconsistent effects on pain (insufficient evidence)
Short-term WOMAC total	3 RCTs	No significant beneficial effect on WOMAC total based on pooled analysis (Low SoE)
Medium-term pain	3 RCTs	No significant beneficial effect on pain based on pooled analysis of 3 RCTs (Low SoE)
Medium-term function	4 RCTs	No beneficial effect on function (insufficient evidence)
Long-term pain	2 RCTs	Inconsistent effects on pain (insufficient evidence)
<i>Custom Shoes</i>		
Medium-term pain	2 RCTs	Inconsistent effects on pain (insufficient evidence)
Medium-term function	1 RCT	Beneficial effect on function (insufficient evidence)
Long-term pain	1 RCT	No beneficial effect on pain (insufficient evidence)
<i>Cane</i>		
Short-term outcomes	1 RCT	Beneficial effect on pain, function, and quality of life (insufficient evidence)
Weight-loss		
Short-term pain and	1 RCT and 1 single-arm	Beneficial effects on pain and function but dose-response not assessed (insufficient evidence)

Intervention/Outcome	Number, design of studies (and participants if pooling)	Findings (strength of evidence)
function	trial	
Medium-term pain	2 RCTs and 4 single-arm trials	Beneficial effect on pain and dose-response demonstrated in 1 trial (Moderate SoE)
Medium-term function	3 RCTs and 3 single-arm trials	Beneficial effect on function but inconsistency in one RCT (Low SoE)
Long-term pain	3 RCTs and 1 single-arm trial	Beneficial effect on pain (Low SoE)
Home-based and Self-Management		
Short-term pain	2 RCTs	Significant beneficial effects on pain (Low SoE)
Short-term function	2 RCTs	Inconsistent effects on function (insufficient evidence)
Medium-term pain	3 RCTs self-management	Significant but inconsistent effects on pain (Low SoE)
Medium-term function	3 RCTs self-management	Significant beneficial effects on WOMAC function (Moderate SoE)
Medium-term other outcomes	2 RCTs	No effects on WOMAC total or quality of life (insufficient evidence)
Long-term outcomes	1 RCT	No effects on WOMAC pain, function, and other outcomes (insufficient evidence)
Key Question 2 Adverse Events		
Non-serious adverse events	40 RCTs, 1 single arm trial	No systematic non-serious AEs with the exception of minor GI complaints among individuals following low-calorie diets (Low evidence)
Serious adverse events	13 RCTs	No systematic findings of SAEs by intervention type (Low-moderate evidence)

Abbreviations: BWM=behavioral weight management; CI=confidence intervals; MCID=minimum clinically important difference; MCII=minimum clinically important improvement; MD=mean difference; N/A=not applicable; NMES=neuromuscular electrical stimulation; N/R=not reported; NRS=Numeric Rating Scale; PCST=pain coping skills training; QoL=quality of life; RCT=randomized controlled trial; RoB=risk of bias; SF=short form; SMD=standardized mean difference; ST=strength training; TENS=transcutaneous electrical nerve stimulation; TUG=timed up and go; VAS=visual analog scale; WBV=whole-body vibration; WOMAC=Western Ontario McMaster Osteoarthritis Index

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Introduction

Background and Objectives

Osteoarthritis (OA) of the knee is a condition characterized by the progressive destruction of the articular cartilage that lines the knee joints, the subchondral bone surfaces, and synovium; accompanied by pain, immobility, and reduction in function and the ability to complete activities of daily living (ADL). In 2005, the estimated prevalence of OA in any joint among adults in the United States (US) (the number of individuals who had ever been told by a doctor that they had the condition) was approximately 27 million cases.¹ Prevalence rates vary by the joint involved and the method of ascertainment (clinical vs. radiographic): symptomatically, the knee is the most frequently affected joint.² The prevalence of OA of the knee is increasing rapidly because of shifting population demographics: The primary risk factors for OA of the knee are aging, obesity, prior injury, repetitive use,³ and female gender. The US Centers for Disease Control have estimated that the prevalence of symptomatic knee OA may reach 50 percent by the age of 85.⁴ From 2002 to 2012, the number of individuals in the US with a total knee replacement (TKR) doubled from some 2 million to approximately 4 million.⁵ The increase in obesity has translated not only into an increase in incidence of OA of the knee but also into a younger age of onset and need for treatment; as a result, by the time individuals with OA of the knee reach the age of Medicare eligibility, the length of time they have had the condition has grown, their cases are more advanced,⁶ and the risk that surgery will be needed has increased. Thus, the aging of the baby boomer population, along with the increased incidence and prevalence of obesity have increased the risk for this condition, all representing an increasing strain on Medicare resources.

Etiology

Two types of OA of the knee are recognized: the more prevalent primary OA of the knee is considered to be a natural consequence of aging, whereas secondary OA of the knee can be caused by trauma, inactivity, overweight, or a disease process such as rheumatoid arthritis. No evidence suggests that the two types are treated differently or respond differently to treatments.⁷

Diagnosis

The clinical diagnosis of OA of the knee is typically based on presentation, including insidious onset of weight-bearing knee pain that is exacerbated by use of the joint and relieved by rest, and that tends to worsen over the course of the day. Radiographic evidence of OA may precede symptomatic OA but may not correlate with symptom severity. Radiologic severity can be estimated and expressed using the Kellgren and Lawrence (K-L) criteria. However, a number of versions of the criteria exist. In addition, at low cutoff scores, correlation with symptoms is poor,⁸ whereas at higher cutoff scores, agreement tends to be higher. The primary impact of the different versions of the criteria may be the challenge that they create in trying to assess, compare, and pool the findings of research studies.⁸ Some longitudinal studies have even used different criteria at different time points within the same study. Because of the variation in scores for radiographic finding under various versions of the criteria (especially for individuals with less-advanced disease), stratification of findings by some other objective functional baseline criteria is important.

Some evidence suggests that among individuals with knee pain, MRI demonstrates physical signs of osteoarthritic changes in the knee before they are visible radiographically.⁹ However, the

sensitivity and specificity of MRI in diagnosis and monitoring of progression have not yet been definitively demonstrated and is not used in routine clinical practice.

Treatment Strategies

The goals of treatment for OA of the knee include relief of pain and inflammation, slowing or reversal of progression (through disease modification), and improvement in or maintenance of mobility, function (including activities of daily living [ADLs]), and health-related quality of life (HRQoL).

Treatment options for OA of the knee include the following:

- analgesics (oral, intra-articular, or topical) and anti-inflammatory agents (non-steroidal anti-inflammatory agents [NSAIDs], intraarticular corticosteroids);
- dietary supplements (including *glucosamine with or without chondroitin* and herbal mixtures), variously proposed to control pain and possibly serve as disease-modifying agents;
- Ayurvedic preparations, Traditional Chinese Medicine preparations, and acupuncture, all aimed at analgesia;
- ***physical treatments*** (including strength or aerobic exercise, physical therapy, stretching, heat, aqua-therapy, whole-body vibration, electrical stimulation therapies (neuromuscular electrical stimulation [NMES] and transcutaneous electrical nerve stimulation [TENS]), massage, and chiropractic manipulation), proposed to strengthen muscles that support the affected joints and to increase range of motion;
- ***bracing, shoe inserts (orthoses), and canes***, intended to slow progression by shifting the weight from the affected joint area;
- ***weight loss*** to decrease the stress on the joint;
- intraarticular viscosupplementation, which involves local injections of the natural joint lubricant, hyaluronic acid (HA),
- biologic agents (anti-nerve growth factor antibodies or anti-tumor necrosis factor antibodies, which are used to treat rheumatoid arthritis, and may have some benefit for OA)
- injections of ***platelet-rich plasma (PRP), plasma products, stem cells, and cartilage tissue***, also aimed at reversing or slowing the progression of the disease.¹⁰
- surgical procedures, including arthroscopy with lavage and/or debridement, and partial or total arthroplasty (knee replacement), which may be recommended for advanced cases if patients fail to obtain satisfactory relief from pain and improved function from the aforementioned treatments.

Information on the FDA status, indications, and warnings for the treatments included in this review (in boldface and italics above) is included in Appendix G.

Numerous recent evidence-based treatment guidelines have been issued, including the 2012 American College of Rheumatology Guidelines¹⁰ and the 2013 American Academy of Orthopedic Surgeons guidelines for the treatment of OA of the knee. These guidelines are not in total agreement about the recommended treatments: For example the 2012 American College of Rheumatology (ACR) Guidelines conditionally recommend HA, while the American Academy of Orthopaedic Surgeons (AAOS) guidelines recommend against its use to treat patients with symptomatic conditions.¹¹

Scope and Key Questions

Scope of the Review

Systematic reviews have been conducted on many of the modalities used to treat OA of the knee, including four reviews by AHRQ Evidence-based Practice Centers since 2007.^{7, 12-14} Uncertainty continues to surround the use of all treatments intended as disease-modifying agents (including HA and glucosamine and chondroitin), acupuncture, physical therapy, exercise, braces and orthotics, and arthroscopic lavage, as well as the comparative efficacy and safety of oral, topical, and intraarticular analgesics and anti-inflammatories.

This review is part of a continuous update review process that aims to repeatedly assess the need to update—and then to update if needed—a systematic review that was conducted in 2007.⁷ That review assessed the efficacy and safety of HA, glucosamine and/or chondroitin, and arthroscopic surgery. Prior to preparing this review, we conducted an updating surveillance assessment that comprised an environmental scan and consultation with a technical expert panel (TEP) to assess the currency of the conclusions of the 2007 review.¹⁵ A document that summarized the findings of this bifurcated process was posted for public review.¹⁶ The treatment modalities selected for inclusion in this review reflect a combination of the findings of the environmental scan, the TEP for the Surveillance process, the public comments, and the TEP for the current review.

The TEP for the surveillance process uniformly advised us that the conclusions of the 2007 report for intraarticular HA, oral glucosamine chondroitin, and arthroscopic surgery remained current and did not need updating. Instead, they recommended reviewing cell-based therapies, physical modalities, SNRIs, topical agents, weight loss, and acupuncture.

The environmental scan supported the TEP’s suggestion that the topics of intra-articular HA and arthroscopic surgery did not need updating. However, we identified several large recent trials on glucosamine-chondroitin that prompted us to want to update the review on this topic. Topics recommended by the TEP but not included in this report will be re-assessed for the need to update (or to conduct a new review) in a later surveillance period.

The included topics (interventions) are listed in the PICOTs outline (Table 1).

Table 1. PICOTs for the Review

Category	Inclusions	Exclusions	Key Question(s)
Participant Population	Adults (age 18 or over) with a diagnosis of primary (or secondary) OA of the knee, as defined by the American Academy of Orthopaedic Surgeons (AAOS, 2013), ACR clinical classification criteria, ¹⁷ or Kellgren-Lawrence stage	Studies of individuals under age 18; those with OA caused by a congenital condition; and those with OA concomitant with a meniscal or anterior cruciate ligament tear will be excluded because these participants have conditions that differ importantly from the vast majority of OA patients	KQ 1 and 2
	Subpopulations of interest include those defined by: sex, disease subtype (e.g., patellofemoral, or medial tibiofemoral), disease severity (stage/pain or functional status), body mass index, fitness/activity level, prior treatment,	Studies that include those who have had knee replacement surgery on the affected limb or for whom outcomes will be measured after knee replacement surgery or who have concomitant joint disease such as rheumatoid arthritis or gout will be excluded because these conditions or procedures will confound assessment of the outcomes of interventions	KQ 1 and 2

Category	Inclusions	Exclusions	Key Question(s)
	concurrent treatment(s), comorbidities		
Interventions	Glucosamine and/or chondroitin	RCTs with <50 participants	KQ 1 and 2
	Cell-based therapies: *Platelet-rich plasma *Intraarticular or arthroscopic administration of mesenchymal stem-cells or chondrocytes or tissue	Phase I or II trials will not be included for efficacy, as the interventions are generally not FDA-approved for use	
	Strength/resistance training	RCTs with <50 participants; Studies that assessed multicomponent interventions without controlling for all but the intervention of interest	
	Agility exercise	Studies that assessed multicomponent interventions without controlling for all but the intervention of interest	
	Aerobic exercise	Studies that assessed multicomponent interventions without controlling for all but the intervention of interest	
	Physical therapy/general exercise programs	Studies that assessed multicomponent interventions without controlling for all but the intervention of interest	
	Manual therapy	Studies that assessed multicomponent interventions without controlling for all but the intervention of interest	
	Balneotherapy/mud therapy	Studies that assessed multicomponent interventions without controlling for all but the intervention of interest	
	Heat/infrared/ultrasound	Studies that assessed multicomponent interventions without controlling for all but the intervention of interest	
	Neuromuscular electrical stimulation (NMES)	Studies that assessed multicomponent interventions without controlling for all but the intervention of interest	
	Transcutaneous electrical nerve stimulation (TENS)	Studies that assessed multicomponent interventions without controlling for all but the intervention of interest	
	Whole-body vibration	RCTs where effects of intervention could not be isolated	
	Braces/orthotics/shoes/cane	Studies that assessed multicomponent interventions without controlling for all but the intervention of interest	
	Weight loss: both RCTs and single-arm trials included	None	
	Self-management programs	None	
Comparators	Glucosamine/chondroitin: placebo-controlled or head-to-head non-inferiority only	Studies that use the untreated knee, participants themselves, or a treatment of unestablished efficacy as a control	KQ 1 and 2
	Cell-based therapies: placebo- or sham-controlled only	Studies that use the untreated knee, participants themselves, or a treatment of unestablished efficacy as a control	
	Physical treatments and/or weight loss: placebo-controlled, usual care-controlled, or wait list-controlled only except for weight loss	Studies that use the untreated knee, participants themselves, or a treatment of unestablished efficacy as a control	

Category	Inclusions	Exclusions	Key Question(s)
	NMES/TENS: sham stimulation without current Wait list Treatment as usual	Studies that use the untreated knee, participants themselves, or a treatment of unestablished efficacy as a control	
Outcomes	Short-term clinical outcomes: Pain (e.g., VAS, WOMAC, KOOS,) Joint stiffness (WOMAC) Function (WOMAC, Lequesne, others) Total WOMAC OARSI physical outcomes (e.g., timed up-and-go, 6-minute walk test,) Patient Reported Outcome Measurement System (PROMIS®) and Osteoarthritis-Computer Adaptive Test (OA-CAT) Inflammation or effusion Medication use	Studies that report only non-clinical outcomes (e.g., muscle strength measures, joint space, interleukin levels)	KQ 1
	Long-term clinical outcomes: Instrumental activities of daily living (IADLs) Quality of life (e.g., SF-36, EuroQuol EQ-5D, Arthritis Self-Efficacy scale, global assessment, patient satisfaction) Surgery (i.e., rate of undergoing knee replacement) Any of the short-term clinical outcomes		
	Adverse events	Studies that fail to report adverse event data separately by study arm will not be included in the adverse event analysis	KQ 2
Timing of followup	≥4 weeks (1 month) from baseline	Studies with maximum follow-up 4 weeks or less	KQ 1 and 2
Study design	RCTs (single arm and prospective cohort studies included for weight loss)	Open trials (except weight loss)	KQ 1 and 2
		Studies that fail to report outcomes for knee alone	KQ 1 and 2
	Large prospective studies		KQ 2
Settings	Any setting		KQ 1 and 2

Key Questions

Based on the findings of the environmental scan, TEP assessments, and public comments, the Key Questions from the 2007 report were revised as follows.

Key Question 1a: What is the clinical effectiveness of cell-based therapies, oral glucosamine and/or chondroitin, physical treatment modalities, weight loss, or home-based and self-management therapies in patients with primary or secondary OA of the knee, compared with appropriate placebo/sham controls or compared with other active interventions?

Key Question 1b: How do the outcomes of each intervention differ by the following population and study characteristics: sex, disease subtype (lateral, patellofemoral), severity (stage/baseline pain and functional status), weight status (body mass index), baseline fitness (activity level), comorbidities, prior or concurrent treatments (including self-initiated therapies), and treatment duration or intensity?

Key Question 2a: What harms are associated with each intervention in patients with primary or secondary OA of the knee?

Key Question 2b: How do the harms associated with each intervention differ by the following population or study characteristics: sex, disease subtype (lateral tibiofemoral, patellofemoral), severity (stage/baseline pain and functional status), weight status (body mass index), baseline fitness (activity level), comorbidities, prior or concurrent treatments (including self-initiated therapies), and treatment duration or intensity?

Analytic Framework

The review was guided by the analytic framework shown in Figure 1.

Figure 1. Analytic Framework for Osteoarthritis of the Knee

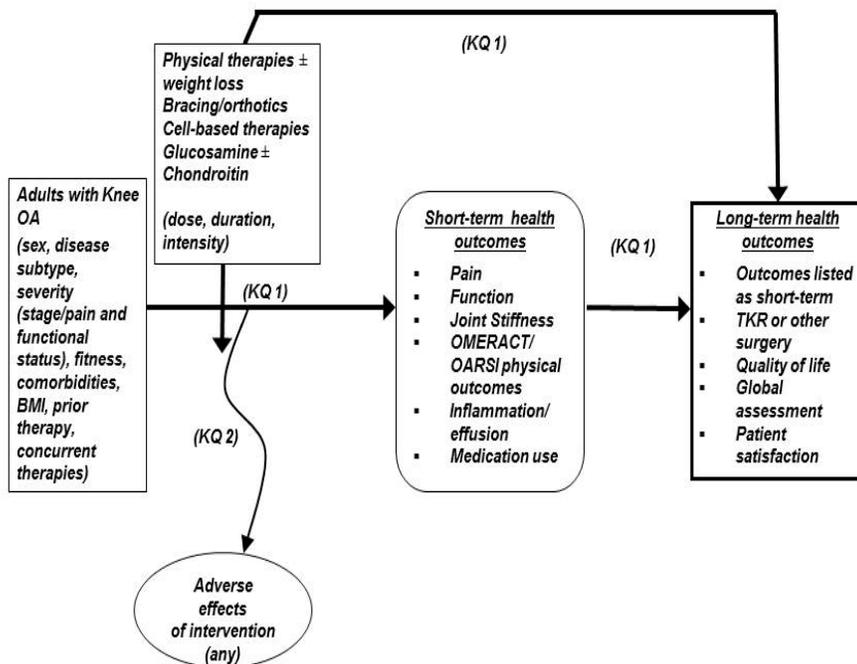


Figure notes: KQ = Key Question; OA = Osteoarthritis; TKR = Total Knee Replacement;

Organization of This Report

The remainder of this report presents the methods used to conduct the literature searches, data abstraction, and analysis for this review; the results of the literature searches, organized by KQ and intervention; the conclusions; and a discussion of the findings within the context of what is already known, the limitations of the review and the literature, and suggestions for future research.

Methods

The methods used to conduct the systematic review portion of this continuous update are based on the EPC Methods Guide.¹⁵

Criteria for Inclusion/Exclusion of Studies in the Review

Included studies are limited to those that fit the inclusion and exclusion criteria listed in Table 1.

Studies in any clinical setting were included as long as they satisfied all other inclusion/exclusion criteria. The results of the report are intended for primary care and acute care settings, and therefore primary and acute settings are preferred. For studies of efficacy and effectiveness, we endeavored to include only randomized controlled trials. However, in the absence of relevant randomized controlled trials, observational studies were included. Observational studies were also included if they reported rare adverse events. Case reports were excluded.

Existing systematic reviews were also considered for inclusion both as sources of original data (reference mining) and for their conclusions, following the methods proposed by Whitlock and colleagues.¹⁸

Searching for the Evidence

The inclusion/exclusion criteria by target population, interventions, outcomes, comparators, setting, and study duration are shown in Table 1. Study design and several additional criteria pertaining to the PICOTs are discussed here and below.

English language studies and those with an English-language abstract were included, if resources were available for translation. We excluded publications with both non-English abstracts and text, because of limited resources. Studies that test interventions that were not available in the US were also excluded. If three or more RCTs that enrolled 50 participants or more per arm were included for a particular intervention, we considered excluding smaller studies of the same intervention unless the study reported a subgroup analysis of interest and was powered to conduct that analysis. This decision was based on repeated observations in prior systematic reviews of interventions for treatment of OA of the knee that inclusion of studies with sample sizes less than 50 per group significantly increased effect sizes and that such studies had higher risks of bias. For the current review, smaller studies were excluded only for two interventions (glucosamine with or without chondroitin and strength training)

Conference proceedings and letters that reported unique data and that reported sufficient information to enable assessment of risk of bias were included.

With the exception of weight loss trials, we limited included studies for assessment of efficacy to randomized controlled trials. We included single-arm trials and prospective cohort studies for weight loss. We included prospective observational studies that reported on adverse events associated with use of the interventions of interest for the treatment of OA of the knee.

Studies without participant and assessor blinding were excluded for dietary supplements and cell-based therapies, based on the findings of prior reviews that the results of such studies can bias the results. However, for studies of physical therapies for which it is difficult to design a placebo control and implement participant blinding, we included studies in which the intervention group was not blinded to their assignment. Studies that compared an intervention of interest only to an intervention with no demonstrated evidence of efficacy (or unclear evidence

of efficacy, such as intraarticular hyaluronic acid) were excluded. Also, studies that combined interventions were included only if the control “intervention” allowed assessment of the specific intervention of interest (e.g., neuromuscular electrical stimulation [NMES] plus strength training versus strength training). Studies were not excluded simply because of low study quality (risk of bias).

The searches commenced with the year 2006, one year prior to the latest search dates of the original review we are updating.⁷ However, because we are also updating topics covered in an EPC review conducted in 2012,¹⁹ we did not re-review studies included in (or actively excluded from) that review unless the study included a treatment group or outcome of interest that the original review did not evaluate. Similarly, when we identified recent systematic reviews on other included topics (e.g., braces and orthotics) that match our review in key questions, outcomes of interest, and exclusion/inclusion criteria, we weighed the feasibility of updating those reviews with any newer original studies rather than simply using those reviews as sources of references and conducting entirely new reviews (see Data Synthesis, below). However, ultimately, we did not include any prior systematic reviews as sources of evidence. The full search methodology is in Appendix A.

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

Based on the methods used for the original report and recent reviews on similar topics, we searched the following databases for peer reviewed literature (dates discussed above): PubMed, EMBASE, the Cochrane Collection, Web of Science, and the Physiotherapy Evidence Database (PEDRO). Based on pilot searches of these databases, we did not include PEDRO search results.

The Web of Science and ClinicalTrials.gov was searched for grey literature and as-yet unpublished peer-reviewed articles, respectively; and the abstracts from the past year of professional practice society annual meetings (e.g., American College of Rheumatology, American Academy of Orthopaedic Surgery) were hand searched by members of the team with the appropriate clinical expertise. In addition, relevant stakeholders, including manufacturers of over-the-counter and prescription medications and medical devices used to treat OA of the knee were contacted by the EPC’s Scientific Resource Center for scientific information packets that contain any unpublished information on the efficacy and/or safety of their products when used specifically to treat OA of the knee; no information was obtained from manufacturers. A notice was also placed in the Federal Register requesting any relevant information on the use of dietary supplements containing glucosamine or chondroitin to treat OA of the knee.

Titles identified by literature searches were screened by pairs of experienced literature reviewers using prespecified criteria, without reconciliation of decisions. Abstracts of those titles selected for inclusion by one or both reviewers were dually screened using prespecified criteria, with disagreements reconciled by the project leaders, if necessary. Full text articles or other documents were obtained for included abstracts. DistillerSR™ software was used for screening, abstraction, reconciliation, and tracking. A 10-percent sample of titles for which no abstract could be identified in the databases was obtained and reviewed in full-text to determine whether we should obtain the full-text publications for all titles of interest that lack an abstract. Such publications are typically commentaries, editorials, and letters to journal editors without original data. Based on the sample screen, which identified no studies that met inclusion criteria, we determined that these publications would not be screened further.

Any references that were suggested by members of the TEP, peer reviewers, or public reviewers were obtained and underwent the same screening and abstraction process. Reference lists from recent systematic reviews on the topics of interest were also screened for relevant articles that had not appeared in the search output.

We will also conduct an update search during peer review and include any relevant studies from the update search in the final report.

Data Abstraction and Data Management

Study-level details were dually abstracted by the reviewers, using abstraction forms designed and piloted by the group (with at least two design iterations and some 10 to 25 articles piloted per iteration, as suggested by the issues that arose during piloting). Disagreements were reconciled between reviewers with mediation by the project leaders if needed. Non-English articles were obtained and abstracted only if a native or knowledgeable speaker was identified. Outcome data were abstracted by experienced reviewers and an experienced biostatistical analyst and audited by an experienced reviewer. Risk of bias was assessed by one reviewer and audited by a second reviewer with extensive SR experience. If primary outcome data appeared to be lacking for a particular study, we did not contact study authors.

Studies that reported outcomes in multiple publications were noted, the publications mapped, and the records linked in Distiller to ensure consistency and avoid duplication of descriptions of study conditions. In such cases, risk of bias (ROB) was assessed at the publication (rather than at the study) level.

The following study-level details were abstracted: mean participant age (by study or study arm), sex, mean body mass index, OA diagnoses (stage, pain levels, functional status and activity level), relevant comorbidities, concurrent or prior treatments; numbers of participants enrolled and numbers who completed; inclusion/exclusion criteria; interventions and comparators, type and location of study site; number of sites; study and investigator funding; and potential conflicts of interest. Information collected as part of assessing risk of bias is described below.

Assessment of Methodological Risk of Bias of Individual Studies

For randomized controlled trials, we employed the Cochrane Risk of Bias Assessment tool to assess ROB of individual studies. We also incorporated a small number of items from the PEDro risk of bias assessment tool. A recent analysis finds that the tools produce different assessments of the same studies, with the Cochrane tool providing a more rigorous assessment.²⁰ Characteristics assessed included evidence of accepted methods for ensuring unbiased recruitment and randomization, allocation concealment, participant and assessor blinding, similarity of participants at baseline, retention, adherence, and intention-to-treat analysis. Based on this assessment, studies were rated as having a low, moderate, high, or unclear risk of bias.

We used the McHarms scale to assess the quality of adverse event assessment and reporting. Adverse events whose numbers were reported separately by treatment group were abstracted and categorized as being serious or non-serious.²¹

Data Synthesis/Analysis

Although efficacy and safety comprised separate key questions, the evidence for efficacy and safety are presented together for each intervention. Results of studies that compared different

interventions head to head are described in the section of the Results chapter that pertains to the primary intervention of interest and then again in a separate section on comparative efficacy.

Outcome data were stratified by length of time from baseline. Short-term outcomes were 4 to 12 weeks, medium-term outcomes were 12 to 26 weeks, and long-term outcomes were longer than 26 weeks. If a study reported outcomes at more than one short-, medium-, or long-term time period, we abstracted the longer one(s).

If three or more studies reported the same outcome measure for the same intervention during the same follow-up time period, we pooled the outcomes using the Hartung Knapp method for random effects meta-analysis.²² Because some studies did not report the scales used for outcome measures and because it was not always possible to determine the scales from the data, we report pooled outcomes as standardized mean differences; we did not pool studies that used different tools to measure a similar outcome (e.g., VAS and WOMAC pain measures), as two tools used in the same study on the same participant population sometimes resulted in different outcomes. The findings of meta-analyses are reported quantitatively with forest plots. All studies for which results are included in the report are described qualitatively (narratively) by the type of intervention and the duration of followup. Descriptions of studies of similar interventions were grouped by outcome measures when feasible.

For pooled studies with significant outcomes, we assessed whether these outcomes met a prespecified minimum clinically important difference (MCID). If studies reported whether their outcomes met a prespecified MCID or improvement (MCII) or reported on the percent of participants who achieved a response, we noted that in the narrative descriptions.

Grading the Strength of Evidence (SoE) for Major Comparisons and Outcomes

We rated the strength of evidence (SoE) of each intervention-outcome-followup time based on the AHRQ Methods Guide. Domains include study limitations (study design, ROB, overall methodological quality), consistency of the direction of effect sizes across studies, precision of the estimate (including number of studies), directness of the relationship between outcomes measured and the outcomes of interest, and magnitude of the effect size.

For outcomes for which no pooling was possible, we estimated a rating based on qualitative assessment of the individual studies that met the inclusion criteria. Consistency was assessed as the direction of the reported effect across studies (or within a single study, if the study reported the same outcome using more than one assessment tool). Precision was assessed in terms of the similarity in effect sizes, the average variance, and the numbers of studies. Directness was assessed as it would be for pooled outcomes. Based on these domains, we rated the SoE for each comparison of interest as high, moderate, low, or insufficient (if no or too few studies were identified that addressed the outcome). Factors that led to downgrading of SoE were lack of pooling, number of studies fewer than three, inconsistency across or within studies, imprecision (confidence intervals wider than approximately four times the effect size), and poor study quality. Directness was rated but was not a factor, as only studies with clinical outcomes were included. We rated applicability of participant populations and interventions separately, as described below.

Trial design was considered in grading SoE as it was a factor in considering study quality. For assessments of safety, we considered the consistency of the findings across trials in assigning a SoE grade.

Assessing Applicability

We considered applicability of participants and interventions separately from our assessment of directness for SoE. For assessing applicability of participant populations, studies that enrolled younger age populations (mean age less than 50), those with only early stage or mild disease, those enrolling participants with mean BMI less than 25, or those with a higher activity level at baseline were considered less applicable.

For assessing applicability of interventions, studies of interventions with very high adherence (especially physical activity) were considered somewhat less applicable than studies with lower adherence.

Follow-up times for studies of OA are nearly always too short for a chronic, progressive disease. Studies with shorter maximum follow-up times (less than 3 months) were considered to have lower applicability.

Peer Review and Public Commentary

(To be added after peer and public review)

Results

This section first describes the results of the literature searches, followed by descriptions of the studies that met inclusion criteria for each of the KQs and the key points (conclusions).

Results of Literature Searches

Our searches identified 8,717 titles/abstracts. An additional search of grey literature and ClinicalTrials.gov resulted in 930 titles. Forty-four references were suggested by experts or were meetings abstracts. This yielded 9,691 titles/abstracts that went out for dual screening, of which 6,973 titles were excluded. At abstract screening, 2,718 were excluded for the following reasons: not human (38), not a population of interest (87), not on OA of the knee (215), not on treating or managing OA of the knee (192), not an outcome of interest (247), study design (including editorials, letters, cross sectional study design, and protocols) (582), study was included in a previous EPC review (135), maximum followup was less than 30 days (7), duplicate study (13), no abstract was indexed (245), or we were unable to retrieve the article (33).

We reviewed 586 full text articles, of which 496 were excluded for the following reasons: not human (6), not a population of interest (5), not on OA of the knee (27), not on treating or managing OA of the knee (5), not an intervention of interest (93), specific interventions with a sample size of less than 50 (38), not an outcome of interest (28), study design (including editorials, letters, cross sectional study design, and protocols) (56), study was included in a previous EPC review (2), maximum followup was less than 30 days (35), comparators not of interest (67), no usable data (75), multi-component interventions (27), duplicate study (32). A list of references by exclusion reason can be found in Appendix B.

The Federal Register posting did not yield any additional materials to review for possible inclusion.

We include 90 new articles in our report. Our literature flow diagram (Figure 2) displays our screening results. Appendix D contains our data abstraction tools that were used for abstracting the data of the 90 included studies.

Figure 2. Literature flow diagram

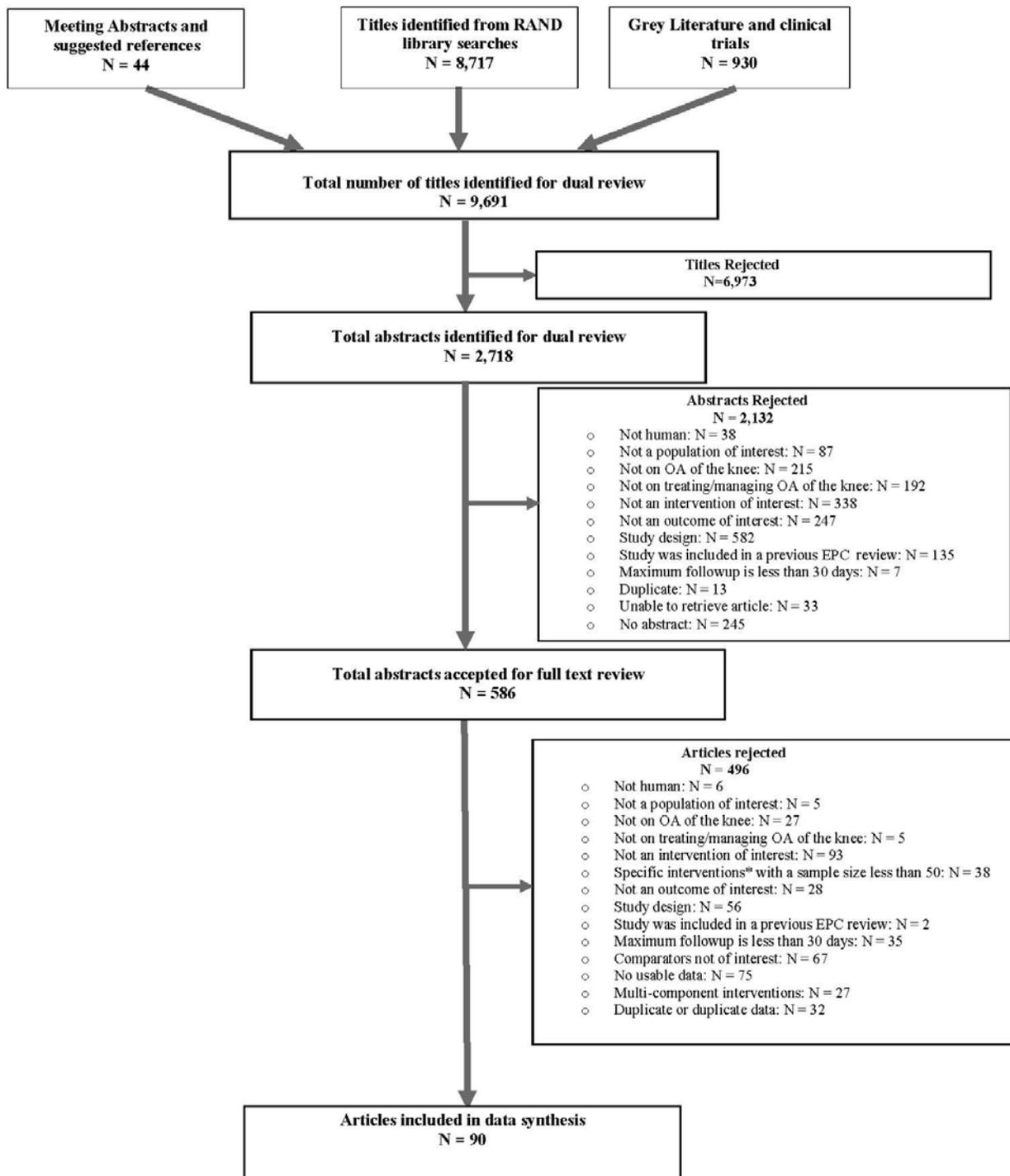


Figure notes: *Interventions with a sample size less than 50 participants: Glucosamine, TENS, Aerobic exercise, and Strength Training

Key Question 1a: What is the clinical effectiveness of cell-based therapies, oral glucosamine and/or chondroitin, physical treatment modalities, weight loss, or home-based and self-management therapies in patients with primary or secondary OA of the knee, compared with appropriate placebo/sham controls or compared with other active interventions?

Key Question 1b: How do the outcomes of each intervention differ by the following population and study characteristics: sex, disease subtype (lateral, patellofemoral), severity (stage/baseline pain and functional status), weight status (body mass index), baseline fitness (activity level), comorbidities, prior or concurrent treatments (including self-initiated therapies), and treatment duration or intensity?

Description of Included Studies

Cell-based Therapies

Cell-based therapies that were considered for treatment of OA of the knee included intra-articular injection of platelet-rich plasma (PRP) as well as introduction of stem cells. We did not identify any studies of stem cell treatments that met the inclusion criteria.

Key Points

- It is unclear whether PRP or other cell-based therapies have any benefit for patients with OA of the knee, as we identified only four small studies on PRP that met inclusion criteria, and results were inconsistent among them.
- Studies showed a low strength of evidence for a beneficial effect of PRP on medium-term pain but not on function or other outcomes. Evidence was insufficient for outcomes at shorter or longer times.
 - Four RCTs, two saline-controlled and two compared with analgesic or treatment as usual, showed significant medium-term (6 months) beneficial effects of PRP on pain (total n=321; average RoB: moderate). Among two RCTs that assessed medium-term effects on function, one showed greater improvement from baseline in the PRP group than in the control group, whereas the other showed equal improvement in both groups

Platelet-rich Plasma

Studies of PRP were included if they compared PRP to sham injections or to use of analgesics but not to injections of other potential therapeutic agents of unclear efficacy. We identified 4 RCTs that compared the use of autologous PRP to that of a sham control or analgesic.²³⁻²⁶ The longest followup time was 6 months from baseline for all studies.

Short-term effects on pain. Two studies reported on short-term effects of PRP treatment on pain.^{23, 26}

A 2013 double-blind RCT conducted in India by Patel and coworkers randomized 78 patients into three treatment groups: a group that received one injection, a group that received two

injections at baseline and at 3 weeks, and a control group, which received saline injections (RoB moderate).²³ WOMAC pain scores at 6 weeks' followup were significantly decreased from baseline and from that of the control group in both active treatment groups (MD -5.22 for one injection, MD -5.10 two injections, at 6 weeks). No significant difference in pain scores or in mean duration of benefit (17 days) was seen between those receiving one injection and those receiving two injections. Response was positively associated with disease severity but not associated with age, sex, or BMI.

A 2014 RCT conducted in Mexico by Acosta-Olivo randomized 42 patients to receive two injections of PRP or instructions to take paracetamol 3 times daily for 30 days; each group also received a 6-month supervised physical rehabilitation program (RoB unclear).²⁶ At 4 months, KOOS pain scores were 51.2(15.4) and 42.2(14.7) for the PRP and control groups, and showed a non-significant between-group difference (MD-9.00, 95% CI -18.11, 0.11).

Short-term effects on function. Patel²³ also assessed the effects of PRP on function and stiffness. At 6 weeks' followup, WOMAC function scores were significantly decreased from those of the control group in both active treatment groups (single injection: MD -15.56, dual injections: -16.24).

Short-term effects on other outcomes. Patel²³ also assessed the effects of PRP on WOMAC total scores. At 6 weeks follow-up, the MD was -21.42 for a single injection and -21.82 for dual injections.

Medium-term effects on pain. Four RCTs assessed the effects of PRP injections at 6 months followup.²³⁻²⁶

Patel²³ reported increases in VAS and WOMAC pain scores in both the single- and double-injection groups compared with the earlier follow-up time, although scores remained significantly lower than control and baseline scores (MD -5.87 for one injection, MD -4.69 for two injections). VAS Pain was significantly decreased in both treatment groups compared with the control (single injection MD -2.45, 95% CI -3.12, -1.78; dual injections MD -2.07, 95% CI -2.81, -1.33).

A 2015 double-blind RCT conducted in Turkey by Görmeli and coworkers randomized 136 consecutive patients to receive a single injection of PRP, three injections of PRP, or a single saline injection (a fourth group received hyaluronic acid; results for this group will not be reported here) (RoB Low).²⁴ EuroQol VAS pain scores at 6 months' followup showed significant between-group differences for one injection (MD-14.00, 95% CI -11.56, -16.44) and three injections (MD-23.40, 95% CI -19.66, -27.14) of PRP compared with the control; three injections had significantly greater effects than a single injection ($p < 0.001$). Treatment response was affected by severity of OA: patients with early (K-L grade I-III) OA achieved significantly greater pain control with three injections than with one injection ($p < 0.005$), whereas among patients with advanced (K-L grade IV) OA three injections provided the same improvement as one injection.

A 2014 RCT conducted in Iran by Rayegani randomized 65 patients to receive two injections of PRP 4 weeks apart or no treatment.²⁵ Both groups were enrolled in an exercise protocol and prescribed acetaminophen as needed (RoB High). At 6 months' follow-up, the PRP group showed non-significantly greater improvement in WOMAC pain scores than did the control group (MD -0.96, 95% CI -2.88, 0.96).

At 6 months' followup, the Acosta-Olivo study reported that KOOS pain scores for the PRP group were significantly improved compared with the paracetamol group (MD -6.90, 95% CI -18.29, 4.49, $p = 0.0008$) and a slight but insignificant decrease from the 4-month score.²⁶

Medium-term effects on function. Patel²³ assessed the effects of PRP on function and stiffness. At 6 months' followup, WOMAC function scores were significantly decreased from that of the control group in both active treatment groups (MD -19.38 for single injection; -17.06 for dual injections).

The 2014 RCT by Rayegani²⁵ showed no significant between-group difference in WOMAC function scores at 6 months.

Medium-term effects on other outcomes. In the Patel study, WOMAC total scores in both treatment groups at 6 months' followup were also significantly decreased from those of the control group (MD -25.91 for single injection; MD -22.61 for dual injections).²⁴

At 6 months followup, the study by Rayegani²⁵ showed a significant improvement in the SF-36 physical domain for the PRP-treated group compared with the control group (MD -1.00, variance not reported).

The 2015 Görmeli RCT reported significant between-group differences in quality of life in favor of PRP, as assessed with the Euroqol (MD -14.00 95% CI -16.44, -11.56 for one injection; MD -23.40, 95% CI -27.14, -19.66 for three injections).²⁴

Long-term effects. No studies reported on long-term effects of PRP.

Other Cell-based Therapies

No studies were identified on other cell-based therapies that met the inclusion criteria for the report.

Glucosamine with or without Chondroitin or Chondroitin Alone

Key Points

- Whether glucosamine, chondroitin, or the combination of glucosamine plus chondroitin have any benefit for patients with knee OA remains unclear. One large non-inferiority trial showed no difference in benefit between glucosamine-chondroitin and NSAIDs, whereas two placebo-controlled trials show no benefit. Benefits of glucosamine alone and chondroitin alone are also inconsistent across time-points and trials.
- Glucosamine + chondroitin: Three RCTs assessed medium and long-term effects. Glucosamine-chondroitin exerted medium-term effects on pain, function, and stiffness, based on two RCTs (Low SoE. No long-term effects on any outcomes were seen, based on three RCTs (Low SoE).
 - The MOVES Trial (n= 603; low RoB) showed significant beneficial medium-term effects on pain, function, stiffness, OMERACT-OARSI outcomes, global assessment of well-being and HRQoL, equivalent to analgesic; this trial did not include a placebo group. A smaller open trial (n=117, high RoB) also showed significant beneficial effects on pain, function, and stiffness.
 - The MOVES Trial, GAIT Trial (n=1,583; low RoB) and LEGS Trial (n=605; low RoB) showed no significant long-term effects of glucosamine + chondroitin on pain or function compared with placebo.
- Glucosamine: No RCTs met inclusion criteria for short- or medium-term outcomes. No long-term effects of glucosamine alone were observed on pain, function, or other outcomes (insufficient evidence).
 - The LEGS Trial and the GAIT Trial showed no significant beneficial effects at 1 or 2 years on pain or function compared with the effects of placebo; a third RCT

(n=190, unclear RoB) showed a smaller worsening of pain and function at 3 years.

- A long-term followup of two RCTs (n=275; low RoB) showed a significant decrease in the risk of undergoing TKR in individuals who took glucosamine sulfate for a minimum of 12 months.
- Chondroitin: Chondroitin alone had beneficial short-term effects on pain and function compared with placebo, based on one RCT (low strength of evidence). Chondroitin alone showed significant medium-term benefit for pain (low strength of evidence) but not function (insufficient evidence), based on two RCTs. Chondroitin alone showed no long-term effect on pain, based on three large RCTs (moderate strength of evidence) and no long-term effects on function (low strength of evidence)
 - One large, multisite placebo-controlled RCT of chondroitin sulfate showed a significant beneficial short-term effect on pain and function (n=352; low RoB) administered as one or two daily doses.
 - Two large, multi-site placebo-controlled RCTs showed a significant beneficial medium-term effect on pain (total n=974; low RoB) but the STOPP trial showed no benefit for function.
- No studies were identified that compared glucosamine sulfate with glucosamine hydrochloride.
- No studies analyzed the time course of effects of glucosamine and/or chondroitin, but studies that examined effects at multiple time points showed that the maximum effects are achieved at 3 to 6 months.

Findings

Because of the existence of several large RCTs, we limited our assessment to studies that enrolled at least 50 participants per study arm. The studies identified for this report include a 2-year followup assessment of GAIT results.²⁷

Glucosamine plus Chondroitin

Four RCTs identified for this report assessed the effects of glucosamine plus (combined with) chondroitin.²⁷⁻³⁰ No studies reported on short-term outcomes as primary outcomes, although one study reported the trajectory of effects over 6 months.

Medium-term effects on pain. Two studies assessed medium-term effects of glucosamine plus chondroitin on pain.^{28, 29}

The Multicentre Osteoarthritis interVENTion trial with SYSADOA (MOVES) study is a 2016 multicenter non-inferiority RCT aimed at comparing the efficacy and safety of glucosamine hydrochloride and/or chondroitin sulfate with that of celecoxib among patients with severe baseline knee pain (RoB low).²⁸ Six hundred three participants were randomised to receive 400 mg chondroitin sulfate plus 500 mg glucosamine hydrochloride three times a day or 200 mg celecoxib for 6 months. The adjusted mean difference in WOMAC pain and the VAS with glucosamine hydrochloride + chondroitin sulfate showed no difference compared with celecoxib, confirming equivalence, and the decrease in pain was considered clinically significant (RR 1.00, 95% CI 0.85, 1.17).

A 2014 open RCT conducted in India by Bellare and colleagues randomized 117 overweight adults with knee OA to a low calorie weight loss diet with glucosamine (1500 mg/d) and chondroitin sulfate (1200 mg/d) supplementation or diet alone (RoB unclear).²⁹ The chemical

form of glucosamine was not specified, and the diet only group did not receive a placebo. At 6 months, weight loss was the same in both groups. The group that received glucosamine and chondroitin had significantly greater improvements in pain than the diet only group, as shown by decrease in WOMAC pain scores (MD -1.59, 95% CI -2.31, -0.87) for the glucosamine plus chondroitin group compared with the diet only group, $p < 0.05$) and VAS scores (MD -2.08, 95% CI -2.40, -1.76).

Medium-term effects on function. The MOVES²⁸ and the diet study²⁹ also reported on the medium-term effects of glucosamine plus chondroitin on function.

The MOVES Trial found no differences at 6 months between treatment groups in the WOMAC function score, with a decrease of 45.5% in the glucosamine plus chondroitin group compared with a decrease of 46.4% in the celecoxib group ($p = 0.53$). The reduction in function was considered clinically important (RR 1.02, 95% CI 0.86, 1.21).

The Bellare diet study²⁹ reported significant improvements in WOMAC function scores and Lequesne function scores in both treatment groups. The group that received glucosamine plus sulfate showed significantly greater improvements in both WOMAC (MD -3.86, 95% CI -6.16, -1.56) and Lequesne (MD -2.56, 95% CI -3.35, -1.77) function measures than did the diet only group.

Medium-term effect on other outcomes. The MOVES study reported no difference in WOMAC stiffness scores between glucosamine plus chondroitin and celecoxib groups, with a decrease of 46.9% in the combination group, compared with a decrease of 49.2% in the celecoxib group ($p = 0.43$). The improvement in stiffness was considered clinically significant.²⁸

The Bellare study reported improvements in WOMAC stiffness scores in both groups with the group that received glucosamine plus chondroitin reporting greater improvements than the diet-only group (5.29[1.12] to 2.60[0.56] vs. 4.94[1.08] to 3.00[0.82], $p < 0.05$).²⁹

The MOVES study reported an OMERACT OARSI response rate of 79%. Similarly, no differences were observed in patients' ($p = 0.51$) and physicians' ($p = 0.33$) global assessments of disease activity or response to therapy ($p = 0.74$ and 0.70 , respectively) or in the EuroQoL-5D assessment of HRQoL (MD 0.00).²⁸

Long-term effect on pain. Three trials that met inclusion criteria assessed long-term effects of glucosamine and chondroitin on pain.^{27, 29, 30} Because one study did not report variation, no pooling was possible.

The GAIT trial, whose 6-month outcomes were reported in the original report, compared the effects of glucosamine sulfate + chondroitin to those of placebo and celecoxib on the decrease in WOMAC pain score from baseline and on the likelihood of experiencing a 20% improvement in pain at 2 years compared with placebo and with celecoxib (RoB low).²⁷ No significant sustained decreases in pain were seen between glucosamine plus chondroitin and placebo (MD 1.04, 95% CI -21.44, 23.51) or celecoxib and placebo (-13.54 (95% CI -35.92, 8.84). The likelihood of achieving a 20% improvement in WOMAC pain scores also did not differ between glucosamine plus chondroitin and celecoxib compared with placebo (OR 0.83, 95% CI 0.51, 1.34 vs. 1.21, 95% CI 0.71, 2.07). All results were adjusted for baseline age, sex, BMI, and K-L grade.

The Bellare open RCT described above assessed the effects of glucosamine plus chondroitin on pain at 12 months. Weight loss was the same in both groups. The group that received glucosamine and chondroitin had significantly greater improvements in pain than the diet only group, as shown by decrease in WOMAC pain scores (MD -3.10, 95% CI -3.69, -2.51) and VAS scores (MD -1.70, 95% -1.99, -1.41).²⁹

The Long term Evaluation of Glucosamine Sulfate (LEGS) study, a 2014 placebo-controlled RCT, randomized 605 participants to receive glucosamine sulfate (750 mg) or placebo and chondroitin sulfate (400mg) or placebo once daily (RoB low).³⁰ The primary outcomes for this study were joint space width (JSW) narrowing and pain. At both 1 and 2 years, participants who received glucosamine plus chondroitin experienced decreases in WOMAC pain scores (adjusted or unadjusted) that did not differ from those in the placebo group (p=0.93).

Long-term effect on function. Three studies assessed the longer term effects of glucosamine plus chondroitin on function.^{27, 29, 30} Because one study failed to report variation, no pooling was possible.

The GAIT trial found decreases (improvement) in WOMAC function scores at 2 years that did not differ from those of placebo or celecoxib.²⁷

The Bellare open RCT described above assessed the effects of glucosamine plus chondroitin on function at 12 months. The group that received glucosamine and chondroitin had significantly greater improvements in WOMAC function, (MD -7.90, 95% CI -10.06, -5.74) and Lequesne scores (0-24 points, MD -3.20, 95% CI -3.86, -2.54) than the diet only group.²⁹

The LEGS study found at both 1 and 2 years that participants who received glucosamine plus chondroitin experienced decreases in WOMAC function scores (adjusted or unadjusted) that did not differ from those in the placebo group.

Long-term effect on other outcomes. Two studies assessed the longer term effects of glucosamine plus chondroitin on other outcomes.^{29, 30}

The Bellare open RCT assessed effects of the combined supplement on the change in WOMAC stiffness scores at 12 months. The supplemented group experienced a significantly greater improvement in stiffness than the diet only group (mean change -3.95[1.15] vs. -2.80[1.01], p<0.05).²⁹

The LEGS trial study found no difference between placebo and glucosamine-chondroitin in SF-12 physical domain scores at 12 months and 24 months.³⁰

Glucosamine Alone

No studies that met inclusion criteria assessed the short- or medium-term effects of glucosamine alone. Two RCTs assessed the longer-term effects of glucosamine alone on pain and function among individuals with OA of the knee,^{27, 30} and one post hoc analysis of two RCTs assessed the association between glucosamine sulfate supplementation and election to receive total knee replacement.³¹

Long-term effects on pain. The GAIT trial compared the effects of glucosamine sulfate alone to those of placebo and celecoxib on the decrease in WOMAC pain score from baseline and on the likelihood of experiencing a 20% improvement in pain at 2 years compared with placebo and with celecoxib.²⁷ Decreases from baseline did not differ between either treatment group and placebo. The likelihood of achieving a 20% improvement in WOMAC pain scores also did not differ between glucosamine and celecoxib compared with placebo (OR 1.16, 95% CI 0.65, 2.04 vs. 1.21, 95% CI 0.71, 2.07). All results were adjusted for baseline age, sex, BMI, and K-L grade.

The LEGS study found that at both 1 and 2 years, participants who received glucosamine sulfate alone experienced decreases in WOMAC pain scores (adjusted or unadjusted) that did not differ from those in the placebo group.³⁰

A 2015 RCT conducted in Bulgaria by Stambolova Ivanova randomized 190 individuals with OA of the knee to receive glucosamine sulfate (1500 mg per day) or a placebo daily for 4 months per year for 3 years (RoB unclear; study reported as a conference proceeding abstract).³² Both

groups also participated in a physical activity program. At the end of the 3-year period, both groups demonstrated an increase in pain compared to baseline: the increase in pain, as measured with the VAS, was significantly lower for the group that received glucosamine (MD -4.60).

Long-term effects on function. The GAIT trial compared the effects of glucosamine sulfate alone to those of placebo and celecoxib on change in WOMAC function scores from baseline to 2 years compared with placebo and with celecoxib.²⁷ Changes from baseline did not differ between either treatment group and placebo: glucosamine 9.56 (95% CI -79.79, 98.91), celecoxib-15.82 (95% CI -102.31, 70.67). Results were adjusted for baseline age, sex, BMI, and K-L grade.

The LEGS study found that at both 1 and 2 years, participants who received glucosamine sulfate alone experienced decreases in WOMAC function scores (adjusted or unadjusted) that did not differ from those in the placebo group.³⁰

The Stambolova Ivanova study compared function between the glucosamine sulfate and placebo-treated groups at 3 years using the Lequesne Index.³² They reported that the placebo group experienced significantly worse function over the 3 years compared with that of the glucosamine treated group.

Long-term effects on other outcomes. Three studies assessed the longer-term effects of glucosamine alone on other outcomes.^{27, 30, 31}

The GAIT trial compared the effects of glucosamine sulfate alone to those of placebo and celecoxib on the likelihood of achieving a 20% improvement in OMERACT-OARSI scores.²⁷ The risk did not differ between glucosamine compared with placebo or celecoxib compared with placebo (OR 1.16, 95% CI 0.74, 1.83 vs. 1.45, 95% CI 0.86, 2.42). All results were adjusted for baseline age, sex, BMI, and K-L grade.

The LEGS study found that at both 1 and 2 years, participants who received glucosamine sulfate alone experienced improvements in SF-12 physical component summary scores that did not differ from those in the placebo group.³⁰

Bruyere and colleagues pooled the data from two 3-year placebo-controlled trials of glucosamine sulfate conducted in 2001 and 2002 to assess the association between use of the dietary supplement and long-term risk for TKR among some 414 adults with knee OA.^{31, 33, 34} The primary outcome of the original trials had been joint space narrowing. Among 340 participants with 12 to 36 months of treatment, of whom 275 could be contacted, the average treatment follow up was 5 years. The risk for TKR was over twice as great among placebo treated participants as among the active (Risk of Bias low based on the two original RCTs).

Chondroitin Alone

Four trials assessed the effects of chondroitin alone compared with placebo.^{27, 30, 35, 36}

Short-term effects on pain. One study that met inclusion criteria assessed short-term effects of chondroitin on pain. A 2013 multicenter placebo-controlled RCT by Zegels and colleagues compared the efficacy and safety of two dosing strategies for chondroitin sulfate among 353 participants over 3 months: a single 1200mg/d dose vs. 400mg/d, three times daily (RoB low).³⁵ The outcome for pain was the 100mm VAS scale. Per protocol analysis was used to test equivalence, and ITT analysis was used to test the comparison with placebo. At 1 and 2 months, no statistically significant differences were observed in VAS scores between the active treatment groups or between active treatments and placebo (p=0.43 and p=0.18, respectively).

Short-term effects on function. The dosing equivalence study by Zegels assessed the effects of chondroitin on function, as measured by the Lequesne Index, at 1 and 2 months of treatment.³⁵ At 1 month, no difference was observed among the two treatment groups and the placebo group

(9.8[3.7] for one 1200mg dose and 9.4[3.1] for three 400mg doses vs. 10.1[3.7], $p=0.32$). At 2 months, the two active treatment groups showed identical mean Lequesne scores (8.4[3.8] and 8.4[3.6]), which were significantly improved compared with the placebo group (9.9[4.3], $p=0.003$).³⁵

Medium-term effects on pain. Two RCTs that met inclusion criteria for this report assessed medium-term effects of chondroitin on pain.^{35, 36}

At 3 months post baseline, the dosing equivalence study by Zegels and colleagues found that both dosing options (1200mg once a day or 400 mg 3 times per day) had identical effects on VAS pain, significantly greater than the placebo effect (MD -7.70, 95% CI -14.43, -0.97 versus MD -8.30, 95% CI -15.20, -1.40).³⁵

The Study on Osteoarthritis Progression Prevention (STOPP) was a two-year placebo-controlled multi-center RCT that assessed the efficacy and safety of chondroitin sulfate (800 mg/d) on 622 participants with mild-to-moderate OA of the knee; the primary outcome was JSW (RoB low).³⁶ The (secondary) effects on pain were reported as the percent of responders. The percent of responders in the chondroitin group significantly exceeded that in the placebo group for 40mm decrease in VAS (RR 0.68, 95% CI 0.51, 0.91), 60mm decrease in VAS (RR 0.44, 95% CI 0.23, 0.85), and 40% reduction in WOMAC pain (RR 0.83, 95% CI 0.68, 1.02).

Medium-term effects on function. The STOPP Trial reported no difference between chondroitin sulfate and placebo in WOMAC function scores at 6 months (data not reported).³⁶

At 3 months post baseline, the dosing equivalence study by Zegels and colleagues found that both dosing options (1200mg once a day or 400 mg 3 times per day) had similar effects on function, as measured by the Lequesne Index, both significantly greater than the placebo effect (MD -2.20, 95% CI -3.37, -1.03 versus MD -1.90, 95% CI -1.90, -0.69).³⁵

Long-term effects on pain. Three RCTs reported on long-term WOMAC pain scores but no pooling was possible because one study failed to report variance.^{27, 30, 36}

At 24 months, the STOPP Trial demonstrated sustained decreases in pain, as measured by the VAS and WOMAC; however, no difference could be seen between the chondroitin group and the placebo group.³⁶

The 2-year follow up of the GAIT trial showed that chondroitin sulfate did not achieve a significant change in WOMAC pain (11.50, 95% CI -15.40, 38.40) or a clinically meaningful pain response (OR 0.69, 95% CI 0.40, 1.21) compared with placebo.²⁷

At years 1 and 2, the LEGS Trial showed significant improvements from baseline for chondroitin in WOMAC pain scores, but no difference from that of the placebo group.³⁰

Long-term effects on function. Two RCTs reported on long-term effects on function.^{27, 30}

The 2-year follow up of the GAIT trial showed that chondroitin sulfate did not achieve a significant decrease in WOMAC function (OR 36.64, 95% CI -64.57, 37.86) compared with placebo.²⁷

At years 1 and 2, the LEGS Trial showed significant improvements from baseline for chondroitin in WOMAC function scores, but no difference from that of the placebo group.³⁰

Long-term effects on other outcomes. The STOPP Trial found no difference between groups in cumulative use of acetaminophen but a trend toward decreased use of NSAIDs in the chondroitin group compared with the placebo group at 2 years.³⁶

Aerobic Exercise

Key Points

- Based on one trial, it is unclear whether aerobic exercise alone has any beneficial effect on patients with knee OA.
- Aerobic exercise showed no significant long-term effects on pain, function, total WOMAC, quality of life, based on one RCT (insufficient evidence).³⁷

Findings

Aerobic exercise for the treatment of OA of the knee was limited to aerobic based exercise programs that did not include other exercise modalities, such as strength training. Studies were included if they compared aerobic exercise to a control group, but not to other exercise programs. We identified one RCT that compared an aerobic exercise program to a control group.³⁷ The longest follow-up time was 18 months.

Short-term effects. No studies reported on short-term effects of aerobic exercise.

Medium-term effects. No studies reported on medium-term effects of aerobic exercise.

Long-term effects on pain. One study reported on the long-term effects of aerobic exercise on pain.³⁷ A 2012 single-blind RCT conducted in Canada by Brosseau and colleagues randomized 222 patients into three treatment groups: a group that received a supervised aerobic walking program, behavioral intervention, and an educational brochure; a group that received a supervised walking program and an educational brochure; and a control group that received an educational brochure (RoB high).³⁷ The group receiving the behavioral intervention and walking program was excluded from this analysis. At 18-months follow-up, WOMAC pain scores were not significantly different between the control group and the aerobic walking program.

Long-term effects on function. Brosseau³⁷ examined the effects of an aerobic walking program on function as measured by WOMAC function scores. At 18 months follow-up, WOMAC function was not significantly different between the control group and the aerobic walking group.

Long-term effects on other outcomes. At 18 months follow-up, Brosseau³⁷ also reported no significant differences in total WOMAC scores, SF-36 functional domain scores, TUG scores, or 6-minute walk test distances between the control group and aerobic walking group.

Strength or Resistance Training

Key Points

- Although it is unclear whether strength and resistance training have a statistically significant beneficial effect on patients with OA of the knee, pooled analysis of five RCTs supports a possible clinical benefit on pain and function, and individual study findings suggest significant benefit on total WOMAC scores.
- Strength and resistance training had no statistically significant beneficial effect on short-term pain (low strength of evidence)
 - Pooled analysis of 5 RCTs (n=270; moderate RoB) that compared strength training with a control group (education or other exercise) showed no statistically significant effect on pain (random effects pooled estimate -0.40, 95% CI -1.22, 0.42).

- Strength and resistance training had no statistically significant beneficial effect on short-term function (low strength of evidence).
 - Pooled analysis of 5 RCTs (n=270, moderate RoB) that compared strength training with a control group showed no significant effect on WOMAC function (random effects pooled estimate -0.34, 95% CI -0.95, 0.28).
- Strength and resistance training showed mixed effects on other short-term function measures based on two RCTs (insufficient evidence).
- Strength and resistance training had a beneficial short-term effect on WOMAC total scores based on three RCTs (Low SoE).
 - Two RCTs (total n=96, moderate RoB) comparing strength training to an education only control showed a benefit; one RCT (n=30; moderate RoB) showed a greater benefit for strength training on an uneven surface than for strength training on an even surface.
- Strength and resistance training showed no beneficial effect on medium-term pain, based on two RCTs (insufficient evidence).
- Strength and resistance training showed no consistent beneficial effects on medium-term function, based on two RCTs (insufficient evidence).
- Strength and resistance training had no benefit on medium-term WOMAC stiffness scores based on one RCT (insufficient evidence).
- Strength and resistance training showed a benefit for long-term pain and function at 32 weeks but only a benefit for function at 52 weeks, based on one RCT (insufficient evidence). The number of studies that assessed outcomes of interest at multiple follow up times was insufficient to assess trends in response to these interventions.
- No studies assessed the effects of any factors such as sex, obesity, or disease severity on outcomes of strength and resistance training.

Findings

The current review defined an intervention as a strength- or resistance training intervention if the study authors explicitly called the intervention a strength or resistance training intervention or if the primary activity of the intervention (based on time spent on that activity) was aimed at improving strength or resistance. These studies generally included several sessions per week of therapist-led individual or group exercise (including a brief period of warm-up aerobic exercise prior to the strength training period and a cool down period following the strength training) with instructions to perform some exercises at home on the other days. The details are described in the evidence table in Appendix C.

Short-term effects on pain. Five RCTs (reported in 6 publications) met our inclusion criteria for assessing short-term effects of strength training interventions on pain.³⁸⁻⁴³

A 2012 Brazilian RCT randomized 100 individuals with OA of the knee to an exercise femoral quadriceps strengthening (exercise) group or an educational group (RoB low).^{38, 39} The exercise group attended an 8-week twice weekly physiotherapist-led class in which resistance loads were individualized based on a ten-repetition maximum test. Both the exercise and the control groups received an educational manual about knee care (with no exercise instructions) and permission to use paracetamol. At 8 weeks, no significant between-group differences were seen in the exercise group compared with the instruction group in WOMAC pain scores³⁸ but a significant group difference was seen in NRS pain scores (MD -1.47, 95% CI -2.71, -0.23).³⁹

A 2012 single-blind RCT conducted in Ireland by Bruce-Brand and colleagues randomized 41 adults with moderate to severe knee OA to a 6-week therapist-supervised home-based resistance training program, neuromuscular electrical stimulation, or a control group (education and physical therapy) (RoB moderate).⁴⁰ No improvement was observed in WOMAC pain scores at 8 weeks in the resistance training group compared with the control group .

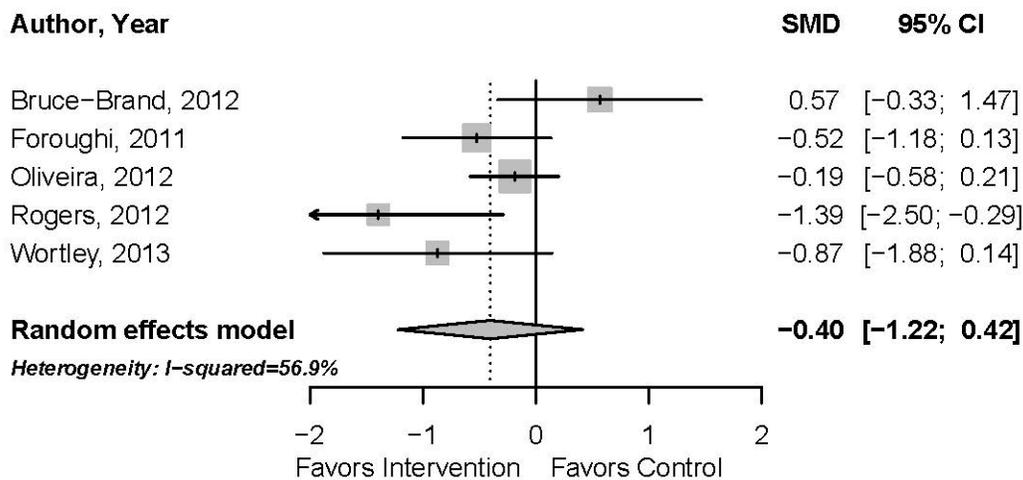
A 2012 US RCT by Wortley randomized 31 older adults with OA of the knee to a 10-week resistance training program, a tai chi program, or a control group (RoB high).⁴¹ At 10 weeks, WOMAC pain scores were not improved significantly compared to the control group.

A 2011 Australian RCT, the REACH study, randomized 54 women to a 6-month resistance training or sham training program (consisting of less intense resistance training)(RoB low).⁴² The primary outcome was assessment of dynamic alignment; WOMAC scores were secondary outcomes. At the end of the intervention, WOMAC pain scores showed no significant between-group differences.

A 2012 RCT conducted in the US by Rogers and coworkers randomized 44 adults age 50 and over to one of four 8-week home-based interventions: kinesthesia, balance, and agility (KBA) training alone, resistance training (RT) alone, a combination of KBA and RT, and a control group that received no intervention (RoB moderate).⁴³ At 4 and 8 weeks, WOMAC pain scores improved significantly for the strength training group compared with the control group (0-20 points, MD -3.75, 95% CI -6.39, -1.11).

Pooling the results for WOMAC pain for the five studies showed that resistance training had no significant effect on short-term pain (random effects estimate MD -0.40, 95% CI -1.22, 0.42) (Figure 3).

Figure 3. Forest Plot for Short-term effects of Strength Training on WOMAC Pain



Short-term effects on function. Five RCTs met our inclusion criteria for assessing short-term effects of strength training interventions on function.^{38, 40-43}

The 2012 Brazilian RCT found that the 8-week strengthening program improved function compared with the educational control group based on Lequesne Index scores (MD -1.98, 95% CI -3.75, -0.21) but the difference was not reflected in WOMAC function scores.³⁸

The study by Bruce-Brand reported no change in WOMAC function scores between the resistance training and control groups at 8 weeks.⁴⁰ However, three other function tests, the

primary outcomes of the study, showed significant improvements from baseline to 8 weeks compared to the control group (described below).

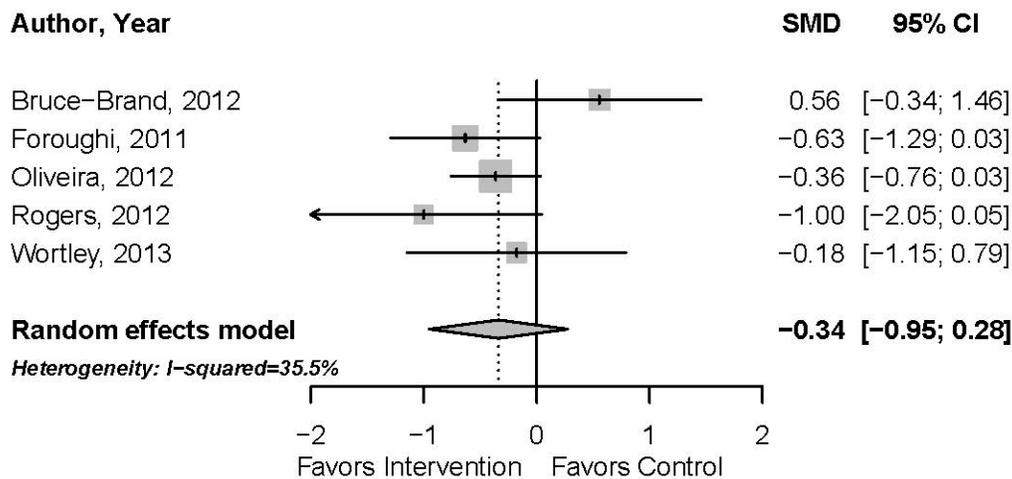
The 2012 RCT conducted by Rogers and coworkers found that at 2 months, WOMAC function scores improved significantly compared with the control group (MD -9.62, 95% CI -19.04, -0.20),⁴³ and met the MCID.

The 2012 US study by Wortley that compared resistance training with Tai Chi and no activity among older adults showed no significant impact of the resistance training intervention on the WOMAC function score compared with the control condition.⁴¹

The REACH study found no difference in WOMAC function between groups.⁴²

Pooling the results for WOMAC function for the five studies showed that resistance training had no significant effect on short-term function (random effects estimate MD -0.34, 95% CI -0.95, 0.28 (Figure 4).

Figure 4. Forest Plot for Short-term effects of Strength Training on WOMAC Function



Short-term effects on other outcomes. Six RCTs (described in seven publications) met our inclusion criteria for assessing short-term effects of strength training interventions on other outcomes of interest.³⁸⁻⁴⁴

The 2012 RCT conducted in the US by Rogers and coworkers reported the WOMAC total scores at 2 months.⁴³ The resistance training and control groups showed a significant between-group difference (MD -13.62, 95% CI -26.27, -0.87).

The 2012 Brazilian RCT assessed the effects of a strengthening program on two additional outcomes of interest: TUG and the physical function domain of the SF-36. The exercise group had a statistically significantly greater improvement in TUG (MD -1.80, 95% CI -2.97, -0.63) compared with the instruction group. The physical domain of the SF-36 showed no significant difference between the groups.^{38, 39}

The 2012 study by Bruce-Brand reported significant improvements from baseline to 8 weeks compared to the control group in three function tests that were the primary outcomes of the study (a chair rise test, walk test, and stair climb test [$p < 0.005$]) but did not find significant between-group differences in the SF-36 Physical domain.⁴⁰

The 2012 US study by Wortley compared results for the WOMAC stiffness scale, the TUG, and 6-minute walk tests between intervention groups.⁴¹ After the 10-week intervention,

participants in the resistance training group showed no between-group improvement compared with the control group on the TUG or the 6-minute walk test.

The 2011 REACH study showed a significant between-group difference in WOMAC total scores at 3 months (MD -10.40, 95% CI -19.94, -0.86).⁴²

A 2014 RCT conducted in the Republic of Korea by Nam randomized 30 sedentary adults (age 60 and older) with knee OA to a program of strength-training exercises carried out on an aero step XL™ or the same exercises performed on a flat surface (3 times a week for 6 weeks) (RoB moderate).⁴⁴ At 6 weeks, a significant between-group difference was observed in total WOMAC scores (MD -2.99, 95% CI -5.48, -0.50)

Medium-term effects on pain. Two RCTs met our inclusion criteria for assessing medium-term effects of strength training on pain.^{40, 45}

The 2012 study by Bruce-Brand found no improvement in WOMAC pain scores at 14 weeks (6 weeks post intervention) in the resistance training group compared with the control group.⁴⁰

A 2016 double-blind (participants and assessors) RCT conducted at two sites in Australia by Bennell and colleagues assessed the effect of strength training combined with pain coping skills training (PCST) compared with PCST or strength training exercises alone (RoB low).⁴⁵ This study randomized 222 individuals with moderate to severe knee OA to three 12-week treatment programs and followed them for 12 months. Comparisons used a model that took into account the physical therapist training, baseline scores, site, and sex. The group that received strength training alone was considered the control. Overall pain was assessed on a 100mm VAS scale with a MCID set at 18mm. At 12 weeks, no between-group differences were seen in VAS or WOMAC measures of pain between the strength training group and the group that received only PCST or the group that received strength training plus PCST. The findings for the comparison between PCST plus strength and strength alone are presented in a later section on PCST. A higher proportion of the PCST + strength training group showed global improvement in pain than did the strength training alone group (RR 1.3, 95% CI 1.1, 1.6).

Medium-term effect on function. Two RCTs met our inclusion criteria for assessing medium-term effects of strength training on pain.^{40, 45}

The 2012 Bruce-Brand study found no difference in WOMAC physical function at 14 weeks in the resistance training group compared with the control group, however several other outcomes indicative of physical function (described below) suggest some at least sustained improvement from the first followup.⁴⁰

The 2016 study by Bennell and colleagues found significantly greater improvements in WOMAC function at 14 weeks in the combined PCST + resistance training group compared with PCST alone (MD -7.9 units, 95% CI -4.7, -11.2). A significantly greater proportion of participants in the PCST + resistance training group achieved global improvement in function (6 units or more) (94%) than in the PCST only group (69%, RR 1.4, 95% CI 1.2, 1.6).

Medium-term effect on other outcomes. One RCT reported on medium-term effects of resistance training on additional outcomes.⁴⁰

The 2012 Bruce-Brand study observed no significant difference in WOMAC stiffness scores in the resistance training group compared with the control group.⁴⁰ This study also found no effects of resistance training on the physical health domain of the SF-36 compared with the control group. However, significant short-term improvements observed in the walking test and chair rise test were maintained in the medium-term ($p < 0.006$).

Long-term effect on pain. One RCT that met inclusion criteria assessed the long-term effect of a strength training intervention on pain.⁴⁵

The 2016 study by Bennell on PCST and resistance training reported significant improvements in VAS pain (MD -8.4 (95% CI -0.3, -16.6), $p < 0.05$) and WOMAC pain (MD -1.2, 95% CI -0.1, -2.4) at 32 weeks in the group that received both interventions compared with PCST alone.

Long-term effect on function. One RCT that met inclusion criteria assessed the long-term effect of a strength training intervention on function.⁴⁵

The 2016 study by Bennell reported significant improvements in WOMAC function in the PCST plus resistance training group compared with the grouping receiving PCST alone at both 32 weeks (MD -6.6, 95% CI -2.3, -10.8) and 52 weeks (MD -5.5, 95% CI -1.6, -9.3) ($p < 0.01$).⁴⁵

Agility Training

Key Points

- It is unclear whether agility training alone has any benefit for patients with knee OA. Identified studies showed inconsistent effects across time points and outcomes.
- Agility training showed a significant beneficial effect on short-term pain compared with passive controls, based on two RCTs and no difference from strength training in one RCT (($n=217$, moderate RoB) (Low SoE).
- Agility training showed no consistent benefit on short-term function, based on three RCTs (insufficient evidence). Agility training showed no consistent benefit on medium-term pain, based on two RCTs (insufficient evidence).
- Agility training showed no long-term differences in pain or function compared with other standard training programs but improvements from baseline were sustained over the long-term. One RCT showed that improvements in both pain and function exceeded the MCID for agility training with or without strength training (insufficient evidence).

Findings

For the current review, we identified seven studies that assessed the effects of agility training.^{43, 46-51} The current review defined an intervention as an agility training intervention if the study authors explicitly referred to the intervention as agility training or if they used the terms joint stabilization, or neuromuscular exercise or proprioception, or if the primary activity of the intervention (based on time spent on that activity) was aimed at improving those functions. These studies generally included several sessions per week of therapist-led individual or group exercise (including a brief period of warm-up aerobic exercise prior to the strength training period and a cool down period following the strength training) with instructions to perform some exercises at home on the other days. The details are described in the evidence table in Appendix C.

Short-term effects on pain. We identified three RCTs that met inclusion criteria and assessed the effects of an agility training intervention on short-term pain.^{43, 46, 47}

A 2012 RCT conducted in the US by Rogers and coworkers randomized 44 adults age 50 and over to one of four 8-week home-based interventions: kinesthesia, balance, and agility (KBA) training alone, resistance training (RT) alone, a combination of KBA and RT, and a control group that received no intervention (RoB moderate).⁴³ At 8 weeks, WOMAC pain scores for the agility training group showed a significant between-group difference compared with those of the control group (MD -3.13, 95% CI, -5.86, -0.40).

A 2013 RCT conducted in the Netherlands by Knoop and coworkers randomized 159 adults to a 12-week program comprising knee joint stabilization therapy plus muscle strengthening or to a program of muscle strengthening alone (RoB low).⁴⁶ The first week of therapy consisted of hydrotherapy in both groups. At 12 weeks, no significant between-group differences were seen in NRS-measured knee pain. The proportion of responders (based on an MCID of 15%) was also the same in both groups: 70 percent compared with 72 percent.

A 2015 RCT conducted in Korea by Ju and colleagues randomized 14 women, 60 years or older, with knee OA to an 8-week program of proprioceptive circuit exercise or a control group (RoB unclear).⁴⁷ At 8 weeks, VAS pain scores improved significantly in the intervention group compared with the control group (1-10 cm: MD -4.00, 95% CI -5.32, -2.68).

Short-term effects on function. We identified three RCTs that met inclusion criteria and assessed the effects of an agility training intervention on short-term function.^{43, 46, 48}

The 2012 Rogers study reported no significant improvements in WOMAC function at 8 weeks compared with the sham control group.⁴³

A 2015 RCT conducted in Brazil by da Silva and colleagues randomized 41 participants with moderate to severe knee OA to an 8-week rehabilitation program that included mobility, functional, and balance exercises in addition to strength training or to a control condition: Both groups received self-management educational sessions (RoB moderate).⁴⁸ At 8 weeks, no between-group difference was seen in Lequesne composite scores. Both exceeded the MCID (defined by the authors as an effect size greater than 0.01).

The 2013 study by Knoop and colleagues assessed WOMAC physical function as its primary outcome.⁴⁶ At 12 weeks, no significant between-group differences were seen, and no difference in the proportion of responders (66% vs. 63%), based on an MCID of 12%.

Short-term effects on other outcomes. The 2015 RCT by da Silva found that at 8 weeks, the intervention group performed significantly better on the TUG (MD -2.05, 95% CI -3.12, -0.98) and the 6-minute walk (MD -50.40, 95% CI -94.26, -6.54) than did the control (education) group. This study also reported a significant difference in scores on the SF-36 Physical Function domain (MD -14.00, 95% CI -26.24, -1.76).⁴⁸

The 2012 Rogers study reported no significant improvements in WOMAC total scores at 8 weeks compared with the control group.⁴³

Medium-term effects on pain. Two RCTs reported on medium-term effects of agility training on pain.^{46, 49}

The 2013 RCT by Knoop found no significant between-group differences in NRS pain at 3 months.⁴⁶

A 2013 RCT conducted in Denmark by Henriksen and coworkers randomized 60 individuals with OA of the knee to a 12-week program of facility-based neuromuscular exercise therapy or to a no-attention control group (RoB unclear; conference proceeding).⁴⁹ The primary outcome was sensitivity to pressure pain. At 12 weeks, KOOS pain, a secondary outcome, was statistically significantly improved in the intervention group compared to the control group (effect size 0.71, $p=0.0179$).

Medium-term effects on function. The 2013 RCT by Knoop found no significant between-group differences in function at 3 months.⁴⁶

Medium-term effect on other outcomes. Two RCTs reported on medium-term effects of agility training on function.^{46, 51}

The 2013 RCT by Knoop found no significant between-group differences in timed up and go (TUG) at 3 months.⁴⁶

A 2013 RCT conducted in Brazil by Barduzzi randomized 15 older adults (60 to 80 years) with OA of the knee to receive water based agility kinesiotherapy, land-based agility kinesiotherapy, or a control condition (RoB High).⁵¹ The intervention consisted of 24 sessions over 4 months with a 45-day break between the 12th and 13th session. At the end of the 4-month period, the water-therapy group showed a significantly better walking speed than the control group ($p < 0.007$). The land-based agility exercise group showed no between-group differences from the control group.

Long-term effects on pain. A 2011 US RCT by Fitzgerald and colleagues randomized 183 individuals with knee OA to a group that received a standard exercise program with agility training for 6 months or to a group that received only the standard exercise program (RoB low).⁵⁰ NRS-assessed knee pain scores were measured at 2 months, 6 months, and 12 months, but only the 12-month measures underwent ITT analysis. No between-group differences in pain were seen.

The 2013 study by Knoop and colleagues assessed pain at 38 weeks (6 months after the end of the intervention).⁴⁶ No significant between-group differences were seen in NRS-measured pain. The proportion of responders was 72% for the intervention group and 57% for the control group, based on an MCID of 12%.

Long-term effects on function. Two RCTs assessed the effects of agility training on long-term function.^{46, 50}

The 2011 Fitzgerald study assessed the effects of the agility training intervention on WOMAC function.⁵⁰ No between-group differences were seen.

The 2013 study by Knoop and colleagues assessed WOMAC physical function at 38 weeks after baseline (6 months after the end of the intervention).⁴⁶ At 38 weeks, no between-group differences were seen in WOMAC function, and no difference was observed in the proportion of responders (62% vs. 61%), based on an MCID of 12%.

Long-term effects on other outcomes. In the 2011 study by Fitzgerald and colleagues, total WOMAC scores at 12 months (10-months after the end of the intervention period) showed no differences between the agility group and the standard exercise group.⁵⁰

General Exercise Therapy

Key Points

- It is unclear whether general exercise programs have benefit for patients with knee OA, as the number of studies was limited, and studies were heterogeneous.
- General exercise improved medium-term pain and function compared with no exercise, based on one RCT (n=180; low RoB) (insufficient evidence).
- General exercise had inconsistent benefit for long-term outcomes, based on two RCTs (insufficient evidence).
 - One RCT showed no beneficial effect on pain, function, or physical quality of life among patients in a weight-loss program vs. no exercise (n=192; low RoB)
 - One RCT showed that a longer program had greater benefits for long-term pain and WOMAC total scores than a shorter program (n=75; moderate RoB).

Findings

For the current review, we identified three RCTs whose exercise interventions did not fit the definitions of any of the other types of exercise therapy.⁵²⁻⁵⁴ These studies generally included

several sessions per week of therapist-led individual or group exercise (including a brief period of warm-up aerobic exercise prior to, and a cool down period following some combination of exercises) with instructions to perform some exercises at home on the other days. The details are described in the evidence table in Appendix C.

Short-term effects on pain, function, or other outcomes. None of the included studies assessed outcomes during the first 12 weeks.

Medium-term effects on pain. A 2014 RCT conducted in Canada by Rosedale and colleagues randomized 180 individuals with knee OA to an exercise group (120) or a non-exercise control group (60) (RoB low).⁵² The exercise intervention that was implemented depended on the intervention participants' responses to the McKenzie System of Mechanical Diagnosis and Therapy (MDT); responders are defined as those who show knee derangements when asked to perform particular movements, and the exercises were focused on these derangements. At 3 months, the combined exercise group had significant improvements in KOOS pain scores (0-100: MD -10.00, 95% CI -15.28, -4.72) and P4 pain scores (0-40: MD -3.00, 95% CI -5.84, -0.16) compared to the control group.

Medium-term effect on function or other outcomes. At 3 months, the combined exercise groups in the study by Rosedale and colleagues had significantly higher KOOS function scores (indicating improvement) than did the control group (0-100 scale: MD -9.00, 95% CI -14.28, -3.72). Comparisons are not shown for the two exercise subgroups, as they were not randomly allocated.⁵²

Long-term effect on pain. A 2015 RCT conducted in New Zealand by Abbott and colleagues randomized 75 adults with OA of the knee to one of four interventions: 12 weekly exercise sessions, 8 weekly sessions plus four additional (booster) sessions every three months over the course of the following 9 months, exercise plus 12 manual therapy sessions, or manual therapy alone (RoB moderate).⁵³ The group that received 12 consecutive weekly exercise sessions was considered the control. The outcomes for the manual therapy group are discussed below with outcomes for other manual therapy studies. Compared with 12 consecutive exercise sessions, the group that received exercise classes over the course of the year had significantly improved VAS pain intensity scores (1-10mm scale: MD -2.00, 95% CI -3.84, -0.16).

A 2015 RCT conducted in Denmark, the CAROT trial, randomized 192 adults who had completed an intensive 4-month weight loss program to continue in a weight maintenance group, to enter an exercise program, or to receive no further interventions for 1 year (RoB low).⁵⁴ The effects of the weight loss phase of the program on outcomes of interest are reported below in the section on weight loss programs.⁵⁵ The exercise program comprised three 1-hour sessions per week of circuit training, which transitioned from group sessions to home-based sessions. Over the year, the weight maintenance group regained the least weight, followed by the control group and the exercise group. At 1 year, no significant group differences were seen between the exercise group and the control group in VAS pain.

Long-term effect on function. The CAROT trial found no between-group differences in KOOS daily function scores.⁵⁴

Long-term effects on other outcomes The CAROT trial found no between-group differences in outcomes for the six-minute walk or for SF-36 physical domain scores at the end of 1 year.

The Abbott RCT reported a significant difference in total WOMAC scores at 12 months between the exercise and the exercise plus booster session groups, favoring the booster session

group (0-240 point scale: MD -56.10, 95% CI -92.70, -19.50).⁵³ Booster sessions had no significant effect on the outcomes of the TUG.

Tai chi

Key Points

- It is unclear whether tai chi has any benefit for patients with OA for the knee, as we identified only two small RCTs (total n=86), and results were inconsistent across time points and outcomes.
- Tai chi had no significant beneficial short-term effect on pain, based on two RCTs (insufficient evidence)
- Tai chi showed inconsistent effects on short-term function, based on two RCTs.
 - An RCT that compared tai chi with resistance training and treatment as usual showed comparable effects on short-term function for tai chi and treatment as usual and no improvement compared with strength training (n=31; high RoB).
 - An RCT that compared tai chi with education showed a significant beneficial effect on function (MD -5.54, 95% CI -9.72, -1.36) (n=55; low RoB)
- Tai chi showed significant benefit for medium-term pain (MD -1.58, 95% CI -2.76, -0.40) and function (MD -5.52, 95% CI -9.70, -1.34) compared with education, based on one RCT (n=55, high RoB).

Findings

Studies of Tai chi were included if they compared tai chi to standard aerobic or strength training regimens, attention control, or treatment as usual (TAU) but not to other specialized exercise interventions of unknown efficacy. We found two RCTs that compared the participation in tai chi to strength training, health education classes, or treatment as usual.^{41,56} One study followed patients for 10 weeks, while the other did so for 21 weeks.

Short-term effects on pain. Both studies reported on the short-term effects of tai chi on pain.^{41,56} In a 2013 RCT based in the US, Wortley and colleagues assigned participants to one of three trial arms for 10 weeks: resistance strength training, tai chi, or usual medication and physical activity. (RoB high)⁴¹ WOMAC pain scores decreased significantly more in the resistance training group than in the tai chi or TAU groups over the 10-week period.

In another 2013 RCT conducted in the US, Tsai and colleagues randomized participants to 20 weeks of tai chi or to an attention control (health education and social activities) (RoB unclear).⁵⁶ At 9 weeks, WOMAC pain scores did not decrease significantly more in the tai chi group than in the attention control group.

Short-term effects on function. Both studies examined short-term effects on function.^{41,56}

Wortley found that WOMAC function did not decrease significantly in the resistance training or TAU groups compared to tai chi.⁴¹ Timed up and go and 6-minute walk scores also did not significantly decrease in the tai chi group compared to changes in the other groups.

Tsai reported that at 9 weeks, treatment effects were significantly larger in the tai chi group for WOMAC function (MD -5.54 95% CI -9.72, -1.36) and get up and go (MD -1.54, 95% CI -0.32, -2.76), but not for WOMAC stiffness, and sit to stand scores.⁵⁶

Medium-term effects on pain. Only Tsai and colleagues assessed medium-term effects on pain.⁵⁶ Pain decreased significantly more in the tai chi group than in the attention control group

at 21 weeks (MD -1.58, 95% CI -2.76, -0.40). At that point, pain had decreased by 2.6 points in the tai chi group and by 1.02 points in the attention control group (p=0.006).

Medium-term effects on function. Tsai found a significant difference in WOMAC function between groups at 21 weeks (MD -5.52, 95% CI -9.70, -1.34).⁵⁶ In addition, WOMAC stiffness significantly decreased by 1.79 points in the tai chi group compared to only 0.22 points in the attention control group at 21 weeks (p=0.01) but not for get up and go, and sit to stand scores.

Long-term effects. Neither study examined the long-term effects of tai chi.

Yoga

Key Points

- It is unclear whether yoga has any benefit for patients with OA of the knee, as we identified only one small RCT (n=36).
- Yoga showed a beneficial short-term effect on pain and function, based on one RCT, compared with a wait-list control (n=36; moderate RoB) (insufficient evidence).

Findings

Studies of yoga were included if they compared yoga to standard aerobic or strength training regimens, a waitlist, an attention control or treatment as usual (TAU) but not other specialized exercise interventions of unknown efficacy. We found 1 RCT that compared the participation in tai chi to a waitlist control group.⁵⁷ This study followed patients for 20 weeks.

Short-term effects on pain. In a 2014 RCT based in the US, Cheung and colleagues assigned participants to either a yoga intervention or a waitlist control for 8 weeks. (Risk of bias 7/10)⁵⁷ WOMAC pain scores decreased significantly from 8.3 points to 5.8 points for the yoga group (p=0.01).

Short-term effects on function. The Cheung study also reported short-term effects on function.⁵⁷ Authors found that WOMAC function decreased from 35 points to 22 points in the yoga group, but that this drop did not significantly differ from the change seen in the control group. Short Physical Performance Battery (SPPB) repeated chair stands scores significantly increased from 2.4 to 2.8 in the yoga group (p=0.03), but there was no significant change in SPPB global, balance, and eight-foot walk scores.

Medium-term effects. This study did not examine the medium-term effects of yoga.

Long-term effects. This study did not examine the long-term effects of yoga.

Balneotherapy and Mud Treatment

Key Points

- It is unclear whether balneotherapy or mud baths show significant short-term benefit for patients with knee OA, based on the small number of RCTs we identified.
- Balneotherapy showed a significant beneficial effect on medium-term pain, based on two single-blind studies (n=60, 77; moderate RoB) (insufficient evidence).
 - One RCT (n=60) reported a significant improvement in VAS pain (0-100 scale, MD -42.50, 95% CI -53.67, -31.33) and WOMAC pain (MD -25.70, 95% CI -34.06, -17.34)
 - One RCT (n=77) reported a significant improvement in VAS pain (0-100 scale, MD -16.00, 95% CI -26.68, -5.32) but no difference in WOMAC pain

- Balneotherapy showed a significant beneficial effect on medium-term function, based on two single-blind studies (n=60, 77; moderate RoB) (insufficient evidence)
 - One RCT (n=60) reported a significant improvement in WOMAC function scores (out of 170 possible points, MD -37.47, 95% CI -46.61, -28.33)
 - One RCT (n=77) reported a significant improvement in WOMAC function scores (out of 100 possible points, MD -8.10, 95% CI -15.82, -0.38).
- Topical mud showed no beneficial short-term effects on pain or function but a beneficial effect on stiffness, based on one RCT (n=50; high RoB) (insufficient evidence)
- Mud bath therapy showed a significant beneficial medium-term effect on pain and stiffness compared with a control condition, based on one RCT (n=103; moderate RoB) (insufficient evidence).
- Mud bath therapy showed no consistent sustained long-term effects on pain, function, or quality of life, based on one RCT (insufficient evidence).

Findings

For the current review, we identified two RCTs that assessed the effects of balneotherapy,⁵⁸ one RCT that tested topical application of mud,⁶⁰ and one RCT of mud bath therapy.⁶¹ The details are described in the evidence table in Appendix C.

Balneotherapy

Short-term effects on pain, function, or other outcomes. No studies that assessed short-term effects of balneotherapy met inclusion criteria.

Medium-term effects on pain. A 2012 RCT conducted in Italy by Fiorvanti and colleagues randomized 60 adults with bilateral knee OA to treatment that consisted of daily baths in sulphate-bicarbonate-calcium water (20 minutes per treatment, 6 treatments per week for two weeks) or usual care (RoB moderate).⁵⁸ After 12 weeks followup, a significant between-group difference was observed in VAS pain scores (0-100mm: MD-42.50, 95% CI -53.67, -31.33) and WOMAC pain scores (MD -25.70, 95% CI -34.06, -17.34).

A 2014 RCT conducted in Hungary by Kulisch and colleagues randomized 77 adults with mild to moderate OA of the knee to baths in Lake Heviz (30 minutes each, 5 times a week for 3 weeks) or to similar baths in tap water (RoB moderate).⁵⁹ The water temperature was the same for both groups, 34C. At week 15, participants who received the mineral bath treatment had significantly greater changes in VAS pain scores at rest (MD -16.00, 95% CI -26.68, -5.32) and on exertion (MD -16.60, 95% CI -25.79, -7.41) than did those who bathed in tap water). WOMAC pain scores did not differ between the two groups

Medium-term effects on function. The 2012 study on balneotherapy by Fiorvanti found significant between-group differences in WOMAC function scores (MD -37.47, 95% CI -46.61, -28.33) and Lequesne scores (MD -7.50, -9.57, -5.43).⁵⁸

The 2014 RCT by Kulisch reported a significant improvement in WOMAC function in the balneotherapy group compared to the control group at 15 weeks (MD -8.10, 95% CI -15.82, -0.38).⁵⁹

Medium-term effects on other outcomes. The 2012 study on balneotherapy by Fiorvanti found significant between-group differences at 12 weeks for the SF-36 functional domain (MD -32.60, 95% CI -49.62, -15.58), and use of rescue pain medication (NSAIDs and acetaminophen) (p<0.001).⁵⁸

The 2014 RCT by Kulisch found no difference in WOMAC stiffness scores between treatment groups at 15 weeks.⁶² The study also reported significant improvements in EQ-5D measure of general HRQoL.

Long-term effects on pain, function, or other outcomes. No RCTs that assessed long-term outcomes of interest met the inclusion criteria.

Mud bath or mud therapy

Short-term effects on pain. A 2009 RCT conducted in Iran by Mahboob randomized 50 participants with OA of the knee to receive topical applications of Lake Urmia mud (prepared as a gel) or a placebo gel (20 minutes per day for 30 days) (RoB unclear).⁶⁰ At the end of the intervention, no significant between-group differences were seen in WOMAC pain scores.

Short-term effects on function. The Mahboob RCT found no significant difference in WOMAC function at the end of the trial, although both groups improved significantly from baseline.⁶⁰

Short-term effects on other outcomes. The Mahboob RCT found significantly greater improvement in stiffness for the intervention group than for the placebo group ($p < 0.05$).⁶⁰

Medium-term effects on pain. A 2015 RCT conducted in Italy by Fiorvanti and colleagues randomized 103 adults 40 to 80 years of age with bilateral knee OA, K-L grade I-III to receive daily mud bath therapy (a combination of warm (42C) mud packs prepared from local mud (15 minutes) and bathing in the warm (37C) spring from which the mud was prepared (20 minutes), in addition to their usual therapy or treatment as usual alone for 2 weeks (RoB moderate).⁶¹

At 6 months, the study reported a significant between-group difference in VAS pain scores (0-100 point scale: MD -15.00, 95% CI -25.63, -4.37).⁶¹

Medium-term effects on function. At 6 months, the Fiorvanti study found a significant difference in WOMAC function scores between the intervention and control group (0-100 point scale: MD -10.00, -15.00, -5.00).⁶¹

Medium-term effects on other outcomes. At 6 months, the Fiorvanti study showed significantly improved WOMAC stiffness scores for the group that received the intervention, compared with the control group.⁶¹ This study also reported no significant improvement in the SF-12 physical domain or the EQ-5D.

Long-term effects on pain. At 12 months, the Fiorvanti study reported no significant between-group differences in WOMAC pain scores or in VAS pain scores.⁶¹

Long-term effects on function. At 12 months, the Fiorvanti study found no significant between-group differences in WOMAC function scores.⁶¹

Long-term effects on other outcomes. At 12 months, the Fiorvanti study showed no between-group differences in WOMAC stiffness scores.⁶¹ The study reported no significant differences in the SF-12 physical component or the EQ-5D.

Heat, Infrared, and Therapeutic Ultrasound,

Key Points

- Heat treatment showed beneficial effects on short-term pain and function compared with pharmacotherapy alone, based on one RCT (n=46; unclear RoB) (insufficient evidence).
- Infrared treatment showed no beneficial effect on short-term pain compared with a sham control, based on one RCT (n=72; low RoB) (insufficient evidence).

- Ultrasound (U/S) showed inconsistent effects on short-term and long-term pain, based on two RCTs (insufficient evidence).
 - Continuous or pulsed U/S combined with exercise had a beneficial effect on short-term pain but comparable to that of exercise alone and no significant effect (n=30; unclear RoB).
 - Continuous and pulsed U/S showed no long-term beneficial effects on pain compared with a sham control (n=60; moderate RoB).

Findings

For the current review, we identified one RCT that assessed the effects of heat,⁶³ one that assessed the effects of infrared,⁶⁴ and two that assessed the effects of pulsed and continuous U/S on outcomes of interest.^{65,66} The details are described in the evidence table in Appendix C.

Short-term effects on pain. For the current review we identified one RCT that assessed the effects of heat, one that assessed the effects of infrared, and one that assessed the effects of ultrasound on short-term pain outcomes.^{63,64,66}

A 2010 RCT conducted in Turkey by Yildirim and colleagues randomized 46 adults seen in a physical therapy clinic for OA of the knee to receive 4 weeks of heat treatment every other day or to continue with usual pharmacotherapy (RoB unclear).⁶³ WOMAC pain scores improved significantly more in the heat therapy group at 4 weeks than in the control group (0-20-point scale: MD -1.85, 95% CI -3.15, -0.55), however the intervention group was not barred from using analgesics.

A 2012 RCT conducted in Taiwan by Hsieh and colleagues randomized 72 individuals with knee OA to two weeks of infrared treatment (three times weekly) or to a passive control (RoB low).⁶⁴ At 4 weeks after baseline, no difference was seen in KOOS pain scores between the two groups.

A 2012 RCT conducted in Brazil by Carlos and colleagues randomized 30 adults 50 to 75 years of age to an 8-week intervention consisting of 4 weeks pulsed U/S plus 4 weeks exercise (strength/resistance training), 4 weeks continuous ultrasound plus 4 weeks exercise, or 8 weeks exercise alone as the control group (RoB unclear).⁶⁶ At 8 weeks, the exercise-only group showed no significant between-group differences in WOMAC or VAS pain compared with either the continuous or pulsed U/S. No difference was seen between continuous and pulsed U/S.

Short-term effects on function. The 2010 RCT by Yildirim found a significant effect of the heat therapy on WOMAC function compared with that of pharmacotherapy alone (0-68 point scale: MD -6.05, 95% CI -9.65, -2.45).⁶³

The 2012 RCT by Carlos found no significant effect of continuous U/S or pulsed U/S on WOMAC function compared with exercise alone.⁶⁶

Short-term effects on other outcomes. The 2010 RCT by Yildirim found no significant effect of the heat therapy on WOMAC stiffness compared with that of pharmacotherapy alone but did find a significant effect on SF-36 Physical function domain score in favor of the control (MD 12.61, 95% CI 3.73, 21.49).⁶³

The 2012 RCT by Carlos found no between-group differences in the effects of U/S on total WOMAC scores.⁶⁶

Medium-term effects on pain, function, or other outcomes. No studies were identified that assessed medium-term effects of heat, IR, or U/S on outcomes of interest.

Long-term effect on pain. A 2014 RCT conducted in Turkey by Cakir and colleagues randomized 60 adults with OA of the knee to a 2-week intervention of continuous U/S, pulsed

U/S, or sham U/S (RoB moderate).⁶⁵ All three groups participated in a simultaneous exercise program. At the end of 6 months, no significant differences were observed in WOMAC pain or VAS pain between either the continuous or pulsed U/S groups and the sham U/S group. All three groups experienced comparable improvement, defined as 40% improvement or a decrease of 8 units in the WOMAC pain score from baseline.

Long-term effect on function. The 2014 Cakir study found no difference between either the continuous or pulsed U/S group and the sham U/S group in WOMAC function at 6 months.⁶⁵

Neuromuscular electrical stimulation (NMES)

Key Points

- NMES combined with exercise showed inconsistent short-term effects on pain compared with exercise alone, based on three RCTs (insufficient evidence).
 - Two RCTs reported a beneficial effect of NMES plus exercise compared with exercise alone on short-term pain (n=100, 63; moderate and low RoB)
 - One RCT reported no difference between NMES plus exercise and exercise alone (n=100, low RoB).
- NMES alone showed no beneficial short-term effect on pain compared with a sham control (n=41; moderate RoB).
- NMES had inconsistent effects on medium-term pain and function, based on two and three RCTs, respectively.

Findings

Studies of NMES were included if they compared NMES to sham or to use of analgesics but not to other treatments of unclear efficacy. We identified 5 RCTs that compared NMES to a control or exercise with NMES to exercise alone.^{40, 67-70} The longest followup time ranged from 6 weeks to 18 weeks from baseline.

Short-term effects on pain. Four studies reported on short-term effects of NMES treatment on pain.^{40, 68-70}

A 2012 single-blind RCT conducted in Ireland by Bruce-Brand et al randomized 41 patients into three treatment groups: a group that received one 20-minute NMES session daily, 5 days per week for 6 weeks, a group that received three 30-minute home-based resistance trainings (RT) per week for 6 weeks, and a control group, which received standard care (RoB moderate).⁴⁰ WOMAC pain score at 8 weeks' followup was significantly decreased from baseline in the NMES group ($p < 0.005$); however, no significant differences in pain were noted between groups after treatments.

A 2013 RCT conducted in Brazil by Imoto and colleagues randomized 100 patients into two treatment groups: a group that received NMES combined with exercise and a group that received exercise alone; both groups received the treatments twice a week, for 8 weeks, with each session lasting about 40 minutes (RoB low).⁶⁸ At 8 weeks' followup, NRS and WOMAC pain scores were significantly decreased from baseline in both NMES+ exercise and exercise groups ($p < 0.0001$), whereas no significant differences between groups were found.

Another 2013 RCT conducted in Brazil by Imoto and coworkers randomized 100 patients into two groups: one that received an educational guide and strength training with NMES and one that received an educational guide and two phone calls as a control group (RoB low).⁶⁹ NRS

pain scores at 8 weeks' followup were significantly decreased in the NMES group compared with the control group (MD -1.44, 95% CI -2.65, -0.23; $p < 0.05$).

A 2013 RCT conducted in Israel by Elboim-Gabyzon et al randomized 63 patients to receive 12 biweekly exercise-only treatments or exercise combined with NMES treatments (RoB moderate).⁷⁰ At 6 weeks' followup, VAS pain scores were significantly improved for the exercise + NMES group compared with those of the exercise-only group (MD -1.70, 95% CI -2.92, -0.42; $p < 0.05$).

Short-term effects on function Bruce-Brand and Imoto^{40, 68, 69} also assessed the effects of NMES on function. At 8 weeks' followup, Bruce-Brand⁴⁰ found no significant differences in WOMAC function either from baseline or between groups; Imoto⁶⁸ reported significant decreases in WOMAC function from baseline in both NMES + exercise and exercise groups ($p < 0.0001$) but no significant differences between groups. In the other 2013 RCT conducted by Imoto⁶⁹, the NMES group showed significantly greater improvement in Lequesne index than did the control group (MD -2.81, 95% CI -4.53, -1.09; $p < 0.05$) at 8 weeks' followup.

Medium-term effects on pain. At 14 weeks' followup, Bruce-Brand⁴⁰ found no significant between-group differences in WOMAC pain scores. Following up patients in the 2013 RCT conducted by Elboim-Gabyzon⁷⁰ for another 12 weeks, Laufer⁶⁷ reported that the greater improvement in VAS pain scores remained for those who received exercise combined with NMES (-1.90, 95% CI -3.25, -0.55; $p < 0.05$) (RoB moderate).

Medium-term effect on function. Bruce-Brand⁴⁰ assessed the medium term effects of NMES on function. At 14 weeks' followup, WOMAC function scores were significantly decreased from baseline in the NMES group ($p < 0.005$) while no differences were seen between the NMES and RT groups or between the NMES and control groups.

Long-term effects. No studies reported on long-term effects of NMES.

TENS

Key Points

- TENS appears to have a small clinically important short-term beneficial effect on pain in patients with knee OA; however effects on function and longer-term effects are inconsistent.
- TENS showed a small but significant beneficial short-term effect on pain compared with sham controls, based on a pooled analysis of three RCTs (moderate strength of evidence).
 - A random effects pooled estimate showed a small beneficial effect of treatment on pain compared with a sham control that met our prespecified minimum clinically important difference of -0.37 (pooled effect size -0.38, 95% CI -0.6, -0.14) (n=343; RoB low-moderate)
- TENS showed no beneficial short-term effect on function or stiffness and no beneficial medium-term effects (low strength of evidence)..

Findings

For the current review, we identified three RCTs that assessed the effects of TENS.⁷¹⁻⁷³ The details are described in the evidence table in Appendix C.

Short-term effects on pain. One RCT assessed the short-term effects of TENS on pain as assessed with the VAS scale,⁷² and three used the WOMAC tool.⁷¹⁻⁷³

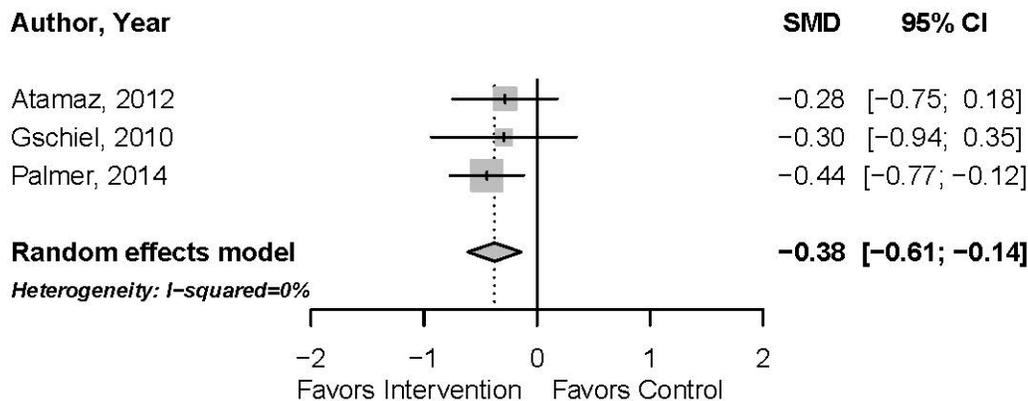
A 2010 RCT conducted in Germany by Gschiel and colleagues randomized 45 participants with uni- or bilateral OA of the knee to receive TENS or sham TENS therapy, 30 minutes twice a day for 3 weeks (RoB moderate).⁷¹ At week 5, no significant difference was observed in WOMAC pain between the active and sham treatment.

A 2012 RCT conducted in Turkey by Atamaz and colleagues randomized 74 participants to TENS or sham TENS treatment 20 minutes per day, 5 times a week for 3 weeks (RoB low).⁷² All participants also participated in an exercise program, 3 times per week for 3 weeks and received a single educational session. At week 4, no between-group differences were seen in VAS pain scores or WOMAC scores.

A 2014 RCT conducted in the UK by Palmer and colleagues randomized 224 participants with knee OA to receive self-administered TENS plus exercise, sham TENS plus exercise, or exercise alone for 6 weeks (RoB low).⁷³ All groups received education sessions. The primary outcome was WOMAC function (below). At 6 weeks, a significant between-group difference was seen in WOMAC pain (MD-2.00, 95% CI -3.46, -0.54) between the TENS and the sham TENS groups.

A random effects pooled estimate for all three studies showed a small effect of treatment compared with a sham control (pooled effect size -0.38, 95% CI -0.6, -0.14) (Figure 5).

Figure 5. Forest Plot for Short-term effects of TENS on WOMAC Pain



Short-term effects on function. Two of the RCTs reported short-term effects of TENS on WOMAC function.

At 4 weeks, Atamaz⁷² found no significant difference between groups in WOMAC function scores.

At 6 weeks, Palmer⁷³ found no difference in WOMAC function scores for TENS vs sham TENS. The percent of participants in the active TENS group who achieved a clinically significant improvement in function (-6.2 points, where the total possible score was 68 points) was lower than that for the sham TENS group or the exercise group.

Short-term effects on other outcomes. At 4 weeks, Gschiel⁷¹ reported no difference in total WOMAC scores between the TENS and sham-TENS treated groups.

At 6 weeks, Palmer⁷³ reported no difference in WOMAC stiffness or total WOMAC scores between TENS and sham-TENS groups.

Medium-term effects on pain. Two RCTs reported on medium-term effects on pain.^{72,73} At 6 months, (4 months after the intervention), Atamaz⁷² reported no between-group differences in VAS pain or WOMAC pain scores.

Palmer⁷³ reported no between-group differences in WOMAC pain between active- and sham TENS groups at 6 months.

Medium-term effects on function. Two of the RCTs reported medium-term effects of TENS on WOMAC function.

At 6 months, although improvements persisted from 4 weeks, Atamaz⁷² found no significant difference between groups in WOMAC function scores.

At 6 months, Palmer⁷³ found no between-group differences in WOMAC function scores for TENS vs sham TENS.

Medium-term effects on other outcomes. At 6 months, Palmer⁷³ reported no difference in WOMAC stiffness or total WOMAC scores between TENS and sham-TENS groups.

Pulsed electromagnetic field (PEMF)

Key Points

- It is unclear whether PEMF has any beneficial effect on patients with knee OA, as we identified only two small RCTs.
- PEMF had inconsistent short-term effects on pain.
 - Among two RCTs that assessed short-term effects on pain, one reported a beneficial effect compared with a sham control group (n=34, low RoB) and the other (n=40; moderate RoB) reported no difference.^{74,75}

Findings

Studies of PEMF were included if they compared PEMF to sham or to use of analgesics but not to other potential therapeutic agents of unclear efficacy. We identified 2 RCTs that compared the use of PEMF to that of a sham control.^{74,75} The longest followup times were 42 days and 4 weeks from baseline.

Short-term effects on pain. A 2013 double-blind RCT conducted in the US by Nelson and colleagues randomized 34 patients into two treatment groups: a group that received PEMF and a group that received sham control (RoB low).⁷⁴ Mean maximum VAS pain scores at 14 days' and 42 days' followup were significantly decreased from baseline and from that of the control group in the active treatment group (VAS 0-10 scale: MD -1.92, 95% CI -2.35, -1.49) (exceeding a MCID of -0.9).

A 2015 double-blind RCT conducted in Turkey by Dundar and colleagues randomized 40 patients to receive PEMF or sham PEMF; each group also received conventional physical therapy (including hot pack, ultrasound, transcutaneous nerve stimulation (TENS) and isometric knee exercise)(RoB moderate).⁷⁵ At 4 weeks' followup, no significant difference in VAS or WOMAC pain scores was found between the active and control groups.

Longer term effects. No studies reported on longer term effects of PEMF.

Whole-Body Vibration

Key Points

- It is unclear whether WBV has any beneficial effect on patients with knee OA, as pooled analysis showed inconsistent significant and clinically important effects on pain and function,
- WBV-based exercise demonstrated inconsistent short-term beneficial effects on pain compared with exercise performed on a stable surface, based on two RCTs (one unclear and one low RoB) (insufficient evidence).
- WBV showed no short-term effects on function or total WOMAC scores in one trial each (insufficient evidence).
- WBV-based exercise showed no significant beneficial medium-term effects on pain, based on four pooled RCTs (n=193; moderate-low RoB) (SMD -0.20, 95% CI -1.12, 0.71) (low strength of evidence).
- WBV-based exercise showed a small but statistically significant medium-term beneficial effect on WOMAC function, based on four pooled RCTs (n=193; moderate-low RoB) (SMD -0.26, 95% CI -0.45, 0.06) (low strength of evidence) that did not meet the MCID of -0.37.
- WBV-based exercise showed no beneficial effect on distance walked in the 6-minute walk, based on four pooled RCTs (SMD -28.16, 95% CI -75.45, 19.13) (low strength of evidence).

Findings

For the current review, we identified six RCTs (in seven publications) that assessed the effects of WBV. The details are described in the evidence table in Appendix C.⁷⁶⁻⁸¹

Short-term effects on pain. We identified two RCTs that assessed the short-term effects of exercise done while undergoing WBV on measures of pain.^{76, 81}

A 2013 RCT conducted in South Korea by Park randomized 44 women age 50 and over to two groups (RoB unclear).⁷⁶ The intervention group received 2 months of WBV (three times per week for 20 minutes each) and was taught a set of exercises to perform at home. The control group received only the home-based exercise instruction. At 2 months, the experimental group reported significantly less NRS-assessed pain than did the control group (MD -2.00, 95% CI -3.77, -0.23).

A 2015 RCT conducted in China by Wang randomized 99 individuals (age 40 to 65) to a strength-training program conducted with WBV or a control strength training program on a stable surface (30 minutes per day, 5 days per week for 6 months) (RoB low).⁸¹ At 1 month, no significant between-group difference was observed in VAS pain scores (10 cm scale, MD -0.50, 95% CI -1.10, 0.10) or WOMAC pain scores (maximum 20 points, MD -0.45, 95% CI -1.40, 0.50).

Short-term effects on function. One RCT assessed the short term effects of WBV on function.⁸¹ At 1 month followup, Wang found no between-group differences in WOMAC function scores (maximum 68 points, MD 0.21, 95% CI -2.63, 3.05)

Short-term effects on other outcomes. The study by Park showed that WOMAC total scores decreased in both groups with no difference between groups (MD -3.36, 95% CI -10.01, 3.29).⁷⁶

Wang⁸¹ identified no between-group differences at 1 month in performance on the 6-minute walk test (MD -3.14, 95% CI -333.26, 326.98), TUG (MD -0.26, 95% CI -1.2, 0.70) or in SF-36 physical domain scores (MD -1.89, 95% CI -5.03, 1.25).

Medium-term effects on pain. Four RCTs conducted by two groups reported medium-term effects of WBV on pain.^{77-79, 81}

A 2011 RCT conducted in Brazil by Avelar randomized 23 adults age 60 and older with knee OA to a 12-week program of strength training (3 times per week for 3 months) conducted with WBV or without WBV on a stable surface (RoB unclear).⁷⁷ At 3 months, no between-group difference was seen in the WOMAC pain score (MD 24.00, 95% CI -60.64, 108.64).

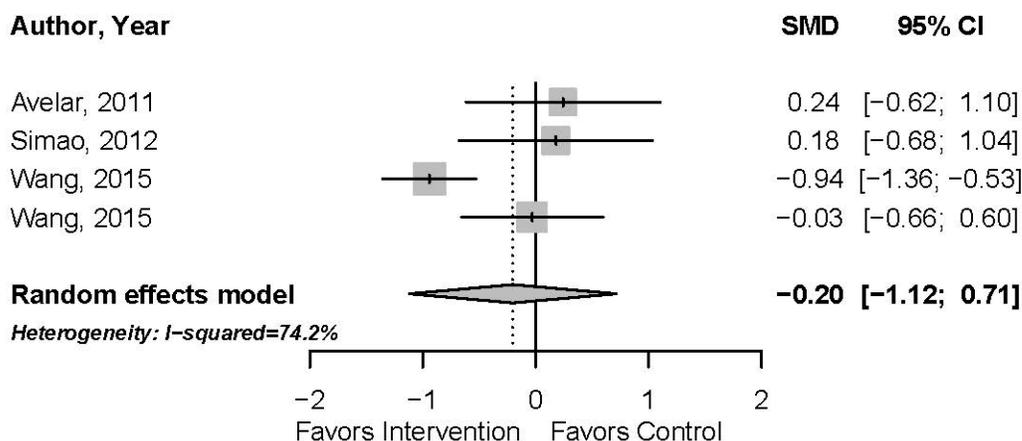
A 2012 RCT conducted in Brazil by Simao randomized 32 individuals, 60 years of age or older, to a strength training program (3 times per week for 3 months) conducted with WBV, a strength training program without WBV, or a no-activity control group (RoB moderate).⁷⁸ At 3 months, neither the WBV group nor the squat training alone group showed differences in WOMAC pain compared with the control group (MD 0.00, 95% CI -98.49, 98.49; MD -25.00, 95% CI -118.39, 68.39, respectively), and they did not differ from each other (MD 25.00, 95% CI -93.83, 143.83).

At 6 months, Wang⁸¹ reported a significant between-group difference in VAS pain scores (MD -0.71, 95% CI -1.21, -0.21) and in WOMAC pain scores (MD -2.49, 95% CI -3.53, -1.45).

Another RCT by the same group randomized 39 individuals with medial knee OA to a pilot trial of the same program, a strength-training program conducted with WBV or a control strength training program on a stable surface (30 minutes per day, 5 days per week for 4 months) (RoB low).⁷⁹ At 4 months, no between-group differences were observed in VAS pain scores (MD -0.60, 95% CI -1.39, 0.19) or WOMAC pain scores (MD -0.10, 95% CI -2.17, 1.97).

A random effects meta-analysis of WOMAC pain scores for these four RCTs showed no significant improvement in WOMAC pain scores with whole-body vibration compared with a control condition (SMD -0.20, 95% CI -1.12, 0.71) (Figure 6).

Figure 6. Forest Plot for Medium-term effects of Whole Body Vibration on WOMAC Pain



Medium-term effects on function. At 3 months, the 2011 RCT by Avelar reported no between-group difference in WOMAC function scores (MD -59.00, 95% CI -373.43, 255.43).⁷⁷

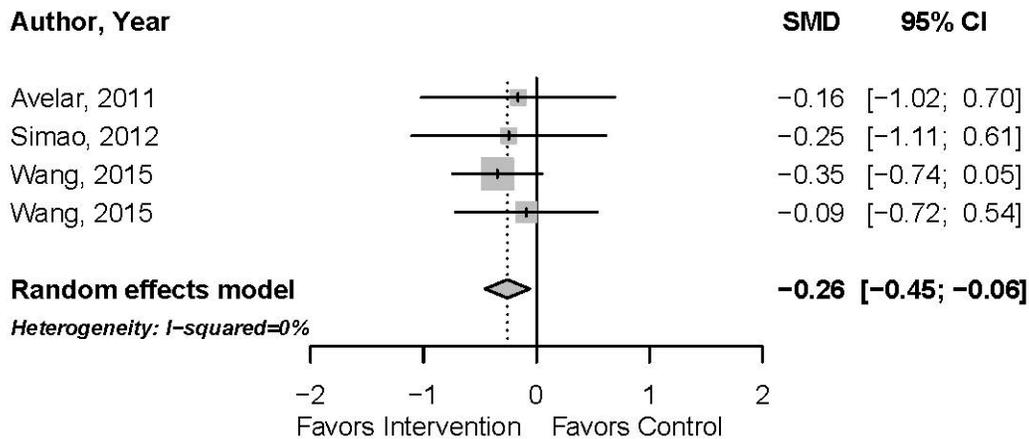
The 2012 RCT by Simao also reported no differences between the WBV group and the exercise only group in WOMAC function (MD -122.50 , 95% CI $-551.90, 306.90$) and no between-group differences (MD -122.5 , 95% CI $-551.9, 306.9$).⁷⁸

At 6 months, Wang⁸¹ reported no between-group difference in WOMAC function scores (MD -2.63 , 95% CI $-5.63, 0.37$) and a small but significant improvement in Lequesne scores (MD -1.19 , 95% CI $-2.30, -0.08$).

At 4 months, Wang⁷⁹ reported no between-group differences in WOMAC function scores in the participants with medial knee OA (maximum WOMAC function score 68 points, MD -0.60 , 95% CI $-4.78, 3.58$).

A random effects meta-analysis of WOMAC function scores for these four RCTs showed a small but significant improvement with whole-body vibration compared with a control condition (SMD -0.26 , 95% CI $-0.45, 0.06$ (Figure 7)).

Figure 7. Forest Plot for Medium-term effects of Whole Body Vibration on WOMAC Function



Medium-term effects on other outcomes. At 3 months, Avelar reported a significant between-group difference in the 6-minute walk test between the WBV group and the stable strength training group (MD -27.62 , 95% CI $-42.80, -12.44$) but no between-group differences in the TUG (MD 0.02 , 95% CI $-0.27, 0.31$).⁷⁷

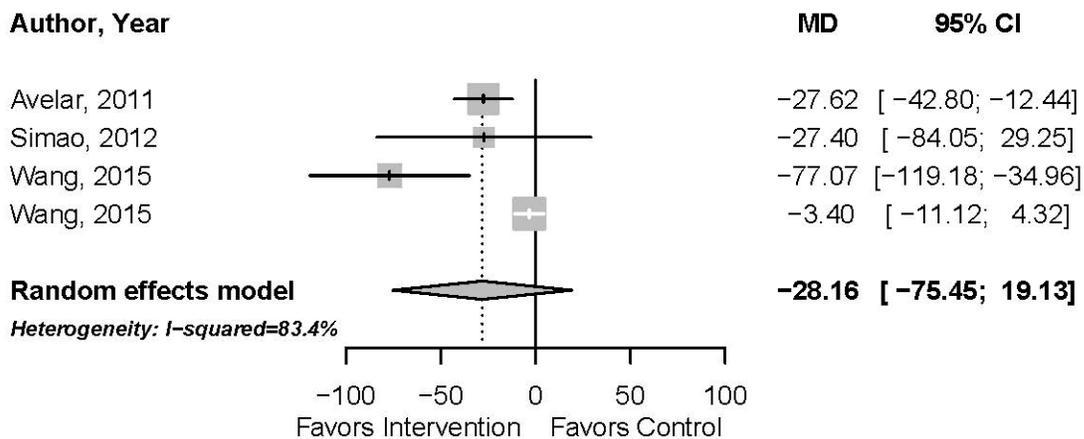
Simao reported no significant between-group differences in WOMAC stiffness scores or the 6-minute walk test between the WBV group and the control (MD -8.00 , 95% CI $-56.10, 40.10$) and no between-group differences.⁷⁸

At 6 months, Wang⁸¹ reported a significant between-group difference in the 6-minute walk (MD -77.07 , 95% CI $-119.18, -34.96$) and the TUG (MD -3.01 , 95% CI $-3.92, -2.10$).

A 2015 RCT conducted in Italy by Rabini and colleagues randomized 50 adults (age 60 or over) to receive focal muscle vibration or a sham treatment, 3 treatments per day for 3 days (RoB low).⁸⁰ At 6 months' follow-up, significant between-group differences were observed in total WOMAC scores (MD -19.04 , 95% CI $-27.43, -10.65$).

A random effects meta-analysis of 6-minute walk distances for these four RCTs showed no significant improvement in distances walked with whole-body vibration compared with a control condition (SMD -28.16 , 95% CI $-75.45, 19.13$ (Figure 8)).

Figure 8. Forest Plot for Medium-term effects of Whole Body Vibration on 6-minute Walk Distance



Braces and Orthoses

Key Points

- It is unclear whether knee braces or orthoses have a beneficial effect on patients with knee OA, as only a small number of RCTs on braces were identified, and studies of orthoses showed inconsistent effects across time points and outcomes.
- Custom knee braces had statistically significant beneficial effects on short-term (one RCT), medium-term (one RCT), and long-term (one RCT) measurements of pain compared to TAU, based on two RCTs (insufficient evidence). Custom orthoses had no consistent beneficial short-term effects on pain (based on four RCTs) or function (based on three RCTs).
- Orthoses showed no beneficial effect on short-term WOMAC total scores, based on pooled analysis of three RCTs.
 - A random-effects meta-analysis of the three trials showed no statistically significant short-term effect of orthotic use on WOMAC total scores (SMD -0.37 , 95% CI $-1.26, 0.53$).
- Orthoses showed no statistically significant beneficial effects on medium-term WOMAC pain, based on pooled analysis of three RCTs.
 - A random-effects meta-analysis of three trials ($n=131$; unclear, moderate, and low RoB) showed no statistically significant effect (SMD -0.4 , 95% CI $-1.35, 0.56$) (low strength of evidence).
- Orthoses showed no consistent beneficial effects on medium-term function, based on four RCTs (insufficient evidence).
- Orthoses showed no consistent beneficial effects on long-term pain or function, based on two RCTs (insufficient evidence).
- Two types of custom shoe demonstrated inconsistent effects on medium-term pain, based on two RCTs and a beneficial effect on function, based on one RCT (insufficient evidence).
- Custom shoes had no long-term beneficial effects on pain, based on one RCT (insufficient evidence).

- Cane use had a significant short-term beneficial effect on pain, physical function, and quality of life but not WOMAC total scores, based on one trial (insufficient evidence).

Findings

For the current report, we identified eight RCTs on orthoses, three RCTs on braces, four RCTs on footwear, and one RCT on cane use that met inclusions criteria. The details are described in the evidence table in Appendix C.

Braces

Short-term effects on pain. A 2015 RCT conducted in the UK by Callaghan and colleagues randomized 126 individuals (40–70 years) with patellofemoral OA to the use of a patellar tracking brace or no brace daily for 6 weeks (brace use averaged 7 hours per day) (RoB moderate).⁸² At 6 weeks, significant between-group differences were seen in pain measured using the VAS (0–10 cm) (MD –1.30, 95% CI –2.01, –0.59) and the KOOS (MD –5.70, 95% CI –10.76, –0.64).

Medium-term effects on pain. A 2015 RCT conducted in the US by Cherian and colleagues randomized 59 adults with moderate to severe (end-stage) knee OA to a custom pneumatic brace or to usual care; the brace group also underwent gait training 3 times a week for 6 weeks (RoB unclear).⁸³ At 3 months, a significant decrease in VAS pain (0–10cm scale) was observed in the brace group compared with the TAU group (MD –2.30, variance not reported).

Long-term effects on pain. A 2011 RCT conducted in Iran by Sattari and Ashraf randomized 60 patients with medial compartment knee OA (35–65 years of age) to receive a custom 3-point valgus knee support, or lateral wedge insoles, or TAU (RoB unclear).⁸⁴ At 9 months, significant differences were seen in VAS pain scores between the brace group and the TAU group favoring the braces (MD –2.80, 95% CI –3.58, –2.02). Among the brace group, 17 of 20 reported significant pain relief.

Orthoses

Short-term effects on pain. Four RCTs assessed the short-term effects of orthoses on pain.⁸⁵⁻⁸⁸

A 2008 RCT conducted in Brazil by Rodrigues that was cited in the 2012 SR but whose data were not included in the analyses randomized 30 women with valgus knee OA to receive and wear a medial 8-mm insole or a neutral insole for 8 weeks (RoB moderate).⁸⁵ At 8 weeks, significant between-group differences were seen in VAS pain with movement (MD –2.20, 95% CI –4.04, –0.36) but not at rest.

A 2009 RCT conducted in Turkey by Koca randomized 37 women with moderate knee OA to receive and wear 6mm wedge insoles or no insoles. Both groups attended an exercise program (RoB unclear).⁸⁶ At 1 month, significant between-group differences were observed in WOMAC pain (MD –3.14, 95% CI –5.96, –0.32) but not in VAS pain at rest or during movement.

A 2014 RCT conducted in Iran by Hatef randomized 118 adults with mild to moderate medial knee OA to wear lateral wedged insoles (5 degrees) or neutral wedged insoles for 2 months (RoB moderate).⁸⁷ At 2 months, pain measured on a 0–100mm VAS showed significant between-group differences (MD–23.05, 95% CI –28.34, –17.76); pain reduction was significant in women but not in men. The likelihood of experiencing a reduction in pain to mild (RR 0.13, 95% CI 0.05, 0.36) or none (RR 0.23, 95% CI 0.03, 2.03) was also assessed and found to be greater in the lateral wedge group.

A 2015 RCT conducted in Brazil by Campos randomized 58 adults with medial knee OA to wear lateral wedge insoles with subtalar strapping or a neutral wedge insole with strapping, bilaterally, for 6 months (RoB low).⁸⁸ At 2 months, no between-group differences were seen in VAS pain or WOMAC pain measures.

Short-term effects on function. Three RCTs were identified that assessed short-term effects of insoles on function.

At 2 months, Rodrigues' RCT showed a non-significant between-group difference in function, as assessed using the Lequesne test (however, the between-group difference in improvements from baseline to followup was significant, $p < 0.002$).⁸⁵ In addition, 100 percent of participants in the medial insole group showed clinically meaningful improvements in function, compared with 78.5 percent of the neutral insole group (RR 0.79, 95% CI 0.59, 1.06).

At 1 month, the 2009 RCT by Koca showed a significant between-group difference in WOMAC function scores in favor of the insole group (MD -10.06, 95% CI -19.68, -0.44).⁸⁶

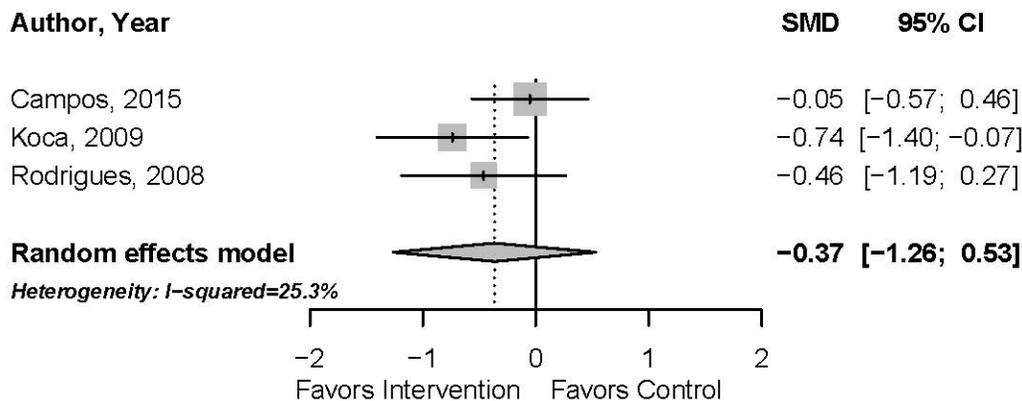
At 2 months, Campos reported no between-group differences in Lequesne scores.⁸⁸

Short-term effects on other outcomes. Three RCTs assessed the effects of insoles on total WOMAC scores.

Rodrigues reported no between-group differences in total WOMAC scores at 2 months.⁸⁵ At 1 month, Koca found a significant impact of insole wear on total WOMAC scores (total possible scores not reported) (MD -15.16, 95% CI -28.42, -1.90).⁸⁶ At 2 months, Campos also reported no between-group differences in total WOMAC scores.⁸⁸

A random-effects meta-analysis of the three trials showed no significant short-term effect of orthotic use on WOMAC total scores (SMD -0.37, 95% CI -1.26, 0.53) (Figure 9).

Figure 9. Forest Plot for Short-term effects of Orthotics on WOMAC Total



Medium-term effects on pain. Three RCTs assessed the medium-term effects of insole wear on pain.^{86, 88, 89}

At 6 months, Campos found no between-group differences in WOMAC or VAS pain scores.⁸⁸

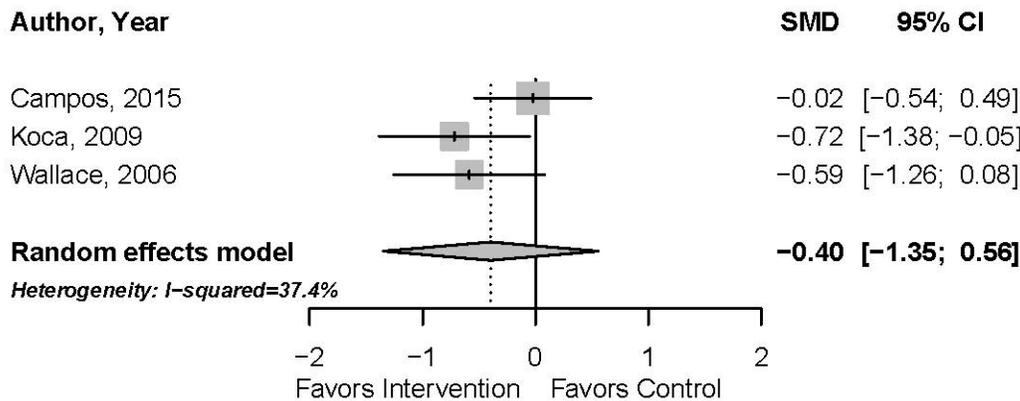
At 3 months, Koca found no between-group differences in any measure of pain using the VAS but did find a small significant difference in favor of the wedge insole for WOMAC pain (MD -3.14, 95% CI -5.96, -0.32).⁸⁶

A 2006 RCT conducted in the US as a dissertation project by Wallace randomized 36 adults age 30 or older with moderate-to-severe medial knee OA to wear a lateral 7-degree wedge insole or a neutral insole for 3 months (RoB unclear).⁸⁹ At 3 months, Wallace reported a significant

between-group difference in VAS pain on descending stairs (0–100mm scale; MD –15.10, 95% CI –25.69, –4.51) but no differences in walking pain or WOMAC pain scores.

A random-effects meta-analysis of the three trials showed no significant medium-term effect of orthotic use on WOMAC pain scores (SMD –0.4, 95% CI –1.35, 0.56) (Figure 10).

Figure 10. Forest Plot for Medium-term effects of Orthotics on WOMAC Pain



Medium-term effects on function. Four RCTs assessed medium-term effects of insoles on function.^{86, 88-90}

At 3 months, Koca reported a significant between-group difference in WOMAC function in favor of the lateral insoles (MD –10.06, 95% CI –19.68, –0.44),⁸⁶ whereas Wallace found no significant difference in WOMAC function scores at 3 months.⁸⁹

A 2006 RCT conducted in Japan by Toda and Tsukimura that randomized 61 women with varus deformity knee OA to lateral wedged insoles with subtalar strapping or traditional in-shoe wedged insoles for 2 years found no between-group difference in function as assessed at 6 months using the Lequesne tool (RoB moderate) (MD –1.50, 95% CI –4.23, 1.23).⁹⁰

At 6 months, the RCT by Campos also found no between-group differences in Lequesne function measures between the lateral-wedged insole group and the neutral insole group.⁸⁸

Medium-term effects on other outcomes. At 3 months, Koca reported a significant between-group difference in WOMAC total scores in favor of the lateral insoles (MD –17.68, 95% CI –30.37, –4.99).⁸⁶

Long-term effects on pain. Two RCTs assessed long-term effects of insoles on pain.^{84, 91}

A 2011 RCT conducted by Bennell and colleagues in Australia randomized 200 individuals 50 and over with knee OA to a 5-degree lateral wedged insole or a neutral insole to be worn daily 12 months (RoB low). The authors reported no between-group differences in WOMAC pain at 12 months, and the decreases did not achieve minimum clinically important difference.⁹¹

The 2011 RCT by Sattari that assessed the effects of a knee brace on pain also assessed the effects of lateral wedged insoles compared with the control group.⁸⁴ At 9 months, the group assigned insoles had a significant improvement in VAS pain compared with the control group (MD –1.60, 95% CI –2.31, –0.89)

Long-term effects on function. Two RCTs assessed long-term effects of insoles on function.^{90, 91}

The 2006 RCT conducted by Toda compared the effects of the wedge with subtalar strapping to that of the shoe insert on Lequesne-assessed function at 2 years. Although the group that wore

the insole with the subtalar strap showed a small but significant improvement in function from baseline, the group that wore the inserted insole did not. No significant between-group differences were observed.⁹⁰

The 2011 RCT by Bennell assessed WOMAC function as a secondary outcome, finding no between-group differences at 1 year.⁹¹

Footwear

For the current review, we identified five RCTs that assessed the effects of therapeutic footwear on measures of pain or function.

Short-term effects on pain, function, and other outcomes. No studies that met inclusion criteria assessed short-term effects of footwear on outcomes of interest.

Medium-term effects on pain. Four RCTs were identified that assessed medium-term effects of footwear on pain.⁹²⁻⁹⁵ Only two studies reported usable data.^{94, 95}

A 2013 RCT conducted in Brazil by Goldenstein-Schainberg and colleagues randomized 24 women with moderate knee OA to wear flexible, non-heeled (“minimalist”) Moleca® footwear or normal footwear for at least 6 hours a day for 6 months (RoB unclear).⁹² No data were provided in the conference proceedings that reported the findings. A significant between-group difference was seen in WOMAC pain scale scores at 6 months in favor of the minimalist shoe (p=0.01).

A second 2013 RCT conducted in Brazil by the same group randomized 28 women to the minimalist shoe or normal footwear for the same time period (RoB unclear).⁹³ At the end of 6 months, a between-group difference was seen in decreases in WOMAC pain scores favoring the minimalist shoe (MD -44.00, variance not reported).

A 2015 RCT conducted in Brazil by the same group randomized 56 women (60 to 80 years of age) with moderate knee OA to wear flexible, non-heeled (“minimalist”) Moleca® footwear or normal footwear for at least 6 hours a day for 6 months (RoB low).⁹⁴ At 6 months, a significant between-group difference was observed in WOMAC pain (MD -38.60, no variance reported).

A 2010 RCT conducted in the US by Erhart and colleagues randomized 79 adults with medial knee OA to wear a variable stiffness walking shoe or a constant stiffness shoe bilaterally for 6 months (RoB moderate).⁹⁵ The between-group difference in mean WOMAC pain scores did not achieve statistical significance (MD -0.3, no variance reported). The proportion of patients in the intervention group who met the MCID was significantly greater than that of the control group (RR 0.49, 95% CI 0.31, 0.79).

Medium-term effects on function. The 2015 RCT by Trombini-Souza found a significant between-group difference in WOMAC function (68-point scale, MD -43.8, variance not reported) and Lequesne scores (24-point scale, MD -4.20, 95% CI -6.29, -2.11) at 6 months, favoring the minimalist footwear.⁹⁴

Medium-term effects on other outcomes. Two RCTs reported medium-term effects of shoes on other outcomes,^{94, 95} although only one reported the actual data.⁹⁴

The 2010 RCT by Erhart reported no significant between-group difference in WOMAC total scores at 6 months.⁹⁵

The 2015 RCT by Trombini-Souza found no significant between-group differences in 6-minute walk distances (MD 11.00m, 95% CI -31.81, 9.81).⁹⁴

Long-term effects on pain. One RCT was identified that assessed long-term effects of a therapeutic shoe on pain.⁹⁶

In a follow-up to their assessment of variable-stiffness walking shoes,⁹⁵ Erhart and colleagues assessed the effects of the shoes on pain at 1 year (RoB 8/10).⁹⁶ WOMAC pain scores were significantly decreased from baseline for both groups, with no significant between-group differences (MD -1.00, variance not reported). Disease severity, as indicated by K-L score, did not affect response to the intervention.

Canes

One 2012 RCT conducted in Brazil by Jones randomized 64 patients with knee OA to 2 months of daily cane use or no cane use (RoB low).⁹⁷ At 2 months, a significant between-group difference in VAS pain (0–10cm, MD -2.11, 95% CI -2.83, -1.39) was observed, favoring cane use. Significant between-group improvements were also seen in Lequesne assessments of function (MD -2.34, 95% CI -4.34, -0.72) and SF-36 physical domain scores (0–100 points, MD -9.06, 95% CI -17.81, -0.31), but not WOMAC total scores (0–96 points, MD -1.06, 95% CI -8.87, 6.75).

Manual Therapy (Including massage and acupuncture)

Key Points

- It is unclear whether manual therapies have any benefit for patients with knee OA. Across eight RCTs, benefits were inconsistent across time points and outcomes. Pooled analysis showed no statistically significant effect, although a clinically important effect could not be ruled out, due to the wide 95% confidence intervals.
- Manual therapy showed no consistent beneficial short-term effects on pain, based on six RCTs and a pooled analysis of three RCTs.
 - A random-effects meta-analysis of three trials (n=244; moderate-high RoB) showed no statistically significant effect of manual therapy (administered by a therapist or by patients themselves) on short-term WOMAC pain (SMD -0.57, 95% CI -1.60, 0.45) (low strength of evidence).
- Manual therapy showed inconsistent effects on short-term function, based on three RCTs. (low strength of evidence).
- Manual therapy showed inconsistent effects on medium-term pain, function, and other outcomes, based on four RCTs (insufficient evidence).
- Manual therapy had a significant beneficial effect on long-term pain when combined with exercise, compared with exercise alone, based on 12-month follow-up of a three-month intervention (n=75; moderate RoB) (insufficient evidence).

Findings

The 2012 SR found low strength evidence from three RCTs that massage improved a composite measure of function and insufficient evidence for effects on other outcomes. For the current review, we identified eight RCTs that assessed the effects of manual therapy techniques, including massage and acupuncture, (alone or combined with exercise programs). The details are described in the evidence table in Appendix C.

Short-term effects on pain. Six RCTs reported on short-term effects of different manual therapies on pain: passive joint mobilization, self-manual therapy (with exercise), acupuncture, and combined manipulation and passive mobilization with physical therapy/exercise.⁹⁸⁻¹⁰³

Because of the differences in interventions and outcome measures, only the results of three RCTs were pooled.

A 2011 RCT conducted in Malaysia by Azlin randomized 22 adults 40 years and older to passive joint mobilization plus their regular exercise or to exercise alone, two sessions per week for 4 weeks (RoB high).⁹⁸ Among the 13 completers, at 4 weeks, both groups experienced pain relief (improvement in VAS scores) at 4 weeks, and no difference was seen between groups (MD -2.99, 95% CI -21.54, 15.56).

A 2014 RCT conducted in the US by Perlman and colleagues randomized 125 individuals to one of five 8-week interventions, comprising 30- or 60-minute weekly or bi-weekly massages or a TAU group (RoB moderate).¹⁰³ At 8 weeks, participants who got two 30-minute massages per week (MD -16.30, 95% CI -30.17, -2.43) and those who received one or two 60-minute massages per week (MD -30, 95% CI -42.09, -17.91) (MD -21.40, 95% CI -33.42, -9.38) had significantly improved VAS pain scores compared with the TAU group but the 30-minute per week massage group did not (MD -4.40, 95% CI -18.27, 9.47). Participants who received one or two 60-minute massages per week (MD -21.60, 95% CI -33.47, -9.73; MD -22.10, 95% CI -33.89, -10.31) had significantly improved WOMAC pain scores compared with the TAU group but the 30-minute once or twice per week massage groups did not (MD -9.50, 95% CI -20.69, 1.69) (MD 3.60, 95% CI -8.70, 15.90).

A 2014 RCT conducted in Thailand by Cheawthamai randomized 43 women to a 12-week home-based self-manual therapy and exercise program or exercise alone (RoB moderate).⁹⁹ At 4 weeks, both groups showed improved KOOS pain scores but no significant difference was observed between the groups (MD 1.90, variance could not be calculated).

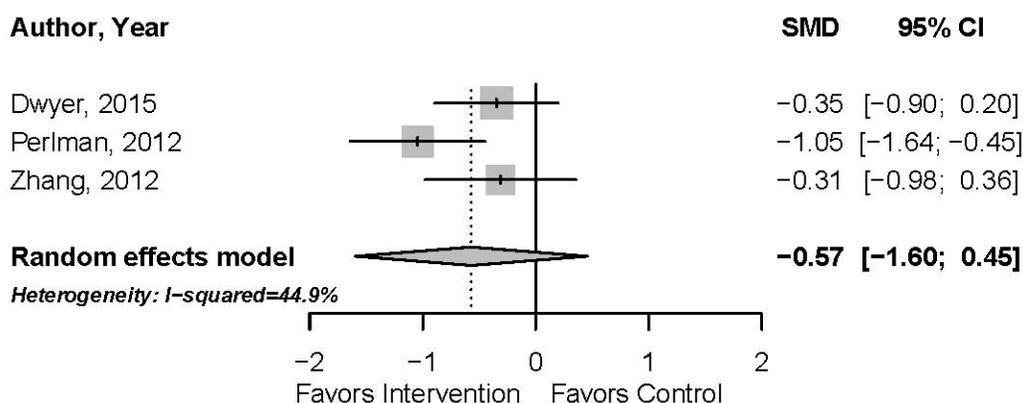
A 2012 pilot RCT conducted in the US by Zhang randomized 36 postmenopausal women to a 12-week self-administered acupressure program (with a training module) or to treatment as usual (RoB moderate).¹⁰¹ At 6 weeks, no significant differences were seen in WOMAC pain scores between the two groups (MD -1.15, 95% CI -3.45, 1.15).

A 2014 RCT conducted in Spain by Godoy randomized 18 women to a 6-week intervention comprising either a combination of massage therapy and exercise or exercise alone (RoB low).¹⁰⁰ At 1-month followup, no differences were observed between groups in VAS pain scores (MD 3.10, 95% CI 0.76, 5.44).

A 2015 two-site pilot RCT conducted in South Africa and the US by Dwyer randomized 83 individuals to one of three 4-week interventions: manual and manipulative therapy (MMT) alone, rehabilitation (rehab, a physical therapist-directed exercise program) alone, and MMT plus rehab (RoB moderate).¹⁰² At 6 weeks from baseline, participants in the MMT plus rehab group had decreases in WOMAC pain scores (less pain) that did not differ significantly from those of the group that received rehab alone (MD -26.90, 95% CI -68.88, 15.08) using a WOMAC scoring system with a maximum of 500 points).

A random-effects meta-analysis of three of the trials¹⁰¹⁻¹⁰³ showed no significant effect of manual therapy (administered by a therapist or by patients themselves) on short-term WOMAC pain (SMD -0.57, 95% CI -1.60, 0.45) (Figure 11).

Figure 11. Forest Plot for Short-term effects of Massage or Acupressure on WOMAC Pain



Short-term effects on function. At 6 weeks, both Zhang and Dwyer reported no significant between-group differences in WOMAC function scores at 6 weeks (MD -3.40, 95% CI -12.56, 5.76 and MD -32.80, 95% CI -191.40, 125.80, using a 1700-point tool, respectively).^{101, 102}

At 8 weeks, Perlman reported significant improvements in WOMAC function compared with TAU in the groups who received one 30-minute massage per week (MD -11.40, 95% CI -20.90, -1.90) or one or two 60-minute massages per week (MD -14.60, 95% CI -24.50, -4.70) (MD -15.40, 95% CI -26.48, -4.32) but not in the group that received two 30-minute massages per week (MD -10.60, 95% CI -21.76, 0.56).

Short-term effects on other outcomes. Four RCTs reported short-term effects on other relevant outcomes.⁹⁹⁻¹⁰²

Zhang reported no significant difference between treatment groups in WOMAC total scores (MD -5.51, 95% CI -16.97, 5.95).¹⁰¹ Dwyer also reported no significant differences between groups in WOMAC total score (MD -63.20, 95% CI -273.72, 147.32).¹⁰² Godoy reported no between-group differences in total WOMAC score (MD 21.42, 9.79, 33.05) or TUG (MD 3.94, 95% CI -4.01, 11.89).¹⁰⁰

Perlman reported differences in total WOMAC scores between the groups who received massages for 30 minutes, twice a week (MD -12.10, 95% CI -23.31, -0.89) and 60 minutes, once a week (MD -17.70, 95% CI -28.02, -7.38) and treatment as usual but not those who received one 30-minute massage or two 60-minute massages per week.¹⁰³

Godoy reported no between-group differences in TUG (MD 3.94, 95% CI -4.01, 11.89).¹⁰⁰

Cheawthamai reported no significant between-group differences in the 6-minute walk test and the SF-36 physical functioning domain.⁹⁹

Medium-term effects on pain. A 2013 RCT conducted in the US by Atkins and Eichler randomized 40 adults (age 50 and over) with knee OA to 8 weeks of supervised self-massage and 4 weeks of unsupervised self-massage or to a waiting list control group (RoB unclear).¹⁰⁴ At the end of the intervention, a significant between-group difference was observed in WOMAC pain scores (MD -0.65, variance not calculable).

At 3-months' followup, the Godoy RCT found no differences between groups in VAS pain scores (MD 2.28, 95% CI 0.44, 4.12).¹⁰⁰ At 12 weeks, Zhang reported no between-group differences in WOMAC pain scores (MD -1.88, 95% CI -10.58, 6.82).¹⁰¹ At 6 months, Perlman reported no differences in WOMAC pain between groups who received one or two massages per week and the TAU group.¹⁰³

Medium-term effects on function. At 3 months, Zhang reported no between-group differences in WOMAC function scores (MD -1.88, 95% CI -10.58, 6.82).¹⁰¹ At 6 months, Perlman reported no differences in WOMAC function scores between groups who received one or two massages per week and the TAU group.¹⁰³ At 3 months, Atkins reported a significant difference in WOMAC function scores (MD -0.80, variance not reported).¹⁰⁴

Medium-term effects on other outcomes. At 3 months, Zhang reported no between-group differences in WOMAC stiffness or total scores.¹⁰¹ Also at 3 months, Atkins reported significant between-group differences in WOMAC stiffness (MD -0.8, no variance reported) and total WOMAC (MD -0.7, no variance reported) scores.¹⁰⁴ At 6 months, Perlman reported no differences from TAU in WOMAC total among any of the massage groups.¹⁰³

Godoy reported no differences in TUG at 3 months (MD 14.04, 95% CI 4.71, 23.37).¹⁰⁰

Long-term effects on pain. A 2015 RCT conducted in New Zealand by Abbott and colleagues randomized 75 participants to one of four interventions: 12 sessions of exercise alone (9 weeks), 8 sessions of exercise (9 weeks) plus 4 additional sessions over the ensuing 8 months, exercise plus 12 sessions of manual therapy, or exercise plus extra sessions plus manual therapy (RoB moderate).⁵³ At one year, compared with the exercise-only group, the group that received exercise plus manual therapy had significantly improved pain intensity scores compared with the group that received exercise alone (MD -2.30, 95% CI -4.07, -0.53).

Weight Loss

Key Points

- Dieting, with or without exercise had a beneficial effect on short-term pain and function, based on one RCT (n=45, RoB unclear) and one single-arm trial, but benefit was not proportional to weight loss (dose-response effects were not established) (insufficient evidence).
 - The RCT showed a significant beneficial effect for diet alone and diet plus exercise on pain (VAS 1-10 cm: MD -2.10, 95% CI -3.32, -0.88; MD -4.56, 95% CI -5.82, -3.30, respectively)
 - The RCT also showed a significant beneficial effect for diet alone and diet plus exercise on WOMAC function (diet only: MD -2.34, 95% CI -3.71, -0.97; exercise+diet: MD -4.01, 95% CI -5.56, -2.46)
- Weight loss had a significant beneficial effect on medium-term pain, based on two RCTs and four single-arm trials. One single-arm trial assessed and reported a dose-response effect between weight and outcomes of interest (moderate-level evidence).
 - One RCT (n=87, RoB moderate) showed a significant beneficial medium-term effect on WOMAC pain with weight loss (MD -2.00, 95% CI -3.25, -0.75).
 - A second RCT that compared the effects of behavioral weight management and behavioral weight management with pain coping skills training with those of standard care found that the combined treatment group, the only group that lost significantly more weight than the standard care group, showed a significant beneficial effect on medium-term WOMAC pain (MD -10.80, 95% CI -15.77, -5.83).
- Weight loss had a significant beneficial effect on medium-term function, based on the same two RCTs and three single-arm trials (low-level evidence)

- Weight loss had a significant long-term beneficial effect on pain based on three RCTs and one single-arm trial (low level of evidence) but inconsistent effects on function and quality of life, based on two RCTs (inconsistent evidence)

Findings

We identified five RCTs¹⁰⁵⁻¹⁰⁹ and five single-arm trials^{55, 110-114} reported in six publications that reported on the effects of weight loss trials among individuals with knee OA on outcomes of interest.¹⁰⁵⁻¹⁰⁹ The details are described in the evidence table in Appendix C.

Randomized Controlled Trials

Short-term effects on pain. One trial reported on short-term effects of a weight-loss trial on outcomes of interest. A 2008 RCT conducted in Tunisia by Ghroubi and coworkers randomized 45 obese adults (BMI>35 or between 30 and 35 with one cardiovascular risk factor) and radiographic OA of the knee to an aerobic and strength training program (exercise) alone, diet plus exercise, diet alone, or a no diet/no exercise control (RoB unclear).¹⁰⁵ At 8 weeks, the diet plus exercise group had lost significantly more weight than the other groups, followed by the diet only group, and then the exercise only group (the control group lost no weight). The diet + exercise group showed a significant between-group difference in VAS pain (1-10cm, MD -4.56, 95% CI -5.82, -3.30) compared with the control, as did the diet alone group (MD -2.10, 95% CI -3.32, -0.88); the exercise only group also showed improvement in pain compared with the control (MD -2.90, 95% CI -4.52, -1.28).

Short-term effects on function. The RCT by Ghroubi assessed the effects of diet with or without exercise on three measures of function.¹⁰⁵ All three active treatment groups showed comparable improvements in WOMAC function scores (exercise only: MD, -3.09 95% CI -4.46, -1.72 ; exercise+diet: MD -4.01, 95% CI -5.56, -2.46; diet only: MD -2.34, 95% CI -3.71, -0.97) and Lequesne scores (exercise only: MD -2.41, 95% CI -3.52, -1.30; exercise+diet: MD -3.73, 95% CI -4.65, -2.81; diet only: MD -2.23, 95% CI -3.30, -1.16) compared with the control.

The proportion of participants who achieved a significant improvement in WOMAC function was greater in each of the active treatment groups compared with the control group (exercise only RR 0.23, 95% CI 0.02, 2.23; exercise+diet: RR 0.16, 95% CI 0.02, 1.39; diet only: RR 0.33, 95% CI 0.03, 3.43).

Short-term effects on other outcomes. The Ghroubi RCT found that exercise alone (MD -39.00, 95% CI -46.47, -31.53) and exercise+diet (MD -53.00, 95% CI -59.33, -46.67) significantly improved 6-minute walk distances but diet alone (MD 2.00, 95% CI -6.51, 10.51) did not.¹⁰⁵

Medium-term effects on pain. Two RCTs assessed the effects of weight loss on medium-term pain.^{106, 109}

A 2006 US RCT, the Physical Activity, Inflammation, and Body Composition Trial, randomized 87 obese adults over 60 years to a 6-month intensive weight loss group or a weight maintenance group; the weight loss goal was a 10% body weight loss (RoB moderate).¹⁰⁶ At 6 months, the weight loss group had lost an average of 8.3±0.8 kg and decreased an average of 8.1±0.7 BMI units (compared with 0.1±0.7 kg and 0.3±0.9 BMI units in the control group). WOMAC pain scores showed a significant between-group difference in favor of the weight loss group (MD -2.00, 95% CI -3.25, -0.75).

The OA Life Study was a 2012 US RCT that randomized 232 obese adults with knee OA to receive standard care, a pain coping skills training (PCST) program, a behavioral weight management (BWM) program alone, or both interventions (RoB moderate).¹⁰⁹ Both the BWM and BWM+PCST groups had significant weight losses compared with the standard care group; only the BWM+PCST group had a significant decrease in BMI compared with standard care (MD -1.80, 95% CI -2.44, -1.16). No difference was observed in WOMAC pain between the BWM group and the standard care group (MD -2.50, 95% CI -7.67, 2.67), but a significant between-group difference was seen between BWM+PCST and the standard care group (MD -10.80, 95% CI -15.77, -5.83).

Medium-term effects on function. Two RCTs assessed the effects of weight loss on WOMAC function.

The Physical Activity, Inflammation, and Body Composition Trial found a significant between-group difference in WOMAC function between the weight loss and weight maintenance groups, favoring the weight loss group.¹⁰⁶

The OA Life Study observed a significant difference in WOMAC function between the PCST+BWM group and the standard care group (MD -12.40, 95% CI -17.29, -7.5) but no significant difference between the BWM-only group (which achieved lower weight loss than the PCST+BWM group) and the standard care group (MD -1.50, 95% CI -6.46, 3.46).¹⁰⁹

Medium-term effects on other outcomes. The 2006 Physical Activity, Inflammation, and Body Composition Trial found a significant between-group difference in the distance walked in the 6-minute walk test (MD -51.00, 95% CI -96.03, -5.97) and in WOMAC total scores (scale not reported, MD -10.70, 95% CI -17.01, -4.39).¹⁰⁶

Long-term effects on pain. A 2011 publication reported on a 2005 RCT conducted in Denmark by Bliddall and colleagues that had randomized 89 knee OA patients to an intensive weight loss program (6 weeks of an intensive low energy diet [LED], along with group counseling) or a control group (moderate calorie restriction and education only); at 1-year, the researchers followed up on the 80 retained patients (RoB moderate).¹⁰⁸ The LED group had lost significantly more weight than the control group (kg, MD -7.30, 95% CI -9.52, -5.08), and was experiencing significantly less pain than the control group, as assessed on the WOMAC scale (0-100 points, MD -7.20, 95% CI -13.30, -1.10). The primary endpoint, WOMAC total score, is reported below.

The Intensive Diet and Exercise for Arthritis (IDEA) Trial is a 2013 US RCT that randomized 454 overweight and obese adults (BMI 27-41) with knee OA to an intensive diet and exercise-based weight loss program, diet alone, or exercise alone (exercise was considered part of standard care) (RoB moderate).¹⁰⁷ At 18 months, weight loss was slightly but significantly greater in the diet+exercise group than in the diet-only group, compared with the exercise-only group (MD -8.10, 95% CI -11.92, -4.28 versus MD -6.00, 95% CI -9.75, -2.25). Primary outcomes were knee-joint loading and interleukin-6 levels. The diet+exercise group experienced a non-significantly greater improvement in WOMAC pain measures than the exercise-only group (20 pts total, MD -0.70, 95% CI -1.41, 0.01), and the diet only group showed no difference in WOMAC pain measures.

At 18 months, the OA Life Study showed that patients in the PCST+BWM group continued to experience less pain than the other groups, although all groups had regained some of the lost weight (no statistics reported).¹⁰⁹

Long-term effects on function. Bliddall found no significant between-group differences in WOMAC function in their diet study.¹⁰⁸

The IDEA trial reported a significant between-group difference in WOMAC function for the diet+exercise group compared with the exercise only group (MD -3.40, 95% CI -6.02, -0.78); the diet-only group did not differ from the exercise-only group.¹⁰⁷

Long-term effects on other outcomes. Bliddall found no significant between-group differences in WOMAC total in their diet study.¹⁰⁸

The IDEA trial reported significant between-group differences in 6-minute walk test performance (meters walked, MD -12.00, 95% CI -33.93, 9.93) and the SF-36 physical domain scores (0-100 points, MD -2.70, 95% CI -4.89, -0.51) for the diet+exercise group compared with the exercise-only group but no significant differences between the diet-only group and the exercise-only group.¹⁰⁷

Single arm trials and cohort studies

We identified five single-arm trials reported in six publications^{55, 110-114} that assessed the effects of weight loss on outcomes of interest.

Short-term effects on pain. A 2015 single-arm trial conducted in Australia by Claes and colleagues followed 203 individuals with knee OA in a 12-week hospital-based weight loss program to assess the effects of a weight loss program on the primary outcomes of weight loss and decrease in waist circumference and secondary outcomes related to knee pain and function.¹¹² Among 127 completers, percentage weight loss and decrease in BMI were significant at 12 weeks. This group demonstrated a significant improvement in KOOS pain scores (MD 5, 95% CI 2.0, 97.9).

Short-term effects on other outcomes. One trial was identified that reported on the association of weight loss with other short-term outcomes of interest.¹¹²

The 2015 trial by Claes reported a significant improvement in the timed up and go (seconds, MD -1.4, 95% CI -1.1 to -1.7) and the 6-minute walk test (meters, MD 36.7, 95% CI 27.2, 46.2) from baseline to 12 weeks.¹¹²

Medium-term effects on pain. Four studies assessed the association between medium-term weight loss and pain.^{55, 110, 112, 113}

A 2014 study conducted in Denmark by Bartels and colleagues followed a cohort of 192 participants (age over 50, BMI 30 or over) in a 16-week weight loss program, part of the CAROT study (Influence of weight loss or exercise on CARtilage in Obese knee osteoarthritis patients) who experienced a significant weight loss (MD 14, 95% CI 13.3, 14.7).⁵⁵ Weight loss was significantly associated with improvement in KOOS pain scores (MD 10.7, 95% CI 8.5, 12.9).

A 2015 study conducted in Australia by Messier, Bennell, and colleagues (Atukorala et al., 2015) enrolled over 3,000 overweight individuals with knee OA in an 18-week weight loss program and assessed the association between percent body weight loss and change in knee pain in 1,383 completers (94 of whom had lost more than 2.5% of their original body weight).¹¹⁰ At 18 weeks, quintiles of weight loss (as % of baseline body weight) showed a significant dose-response relationship with KOOS pain scores (e.g., >10% weight loss [n=431]: MD 16.7, 95% CI 15.2, 18.2) compared to <2.5% weight loss [n=79] MD 6.1, 95% CI 3.2, 9.0; full data reported in Appendix C). Quintiles showed no significant differences in age or sex.

The 2015 study by Claes reported that among 76 participants who were retained at 26 weeks, weight loss was 2.1 ± 4.0 kg and improvement in VAS pain (0-10cm, -0.9 ± 2.0) and changes in KOOS pain at 26 weeks remained significant (MD 5.6, 95% CI 1.6, 9.6).¹¹²

A 2011 single-arm study conducted in France by Richette prospectively assessed the effects of large-scale weight loss among 44 bariatric surgery patients with moderate to severe OA of the

knee on pain after 6 months (RoB not determined).¹¹³ At 6 months, patients experienced a significant improvement in BMI (10.3, 95% CI 7.4, 13.2), and VAS (0-100 scale, MD 25.5, 95% CI 15.5, 35.5) and WOMAC (no scale, MD 93.2, 95% CI 47.1, 139.3) pain scores were significantly improved compared with baseline.

Medium-term effects on function. Three studies^{55, 110, 113} assessed the association of weight loss with function.

Richette demonstrated significant improvements in WOMAC function scores with weight loss at 6 months (MD 371.3, 95% CI 219.6, 523.0).¹¹³

The 2014 study conducted by Bartels and colleagues reported a significant improvement in KOOS function associated with weight loss (MD 12.1, 95% CI 10.0, 14.2).⁵⁵

The study by Atukorala found a significant dose-response relationship between % weight loss and KOOS function scores (>10% loss: MD 17.4, 95% CI 15.9, 18.9 compared with <2.5% loss: MD 7.8, 95% CI 4.8, 10.8).¹¹⁰ Achievement of a MCID in KOOS function was associated with a weight loss of 7.7% or more (95% CI 5.2, 13.3).

Medium-term effects on other outcomes. We identified three single-arm trials that assessed medium-term effects on other outcomes of interest among weight loss patients with OA.

At 6 months, patients in the bariatric surgery trial by Richette showed significant improvements in WOMAC stiffness scores (MD 31.8, 95% CI 11.7, 51.9).¹¹³

The 2015 trial by Claes reported a significant improvement in the timed up and go (seconds, MD 2, 95% CI 1.4, 2.6) and the 6-minute walk test (meters, MD 44.0, 95% CI 31.5, 56.5) from baseline to 26 weeks.¹¹²

The 2015 study by Atukorala also identified a significant dose-response association of % body weight lost and the SF-12 physical domain (<2.5%: mean 3.16 [SD 8.24]; 2.5-5%: 4.07 [8.02]; 5.1-7.5%: 6.73 [7.83]; 7.6-10%: 6.65 [8.17]; > 10%: 8.60 [8.18], p=0.000).¹¹¹

Long-term effects on pain. We identified one single-arm trial that assessed long-term effects on pain.

A 2015 US study by Stefanik and colleagues, the Osteoarthritis Before and after Bariatric Surgery study, is assessing the effect of large-scale weight loss on knee OA outcomes among individuals with BMI 35 or higher (RoB not assessed).¹¹⁴ At 1 year, among 23 individuals who have completed the study so far, VAS (0-100mm, MD 27.8) and WOMAC (0-20 points, MD 5.1) pain scores have improved.

Home-based and Self-Management Interventions

Key Points

- A home-based exercise program and a self-management plus exercise program showed significant beneficial short-term effects on pain, based on two RCTs (low-moderate RoB) (low-level evidence).
- A home-based and self-management program showed inconsistent effects on short-term function (insufficient evidence).
 - The self-management program showed increased proportions of participants achieving minimum clinically important improvements (MCII) in short-term function and quality of life.
- Self-management and PCST plus strength training showed beneficial but inconsistent medium-term effects on pain, based on three RCTs (Low SoE).

- A weight-loss program that employed PCST showed medium-term improvements in weight loss and pain in the group that received combined PCST and behavioral weight management (BWM) skills training, compared with standard care (n=232; moderate RoB).
- The 8-week OAK self-management program no longer showed beneficial effects on pain at 6 months (n=146; low RoB)
- A combined PCST and strength training program had a beneficial effect on VAS walking pain but not on VAS pain at rest or WOMAC pain (n=222; low RoB)
- Self-management programs had significant beneficial effects on medium-term function compared with control conditions, based on three RCTs (moderate-level evidence).
 - A weight-loss program that employed PCST showed medium-term improvements in function in the group that received combined PCST and behavioral weight management (BWM) skills training, compared with standard care (n=232; moderate RoB)
 - The 8-week OAK self-management program showed continuing beneficial effects on function at 6 months (n=146; low RoB)
 - A combined PCST and strength training program had a beneficial effect on WOMAC function compared with strength training alone (n=222; low RoB)
- Self-management programs had inconsistent medium-term effects on WOMAC total and quality of life, based on two RCTs (insufficient evidence).
- Self-management plus strength training had no beneficial effect on long-term pain or WOMAC function, based on one RCT (insufficient evidence).

Findings

Most RCTs included in the current report expected participants to perform exercises at home, but none of these trials assessed the effects of compliance or adherence with the home exercise assignments. We identified four RCTs that reported on the effects of home-based or self-management interventions (described as self-management or coping skills training) among individuals with knee OA on outcomes of interest. Three of these studies have been described in previous sections of the report, and the details are described in the evidence table in Appendix C.

Randomized Controlled Trials

Short-term effects on pain. Two RCTs that met inclusion criteria assessed short-term effects of self-management or home-based interventions on pain.^{43, 115}

A 2012 RCT conducted in the US by Rogers and coworkers randomized 44 adults age 50 and over to one of four 2-month home-based interventions: kinesthesia, balance, and agility (KBA) training alone, resistance training (RT) alone, a combination of KBA and RT, and a control group that was told to apply a lotion to the affected areas (RoB moderate).⁴³ At 2 months, WOMAC pain scores improved significantly for all groups compared with the control group (Strength training alone: MD -3.75, 95% CI -6.39, -1.11; agility training alone: MD -3.13, 95% CI -5.86, -0.40; strength+agility training: MD -3.00, 95% CI -5.45, -0.55), with no significant differences between any of the groups.

A 2012 RCT conducted in Australia by Coleman and colleagues, the OAK Self Management Program (OAK) study, randomized 146 adults to a 6-week self-management intervention tailored to knee OA patients (based on the Stanford Arthritis Self-management Program) or to a waiting list control group (RoB low).¹¹⁵ At 2 months, a significant between-group difference was seen in

WOMAC pain scores (MD -1.50, 95% CI -2.33, -0.67). VAS pain decreased significantly over the same time period (0-10cm MD 2.54, 95% CI 1.66, 3.41), and the likelihood of achieving a minimum clinically important improvement (MCII) was significantly greater in the SM group (RR 0.20, 95% CI 0.08, 0.49).

Short-term effects on function. Two RCTs that met inclusion criteria assessed short-term effects of self-management or home-based interventions on function.^{43, 115}

The Rogers trial reported significant between-group differences in WOMAC function at 2 months for the combined strength+agility training group (MD -11.98, 95% CI -19.15, -4.81) and the strength training group (MD -9.62, 95% CI -19.04, -0.20) compared with the controls but not the group that performed agility exercises alone.⁴³

The 2012 OAK study found a significant between-group difference in WOMAC function scores at 2 months (MD -5.30, 95% CI -7.24, -3.36).¹¹⁵ In addition the proportion achieving a MCII was significantly different (RR 0.24, 99% CI 0.11, 0.51).

Short-term effects on other outcomes. Two RCTs that met inclusion criteria assessed short-term effects of self-management or home-based interventions on other outcomes.^{43, 115}

The Rogers trial of home-based interventions reported significant between-group differences in WOMAC total at 2 months for the combined strength+agility training group (MD -15.26, 95% CI -25.16, -5.36) and the strength training group (MD -13.62, 95% CI -26.37, -0.87) compared with the controls but not the group that performed agility exercises alone.⁴³

The 2012 OAK self-management study found significant between-group differences in WOMAC total scores at 2 months (MD -7.20, 95% CI -9.97, -4.43). The study also found significant between-group differences in SF-36 physical domain scores at 2 months (MD -5.60, 95% CI -9.48, -1.72) and a significant increase in the likelihood of achieving a MCII (RR 0.57, 95% CI 0.38, 0.84). Significant between-group differences were seen in 2-month TUG scores (MD -1.00, 95% CI -1.55, -0.45) and in the likelihood of achieving a MCII in TUG (RR 0.32, 95% CI 0.20, 0.52).¹¹⁵

Medium-term effects on pain. Three RCTs assessed medium-term effects of home-based or self-management interventions on pain.^{45, 109, 115}

A 2016 double-blind (participants and assessors) RCT conducted at two sites in Australia by Bennell and colleagues assessed the effect of strength training combined with pain coping skills training (PCST) compared with PCST or strength training exercises (the control) alone (RoB low).⁴⁵ This study randomized 222 individuals with moderate to severe knee OA to one of three 3-month treatment programs and followed them for 12 months. Overall pain was assessed on a 100mm VAS scale with a MCID set at 18mm. Comparisons used a model that took into account the physical therapist training, baseline scores, site, and sex. At 3 months, no significant differences were observed in overall pain in the group that received strength training+PCST or the group that received PCST alone compared with the group that received strength training alone. A significant between-group difference was observed in VAS walking pain, favoring the group that received strength training+PCST over that of strength training alone (MD -8.20, 95% CI -15.32, -1.08). Using WOMAC pain as the outcome, a non-significant difference was seen in the strength training+PCST group compared with strength alone and no difference was seen comparing PCST alone with strength training.

The OA Life Study was a 2012 US RCT that randomized 232 obese adults with knee OA to receive standard care, a pain coping skills training (PCST) program, a behavioral weight management (BWM) program alone, or both interventions (RoB moderate).¹⁰⁹ Both the BWM and BWM+PCST groups had significant weight losses compared with the standard care group;

only the BWM+PCST group had a significant decrease in BMI compared with standard care (MD -1.80, 95% CI -2.44, -1.16). No difference was observed in WOMAC pain between the BWM group and the standard care group (MD -2.50, 95% CI -7.67, 2.67), but a significant between-group difference was seen between BWM+PCST and the standard care group (MD -10.80, 95% CI -15.77, -5.83).

The 2012 OAK self-management study found no remaining between-group differences in WOMAC pain at 6 months.¹¹⁵

Medium-term effects on function. Three RCTs assessed medium-term effects of home-based or self-management interventions on function.^{45, 109, 115}

The Bennell trial that compared strength+PCST training with each one alone observed a significant between-group difference in WOMAC function at 3 months, favoring the strength+PCST group over strength training alone (0-68 points, MD -3.80, 95% CI -7.06, -0.54).⁴⁵

The 2012 OA Life Study observed a significant between-group difference in WOMAC function between the BWM+PCST group and the standard care group (0-100 points, MD -12.40, 95% CI -17.29, -7.51) but no other between-group differences.¹⁰⁹

At 6 months, the 2012 OAK self-management study found a continuing between-group difference in WOMAC function (MD -3.50, 95% CI -6.14, -0.86) and an increase in the likelihood of achieving a MCII in function compared with the control group (RR 0.56, 95% CI 0.33, 0.95).¹¹⁵

Medium-term effects on other outcomes. Two RCTs assessed medium-term effects of self-management or home interventions on other outcomes of interest.^{45, 115}

The Bennell trial, which compared strength+PCST training with each one alone observed no between-group differences in TUG or in quality of life at 3 months.⁴⁵

At 6 months, the 2012 OAK self-management study found a continuing between-group difference in WOMAC total scores (MD -4.10, 95% CI -7.43, -0.77). The study also found significant persistent between-group differences in SF-36 physical domain scores at 6 months (MD -5.70, 95% CI -10.97, -0.43) and a significant increase in the likelihood of achieving a MCII (RR 0.73, 95% CI 0.52, 1.02). Significant between-group differences persisted at 6 months in TUG scores (MD -1.00, 95% CI -1.55, -0.45) and in the likelihood of achieving a MCII in TUG (RR 0.68, 95% CI 0.47, 0.99).¹¹⁵

Long-term effects on pain. At 1 year, the Bennell trial, which compared strength+PCST training with each one alone, observed no between-group differences in VAS pain or WOMAC pain.⁴⁵

Long-term effects on function. The Bennell trial, which compared strength+PCST training with each one alone, observed no between-group differences in WOMAC function at 1 year.⁴⁵

Long-term effects on other outcomes. At 1 year, the Bennell RCT identified a significant between-group difference in quality of life (Australian Quol-6D) between the strength+PCST and the strength-only group (range -0.04-1 MD -0.06, 95% CI -0.11, -0.01),⁴⁵ but no differences in the TUG.

Key Question 2a: What harms are associated with each intervention in patients with primary or secondary OA of the knee?

Key Question 2b: How do the harms associated with each intervention differ by the following population or study characteristics: sex, disease subtype (lateral tibiofemoral, patellofemoral), severity (stage/baseline pain and functional status), weight status (body mass index), baseline fitness (activity level), comorbidities, prior or concurrent treatments (including self-initiated therapies), and treatment duration or intensity?

Key Points

- Of 45 studies that described some assessment of adverse events, fourteen studies reported on serious adverse events (SAEs). Most reported only whether any SAEs were identified. SAEs were extremely rarely reported and not limited to active treatment groups. AEs are shown by study in Appendix H.
- No studies assessed differences in adverse events by characteristics of subpopulation.

Detailed Synthesis

Of the 90 studies included in the report, 44 reported adverse events (AEs). A large proportion of these studies declared that no AEs were reported. All AEs are shown in Table 2 by study, type, and number and percent per study arm. In this section, we highlight differences in AEs across study arms of interest. No differences in AEs were reported by any patient characteristics.

The quality of AE reporting was assessed using the McHarms tool. Findings are shown in Appendix F and described in the Discussion section.

Platelet-rich plasma (PRP). Of two studies on PRP that reported on AEs, one reported no serious AEs (SAEs),²⁵ and the other reported a significant increase in pain and stiffness with single injections, which doubled with two injections.²³

Glucosamine with or without Chondroitin. The GAIT trial reported on a large number of AEs, but almost none were observed across study arms. SAEs were rare and as likely to occur in the celecoxib and placebo controls as in glucosamine or chondroitin treatment groups. Notably, withdrawal due to AEs was slightly but probably not significantly higher for chondroitin alone than for any of the other interventions.¹¹⁶ However, a 2-year trial of chondroitin sulfate compared with placebo found no difference in gastrointestinal AEs or withdrawal due to AEs.³⁵ The LEGS trial assessed withdrawals due to blood glucose issues and found no difference from placebo.³⁰

Physical Modalities. No AEs of note were reported among studies of strength or agility training. Mud baths were associated with mild hypotension among 5.66 percent of participants compared with no instances among sham controls.⁶¹

Braces, orthotics, and custom shoes. Among three RCTs that reported on AEs in studies of orthoses (lateral insoles) compared with neutral or no insoles, one reported significantly greater back pain, foot pain, and difficulty with shoe fit, but less knee pain among the lateral insole users.⁹¹

TENS, NMES, and WBV. No differences were seen in AEs between active and control groups.

Weight Loss with or without Exercise. One study of weight loss that tracked a large number of non-SAEs found an increase in minor GI AEs among those in the diet group.⁵⁴

Pain Coping Skills Training (PCST). One study that compared a large number of categories of AEs among participants randomized to a PCST and exercise intervention with those among a group who received only exercise or only PCST found that PCST plus exercise was associated with a lower number of numerous types of AEs than the group that received only exercise.⁴⁵

Discussion

Summary of Key Findings and SoE

The key findings for each intervention appear in the Results section. Table 3 summarizes the findings, conclusions, and strength of evidence ratings that are reported in full in Appendix E.

In general, for the outcomes of interest, findings were insufficient to draw conclusions, or conclusions were supported by low levels of evidence. No conclusions were supported by a high level of evidence. This section highlights findings and conclusions for which we found medium or low-medium, or for which a low SoE was noteworthy.

Cell-based Therapies

RCTs that met inclusion criteria were identified only for platelet rich plasma (PRP). Although we identified only a low strength of evidence for a significant effect of PRP (compared with saline injections) on medium-term pain, the number and size of studies were small .

Glucosamine Chondroitin, Glucosamine, or Chondroitin

No studies were identified that assessed short-term outcomes of dietary supplementation with glucosamine, chondroitin, or the combination. Glucosamine combined with chondroitin showed a significant beneficial effect on medium-term pain. This conclusion is based only on low SoE, because of the number of newer (albeit large) trials and lack of pooling. Moderate levels of evidence from three large trials support no long-term effects of chondroitin sulfate alone on pain.; Chondroitin also failed to show a long-term effect on function and other outcomes, but these findings are supported by only a low level of evidence.

Physical Modalities

Low-level evidence supports a lack of significant short-term benefits of strength/resistance training programs on pain or function (based on 5 pooled RCTs, each). The strength of evidence was low because of inconsistency across the trials and study quality. A significant short-term effect of strength training was seen on total WOMAC across three RCTs, but these studies could not be pooled. The reason for the disparity between effects on WOMAC pain and function and on total WOMAC scores is unclear: two of the three studies that reported total WOMAC scores were also included in the pooled analyses, and these studies themselves reported no difference in pain or function but significant differences in total WOMAC.

Low-level evidence from three pooled studies and three studies that could not be pooled supports a lack of short-term effect of manual therapy (massage, acupressure, self-massage) on pain, function, or WOMAC total scores. However, too few studies assessed similar enough interventions to consider this conclusion to be truly meaningful.

Moderate-level evidence from 3 pooled RCTs supports a short-term beneficial effect of TENS on pain compared with a sham control, but only low-level evidence supports a benefit on function. No significant differences were observed across two RCTs in function scores but a significant difference was observed in the proportion of participants achieving a MCID. Low-level evidence supports a lack of effect of TENS on medium-term outcomes. No RCTs were identified that assessed effects of TENS on long-term outcomes.

Pooled analysis of four RCTs on WBV showed a statistically significant beneficial effect on medium-term function that did not meet the MCID (low SoE). No significant benefit was found for pain.

Weight Loss

For this outcome, we included RCTs and single-arm trials. Moderate-level evidence (based on 2 RCTs and four single-arm trial) supports medium-term benefits of weight loss (with or without exercise) on pain, function, and other outcomes, including total WOMAC and stiffness. Low-level evidence supports a benefit on long-term pain but evidence was insufficient to assess other potential long-term benefits. Too few studies were identified to determine the contribution of exercise.

Self-Management and Home-based Programs

A beneficial effect of self-management and home-based exercise programs on medium-term function is supported by medium SoE. However, only low-level evidence supports a medium-term beneficial effect of both self-management and home-based exercise programs on pain.

Adverse Events

Low-to moderate-level evidence supports a lack of systematic non-serious AEs and SAEs among interventions. Assessment and reporting were inconsistent.

Summary of Findings in Relationship to what is Already Known

Platelet-rich Plasma. The current review identified beneficial short-term effects of PRP. Several 2015 SRs reviewed the effects of PRP, however all prior reviews included studies comparing PRP to hyaluronic acid or corticosteroid injections. We included only studies that compared PRP to saline injections to control for any placebo effect. Thus, we identified too few studies to pool.

Glucosamine with or without Chondroitin. The 2007 SR found no significant benefit for glucosamine, glucosamine plus chondroitin, or chondroitin alone, compared with placebo, based on the large (n=1,583) GAIT trial.

New RCTs identified for this review provided conflicting evidence for effects of supplemental glucosamine, chondroitin, or the combination. A large non-inferiority trial found comparable short-and medium-term effects for glucosamine plus chondroitin compared with NSAIDs, but no long-term effects of either. This trial did not include a placebo control. The 2008 post hoc analysis conducted by the authors of the GAIT trial found that when participants were stratified by baseline pain, those with moderate to severe pain demonstrated a trend toward improvement from glucosamine plus chondroitin (proportion experiencing 20 percent or greater improvement in pain).¹¹⁶ The effect was moderated by the large placebo response. No new trials assessed short- or medium-term effects of glucosamine sulfate alone; three RCTs found no consistent long-term effects on outcomes of interest. Chondroitin showed evidence of short-and medium-term effects but no long-term effects, in three new trials and a long-term followup of the GAIT trial. The

analysis also found that the effect of chondroitin on swelling was seen predominantly in those with less-advanced disease.

Strength and Resistance Training. The 2012 SR found low-level evidence that “strengthening exercise” decreased pain and improved several other outcomes among individuals with OA of the knee, but no evidence for improvement in function was supported. That review did not describe their criteria for categorizing an intervention as a strengthening exercise intervention; therefore we have not attempted to pool studies identified for this report with theirs.

The current review did not identify sufficient evidence to strengthen the findings of the 2012 review on beneficial effects of strength and resistance training on pain and function. However, we identified moderate evidence for a significant beneficial effect on total WOMAC score. This finding seems at odds with the finding of no significant effect on pain and function, two of the three components of the total score. One explanation for this apparent discrepancy may be the larger number of studies that assessed total WOMAC scores, compared with the number of studies that assessed pain and function.

Agility Training. The current report identified evidence from five RCTs that strengthened the findings of the 2012 report on beneficial effects of agility training on long-term pain,¹⁹ as well as providing evidence on short-term benefits for pain and function and long-term function. The current report did not identify evidence to augment the findings of the 2012 report on aerobic exercise, tai chi, or yoga.

Manual Therapy. For the current review, we found low-strength evidence for a lack of beneficial effect of manual therapy on short-term pain, based on three pooled RCTs, but no consistent effects on medium-term pain, function, or other outcomes, likely due to wide variation among the interventions. The 2012 SR reported a low strength of evidence for an effect of massage on function based on two pooled studies (6-13 weeks) and reported improvements in disability and other outcomes based on three unpooled studies.

WBV. The current review identified a significant beneficial effect of WBV on medium-term function but not on medium-term pain, based on pooled analysis of three RCTs (low-strength evidence). Insufficient evidence was found for short- and long-term effects. The 2012 SR did not consider WBV as an intervention, and no other recent high-quality SRs assessed the effects of WBV on pain or function.

TENS and NMES. The current review found a beneficial short-term effect of TENS on pain, based on a MA of three RCTs (moderate-level evidence), but no consistent effects on function and no medium- or long-term effects.

The 2012 SR identified a beneficial effect of electrical stimulation, (including TENS and NMES) on short-term pain, based on meta-analysis of seven RCTs, but no other significant effects of electrical stimulation.¹⁹

Braces and Orthoses, Shoes, and Cane Use. The 2012 SR identified low-level evidence for an effect of orthoses on function.¹⁹ That review did not identify studies on cane use, braces, or shoes.

The current review found no beneficial effects of orthoses on pain or function in pooled analyses. A 2015 Cochrane update review assessed the efficacy of orthoses (including one type of shoe, a custom variable-stiffness shoe) and knee braces.¹¹⁷ That review included only one RCT that was published since the 2012 SR (included in the current review) and, in agreement with the current review, concluded that braces and orthoses had no consistent effects on pain or function.

Other Physical Modalities. The current report did not identify evidence of sufficient strength to augment or contradict the findings of the 2012 SR on tai chi, yoga, ultrasound, PEMF, heat, balneotherapy or mud therapy.¹⁹

Weight Loss. The 2012 SR did not consider the effects of weight loss, and no other systematic reviews were identified that assessed the effects of weight loss on the outcomes of interest for this review.

The current review identified low-moderate evidence from RCTs and single-arm trials supporting a beneficial of weight loss on medium-term pain and function and a low level of evidence supporting a beneficial effect of weight loss on long-term pain. Dose-response effects between weight loss and effect sizes were inconsistent across studies.

Home-based and self-management interventions. The 2012 SR included a number of studies that assessed the effects of home-based or self-management interventions but did not assess these interventions as a category. Two 2015 SRs reviewed the effects of home exercise programs¹¹⁸ and self-management interventions¹¹⁹ for the treatment of OA of the knee or knee conditions in general. These SRs reported positive effects of home exercise programs and self-management programs with exercise on pain and function but noted the heterogeneity of interventions and challenges in study design. Most RCTs of exercise interventions included in the current report expected participants to perform exercises at home, but the studies we analyzed in this category explicitly assessed home-based or self-management programs. These programs showed beneficial effects on medium-term pain and function (low- and moderate-level evidence, respectively).

Adverse Events. The 2007 SR reported that, in general, AEs for glucosamine with or without chondroitin did not differ between treatment and placebo groups, and no SAEs were reported. Likewise, the 2012 SR on physical modalities reported that AEs did not differ significantly between treatment and control groups and did not deter individuals from continued participation in trials. Approximately half of the studies included in the current review reported having assessed AEs. However, this number includes studies that simply reported that no AEs were found. Of the 13 RCTS that mentioned SAEs, most reported no SAEs or SAEs that could not be attributed to the intervention. Of note, AEs associated with glucosamine and chondroitin did not differ between groups in the placebo-controlled or non-inferiority trials. WBV, which was not assessed in the 2012 SR, was not associated with any AEs. PRP was associated with pain and stiffness that increased with the number of injections.

Applicability

The applicability of the results of the trials included in the current review may be somewhat limited for several reasons.

First, the studies of glucosamine and chondroitin used forms and preparations of the dietary supplements that are not available commercially. In addition, the composition and purity of these supplements could be rigorously tested and ensured, unlike most commercial-grade supplements.

Likewise, the studies of PRP each prepared their material using proprietary processes, although at least one publication described the process.

As we discuss further below in the section on limitations of the literature, the results of studies of physical modalities may be influenced heavily by the ability of academic research centers to recruit highly motivated study participants. Even so, much of the success of such interventions in the community is likely to depend on the compliance of patients not only with respect to attending clinic appointments but also with their engaging in regular workouts away from the clinic. Only a

small proportion of the studies were considered community based, and even those tend to attract the most motivated participants.

Limitations of the Evidence Base

Limitations Due to Study Quality. The results of the RoB assessments for each study appear in Table F1 in Appendix F of the report. In the Results section of the full report, we have provided summary RoB scores for each study. The most prevalent limit to study quality was participant blinding: Only 33 of 85 RCTs reported an attempt to blind participants appropriately, using sham injections, placebo pills, sham applications of a treatment such as TENS, or in the case of exercise interventions, a control condition that could be considered an intervention itself. Many RCTs of physical interventions reported that participants were not or could not be blinded. Although outcome assessors were often reported to have been blinded in these studies, many of the outcomes of interest to this report were self-assessed (such as pain and WOMAC function). This lack of blinding significantly limits conclusions we can draw from the literature and is further discussed below in regard to comparators.

Another quality issue is the large number of RCTs for which adequate concealment of allocation could not be ascertained: 46 of 85. The inability to ascertain allocation concealment might sometimes be attributed to word limitations in publications, but is still a concern.

A third quality concern is the finding that 41 studies did not indicate use of intent-to treat analysis; since participants who are not experiencing benefit from treatment are more likely to drop out before study completion, per protocol analysis could artificially inflate apparent effects.

Fourth, 31 RCTs indicated evidence of incomplete adherence. This figure is actually deceptively low, as most interventions involving exercise require that participants work out on their own on days when they are not being supervised. Most studies did not attempt to monitor offsite compliance, and no studies assessed the effect of such compliance or adherence on outcomes.

Finally, Although most studies demonstrated that participants were similar at baseline, some similarities were not routinely considered, such as weight status, or disease stage or severity, and almost no studies stratified outcomes by any baseline characteristics.

Additional Limitations. The applicability of the findings of many of the studies to community settings may be limited by their having been conducted in an academic setting and enrolling highly motivated participants. For this reason, we attempted to assess the effects of home-based interventions; however, these interventions are limited in number, and also tend to be highly supervised. Related to this concern, compliance or adherence was almost never reported.

The applicability of studies of the dietary supplements, glucosamine and chondroitin, may be limited as they either did not report sources, did not ensure purity and concentration of active ingredients, or used forms and preparations that are not available commercially. Likewise, the studies of PRP each prepared their material using proprietary processes, although at least one publication described the process.

Another intervention-related limitation concerns the fact that many studies employed (or failed to prevent) multicomponent interventions. We purposely excluded studies whose multicomponent intervention design precluded assessment of the effect of a single component of interest. However, studies of physical modality interventions often implemented or focused on one type of activity added to a regimen of other activities (with the control group receiving the “other activities” only). In addition, many of the studies permitted continued use of analgesics or other treatments,

preventing attribution of improvement to a specific intervention (or blunting the potential effects of an intervention). This problem is discussed further below.

Duration of interventions and followup was a concern. We limited inclusion to studies with a minimum followup of four weeks, because OA of the knee is a chronic, progressive condition. This decision had several implications; for example, no studies of taping met inclusion criteria, as the follow-up time was usually brief. Also, we did not consider the duration of an intervention as an inclusion criterion (as interventions such as PRP injection have no duration). Thus, the interval between the end of an intervention and outcome assessment, especially medium- or long-term followup, differed across studies. In categorizing studies by the length of followup times for potential pooling, we did not consider the duration of the intervention, itself. This limitation could explain a lack of significant medium- and long-term effects, as few, if any, of the interventions included in this report are thought to have disease-modifying effects that last beyond the intervention.

Another major challenge concerns the choice of study comparators. Contributing to this challenge is the self-reported, subjective nature of pain as an outcome. The placebo effect observed in large placebo-controlled RCTs of glucosamine with or without chondroitin diminished the effect of the active intervention. At the same time, a recent trial comparing glucosamine plus chondroitin to an NSAID found comparable beneficial effects of both. For the current report, we excluded studies that used only comparators of unclear efficacy (e.g., HA as a comparator for PRP) to make it possible to discern the magnitude of the placebo effect. We also excluded studies that used a participant's less-painful knee as the comparator. However, the selection of appropriate comparators is a concern, particularly for studies of physical modalities such as strength training. Many of the studies we included employed usual care as a control; however, as described above, usual care often included a physical therapy program (usually some combination of strength and agility exercises and manipulation). Therefore, the failure to see a difference in outcomes between an intervention and a usual care control group might be attributable to there simply being a limit to the improvement that might be possible over that from standard physical therapy (especially over the often short duration of a study, and without major effort being expended by participants to work out on their own on days they do not attend the study classes). This conclusion is particularly likely, given that most studies that reported no differences in outcomes between interventions and active controls did report significant improvements from baseline. It is unclear what the most appropriate control is for studies of physical modalities or even studies of weight loss that include exercise: the findings of studies that compared diet alone to exercise and to diet plus exercise were difficult to interpret because exercise might have the same beneficial effects as weight loss, and whether they are synergistic or one actually masks the other could not be determined. That some studies used only active comparators while others used only inactive comparators also limited the numbers of studies that could be pooled or even compared.

A number of outcomes of interest were not reported in the included studies or were reported only sporadically. Risk for undergoing TKR was a prespecified outcome of interest in only one RCT. Many factors that cannot be accounted for influence the decision to undergo TKR. Thus, TKR has not proven to be a useful outcome for assessing the effectiveness of interventions.

We ideally hoped to assess the clinical as well as the statistical significance of any beneficial findings. To do so, we would assess whether statistically significant outcomes met a prespecified minimum clinically important difference (MCID). However, we encountered several major challenges in trying to do so. First, some publications failed to include the numerical scales used with their assessment tools. As a result, it was impossible to assess the potential clinical

significance of their findings. Second, published MCIDs depend on the disease severity of the participants; the included studies varied widely in the disease severity of included participants, and some did not report it. Nevertheless, a wide variety of MCIDs have been derived and applied in reviews of similar patient populations (see Appendix I for a summary of published values). We selected and applied one set of values that has been applied in a number of similar reviews¹²⁰ to the small number of statistically significant outcomes for which we had pooled standardized mean differences or for which we were able to identify the numerical measurement scales. But, thirdly, it is important to note that MCIDs are derived by translating patients' responses on a scale of multiple items (e.g., the full WOMAC scale contains 24 items), each item graded using numerical rating scales of 4-100 points, to their response to a small number of subjective anchoring question; thus, their validity continues to be debated.

Finally, because of the heterogeneity among studies with regard to interventions, comparators, outcome measures, durations of treatment and followup, and even reporting of the scales used for some outcome measures, few studies could be pooled. Although, we describe each study narratively in the report, the inability to pool results limits our confidence in the strength of evidence.

Future Research Recommendations

In general, future studies need to enroll sufficient numbers of participants to enable prespecified subgroup analysis according to important participant characteristics and to enable assessment of both statistical and clinical improvement. Studies also need to employ designs that permit assessing the effects of specific interventions and to consider including both active (sham) and passive comparison groups to enable participant blinding. Isolation of the interventions being assessed needs to be accomplished both by careful design of the interventions themselves and by prohibiting participants from using alternative modes of therapy. In addition, many interventions need to be conducted for longer durations and mechanisms need to be developed to better measure compliance. Reported outcomes need to include the percent of participants who experience improvement as well as an estimate of whether the effect size achieves a MCID.

Recent OARSI guidelines on design of clinical trials for knee OA therapies include 25 recommendations. Among them are clear definition (of and rational for) inclusion/exclusion criteria; assessment and reporting of disease severity; ensuring randomization, blinding (to the extent possible), and similarity of important characteristics at baseline; use of validated outcome measures and steps to minimize bias in patient-reported outcomes.¹²¹ Recommendations specific to particular interventions are described below.

Cell-based Therapies: Based on our finding of a significant effect of PRP in a small number of small, high RoB studies, and the number of studies that did not meet inclusion criteria because they compared PRP only to HA, we believe a large, saline-controlled trial is needed. Although corticosteroids could provide an additional comparator for non-inferiority, the immediate adverse effects of intraarticular injection of corticosteroids would be impossible to mask. Residual benefits that remain after the intervention is discontinued (and the effect of follow up treatment) also need to be assessed.

In addition, no studies of stem-cell therapy or other cell-based therapies met inclusion criteria. A large multisite commercial clinic that was contacted for trial results did not respond to the request. Clinicaltrials.gov lists several registered trials of stem-cell treatments for OA of the knee, which should be monitored for published findings. We also identified four published studies of gene therapies (using autologous chondrocytes genetically modified to deliver a growth factor and

designed to be injected intraarticularly), which to date, have been tested only in Phase II trials.¹²²⁻¹²⁵

Glucosamine with or without chondroitin: The 2016 MOVES Trial found significant beneficial medium-term effects on pain, function, stiffness, and quality of life for a prescription form of glucosamine hydrochloride plus chondroitin that were comparable with those of a Cox-2 inhibitor in a large patient population with severe pain. The rate of AEs was relatively small and similar across groups (individuals with cardiovascular conditions were excluded). Thus far, longer-term outcomes have not been reported but would need to be considered in formulating guidelines regarding the use of a prescription grade form of the supplement, especially in light of the findings of the LEGS Trial that glucosamine, chondroitin, and the combination had no beneficial effects at 1 and 2 years compared with placebo. In addition, a head-to-head trial similar to MOVES should be conducted using a combination of glucosamine sulfate and chondroitin, as some evidence has suggested glucosamine sulfate is more effective than glucosamine hydrochloride.

Physical modalities: The studies on strength, agility, and aerobic training that met inclusion criteria usually combined the training modality that was being tested with additional exercises, for example, a strength training intervention would include aerobic exercise as a warm-up and would sometimes include a brief session of exercises aimed at improving agility or gait as well. This design matches the physical therapy regimens in current use and probably makes sense as a therapeutic regimen, but it requires that studies that aim to test a specific modality are carefully designed to ensure that the results can be attributed to the intervention being tested. Other SRs have also noted the difficulty in drawing conclusions regarding the clinical utility of various physical modalities.

The efficacy of individually tailored multicomponent interventions also needs to be assessed but traditional clinical trial methods may not be well-suited to assess such interventions, because testing custom interventions essentially requires that patients serve as their own controls. A number of the trials included in our review modified interventions based on an assessment of individual participant deficits but only one assessed the effects of doing so and found no differences from participants who received a non-tailored therapy.

No studies of aquatherapy, and few studies of yoga or tai chi, met inclusion criteria. Larger trials of these modalities alone compared with both active comparators (to mask the intervention of interest) and waiting list (or other passive) comparators are needed, as they can easily be undertaken by sedentary individuals with no prior training.

OARSI recently published guidelines for the design and conduct of clinical trials of rehabilitation interventions, which include the physical modalities.^{121, 126} Recommendations are similar to those of the OARSI guidelines for assessing interventions for OA of the knee.¹²¹ Emphasis is on participant blinding when possible; assessor blinding; use of both sham (active) and passive comparators; description of baseline severity (with clinical measures, if desired); prespecification of adverse events for assessment; use of valid outcome measures with a benchmark, if possible; and assessment of the percent of participants who achieve improvement. Comparative effectiveness trials are advocated for testing novel treatments against those with established effectiveness or when blinding is not otherwise possible. Caution is suggested in applying published MCIDs, as they have been shown to differ by population and other factors.¹²⁷

Weight Loss: This review showed beneficial effects of weight loss interventions on pain and function. Future studies need to clarify the roles of exercise and self-efficacy education in the observed effect to assess whether exercise and/or self-efficacy have their own effects, independent

of caloric restriction and weight loss or if these co-interventions assist with weight loss and weight maintenance.

The OARSI recently released guidelines on design and conduct of diet and exercise interventions for OA.¹²⁶ Most of the recommendations were similar to those provided for rehabilitation and for OA of the knee interventions in general, in copublications. However, they also provided several additional noteworthy recommendations. These include the need to determine in Phase 1 trials whether high-intensity strength training, aimed at increasing quadriceps muscle strength, is safe in older adults with knee OA. Also recommended is allowing monitored use of rescue medication (analgesics), as weight loss trials tend to be longer in duration than other studies.

Home-based therapies: Our results, based on only a small number of studies, suggest home-based therapies with periodic supervision show beneficial effects on pain and function. This model has the advantage of requiring few clinic visits but the disadvantages of lack of monitoring of compliance and correct form when performing activities. The 2016 SR of home-based therapies by Anwer and colleagues also cites the issue of difficulty assessing compliance with home-based interventions.¹¹⁸ Future research studies of home-based exercise could easily employ any one of a number of fitness monitoring devices to assess adherence and could use applications like Skype to periodically monitor performance.

Adverse effects: Future studies need to prespecify AEs of concern. Researchers need to actively and systematically collect information on adverse effects of interventions at defined intervals, particularly for cell-based therapies and intensive exercise programs.

Finally, because of the heterogeneity among studies with regard to interventions, comparators, outcome measures, and even reporting of the scales used for some outcome measures, few studies could be pooled. Therefore, no attempt could be made to assess whether any pooled effect sizes met or exceeded established MCIDs or MCIIIs. For that reason, when individual studies reported their findings in those terms, we attempted to capture those data.

Conclusions

Among the interventions assessed for efficacy and safety for the management of OA of the knee in this review, several show moderate evidence for beneficial effects on pain or function, including weight loss and home-based and self-management programs, and TENS (for pain only). Interventions that show low or moderate evidence for beneficial effects on short- or medium-term pain or function include platelet-rich plasma, glucosamine-chondroitin, strength training, whole body vibration (on function but not pain). Insufficient evidence was found for other interventions and for additional outcomes, such as stiffness, swelling, quality of life, avoidance of knee replacement, for any outcome.

Larger randomized controlled trials are needed, with more attention to appropriate comparison groups and longer duration, to assess newer therapies and to determine which types of physical modalities are most effective.

Table 2. Summary strength of evidence

Intervention/Outcome	Number, design of studies (and participants if pooling)	Findings (strength of evidence)
KQ 1 Platelet-rich plasma		
Short-term outcomes	2 RCTs	Beneficial effect on pain vs. placebo in one RCT; no difference vs. analgesic in one RCT Beneficial effect on function vs. placebo; Beneficial effect on WOMAC total vs. placebo (Insufficient evidence)
Medium-term pain	4 RCTs	Beneficial effects of single and multiple injections vs. placebo and analgesic (Low SoE)
Medium-term other outcomes	2 RCTs	Beneficial effect on WOMAC function vs. placebo in one RCT; no difference vs. analgesic in one RCT Beneficial effect on WOMAC total vs. placebo (Insufficient evidence)
Long-term outcomes	0 RCTs	(Insufficient evidence)
Glucosamine with or without chondroitin		
<i>Glucosamine plus chondroitin</i>		
Short-term outcomes	0 RCTs	(Insufficient evidence)
Medium-term outcomes	2 RCTs	Beneficial effect on WOMAC pain, function, and stiffness vs. analgesic and placebo (Low SoE)
Long-term outcomes	3 RCTs	No consistent beneficial effect on pain, function, QoL (Low SoE)
<i>Glucosamine</i>		
Short-term outcomes	0 RCTs	(Insufficient evidence)
Medium-term outcomes	0 RCTs	(Insufficient evidence)
Long-term outcomes	3 RCTs and post-hoc analysis	No consistent beneficial effect vs. analgesic or placebo on pain or function at 1-2 years in 3 RCTs but a post hoc analysis of 2 RCTs showed decreased risk for TKR (Low SoE)
<i>Chondroitin-sulfate</i>		
Short-term outcomes	1 RCT	Beneficial effect on pain and function vs. placebo (Low SoE)
Medium-term pain	2 RCTs	Beneficial effect on pain vs. placebo (Low SoE)
Medium-term function	2 RCTs	No beneficial effect on function (vs. placebo) (insufficient evidence)
Long-term pain	3 RCTs	No beneficial effect on pain (moderate evidence)
Long-term function	3 RCTs	No beneficial effect on function (Low SoE)
Strength/resistance Training		
Short-term pain	5 RCTs	No significant beneficial effect vs. educational, other exercise, or no intervention (Low SoE)
Short-term function	5 RCTs	No significant beneficial effect vs. educational, other exercise, or no intervention (Low SoE)
Short-term WOMAC total	3 RCTs	Significant beneficial effect on WOMAC total (Low SoE)
Short-term quality of life	2 RCTs	Significant beneficial effect on quality of life (insufficient evidence)
Medium-term outcomes	2 RCTs	No significant beneficial effect on pain, function, quality of life (insufficient evidence)
Long-term outcomes	1 RCT	Significant beneficial effects in pain and function (insufficient evidence)
Agility Training		
Short-term pain	3 RCTs	Beneficial effect on pain vs. placebo and not different from strength training (Low SoE)

Intervention/Outcome	Number, design of studies (and participants if pooling)	Findings (strength of evidence)
Short-term function	3 RCTs	No consistent beneficial effect on function vs. placebo (insufficient evidence)
Medium-term pain	2 RCTs	No consistent beneficial effect vs. placebo (insufficient evidence)
Long-term outcomes	2 RCTs	No consistent beneficial effect on long-term pain or function (insufficient evidence)
Aerobic Exercise		
Short-term outcomes	0 RCTs	(insufficient evidence)
Medium-term outcomes	0 RCTs	(Insufficient evidence)
Long-term	1 RCT	No beneficial effect on pain or function vs. educational control (insufficient evidence)
Exercise, not specified		
Medium-term outcomes	1 RCT	Exercise had a beneficial effect on pain and function compared with no exercise (insufficient evidence)
Long-term outcomes	2 RCTs	Exercise had inconsistent effects on pain, function, and quality of life compared with no exercise or less exercise (insufficient evidence)
Tai Chi		
Short-term outcomes	2 RCTs	No consistent beneficial effect on pain and inconsistent beneficial effects on function vs. strength training and passive controls (insufficient evidence)
Medium-term outcomes	1 RCT	Significant beneficial effect on pain and function vs. education (insufficient evidence)
Yoga		
Short-term pain	1 RCT	Significant beneficial effect on pain and function vs. wait list control (insufficient evidence)
Manual Therapy		
Short-term pain	3 pooled RCTs, 3 unpooled	No significant beneficial effect of manual therapy on pain (Low SoE)
Short-term function	3 RCTs	No beneficial effect on function (insufficient evidence)
Medium-term outcomes	4 RCTs	No consistent beneficial effects on pain, function or other outcomes (insufficient evidence)
Long-term outcomes	1 RCT	Significant beneficial effect on pain when combined with exercise compared with exercise alone (insufficient evidence)
Balneotherapy and Mud Therapy		
<i>Balneotherapy</i>		
Medium-term pain	2 RCTs	Inconsistent beneficial effect on pain (insufficient evidence)
Medium-term function	2 RCTs	Significant beneficial effect on function, and quality of life, but not stiffness (insufficient evidence)
<i>Topical Mud therapy</i>		
Short-term outcomes	1 RCT	No beneficial effect on pain or function but beneficial effect on stiffness vs. placebo (insufficient evidence)
<i>Mud bath therapy</i>		
Medium-term outcomes	1 RCT	Significant beneficial effect on pain and stiffness vs. usual care (insufficient evidence)
Long-term outcomes	1 RCT	No significant beneficial effects on pain, function, or stiffness (insufficient evidence)
Heat, Infrared, Ultrasound		
Short-term pain	3 RCTs	Heat showed a beneficial effect on pain, comparable to analgesics; infrared showed no beneficial effect on pain vs. placebo; ultrasound plus exercise had a beneficial effect that was comparable with exercise alone (insufficient evidence)

Intervention/Outcome	Number, design of studies (and participants if pooling)	Findings (strength of evidence)
Short-term function	2 RCTs	Heat showed a beneficial effect on function, comparable to analgesics; ultrasound showed no benefit for function, vs. exercise (insufficient evidence)
Long-term outcomes	1 RCT	Continuous and pulsed ultrasound showed no long-term benefit for pain or function vs. sham ultrasound. (in sufficient evidence)
Pulsed Electromagnetic Field		
Short-term outcomes	2 RCTs	Inconsistent effect on pain (insufficient evidence)
Transcutaneous Electrical Nerve Stimulation (TENS)		
Short-term pain	3 RCTs	Significant beneficial effect on pain, exceeding MCID (moderate strength of evidence)
Short-term function	2 RCTs	No beneficial effect on function (Low SoE)
Medium-term outcomes	2 RCTs	No beneficial effect on medium-term outcomes (Low SoE)
Neuromuscular Electrical Stimulation (NMES)		
Short-term	4 RCTs	Inconsistent effects of NMES alone or combined with exercise on short-term pain (insufficient evidence)
Medium-term outcomes	2 RCTs	No beneficial effects of NMES on pain or function (insufficient evidence)
Whole-body Vibration(WBV)		
Short-term outcomes	2 RCTs	Inconsistent effects of WBV-based exercise on pain and function (insufficient evidence)
Medium-term pain	4 RCTs, pooled	No significant beneficial effect on WOMAC pain (low strength of evidence)
Medium-term function	4 RCTs, pooled	Significant beneficial effect on WOMAC function that does not meet an MCID (low strength of evidence) No significant beneficial effect on the 6-minute walk (low strength of evidence)
Braces and Orthoses		
<i>Braces</i>		
Short-term pain	1 RCT	Beneficial effect on VAS pain (insufficient evidence)
Medium-term pain	1 RCT	Beneficial effect on pain (insufficient evidence)
Long-term pain	1 RCT	Beneficial effect on pain (insufficient evidence)
<i>Orthoses</i>		
Short-term pain	4 RCTs	Inconsistent effects on pain (insufficient evidence)
Short-term WOMAC total	3 RCTs	No significant beneficial effect on WOMAC total based on pooled analysis (Low SoE)
Medium-term pain	3 RCTs	No significant beneficial effect on pain based on pooled analysis of 3 RCTs (Low SoE)
Medium-term function	4 RCTs	No beneficial effect on function (insufficient evidence)
Long-term pain	2 RCTs	Inconsistent effects on pain (insufficient evidence)
<i>Custom Shoes</i>		
Medium-term pain	2 RCTs	Inconsistent effects on pain (insufficient evidence)
Medium-term function	1 RCT	Beneficial effect on function (insufficient evidence)
Long-term pain	1 RCT	No beneficial effect on pain (insufficient evidence)
<i>Cane</i>		
Short-term outcomes	1 RCT	Beneficial effect on pain, function, and quality of life (insufficient evidence)
Weight-loss		
Short-term pain and function	1 RCT and 1 single-arm trial	Beneficial effects on pain and function but dose-response not assessed (insufficient evidence)
Medium-term pain	2 RCTs and 4 single-arm trials	Beneficial effect on pain and dose-response demonstrated in 1 trial (Low-moderate evidence)

Intervention/Outcome	Number, design of studies (and participants if pooling)	Findings (strength of evidence)
Medium-term function	3 RCTs and 3 single-arm trials	Beneficial effect on function but inconsistency in one RCT (Low SoE)
Long-term pain	3 RCTs and 1 single-arm trial	Beneficial effect on pain (Low SoE)
Home-based and Self-Management		
Short-term pain	2 RCTs	Significant beneficial effects on pain (Low SoE)
Short-term function	2 RCTs	Inconsistent effects on function (insufficient evidence)
Medium-term pain	3 RCTs self-management	Significant but inconsistent effects on pain (Low SoE)
Medium-term function	3 RCTs self-management	Significant beneficial effects on WOMAC function (moderate evidence)
Medium-term other outcomes	2 RCTs	No effects on WOMAC total or quality of life (insufficient evidence)
Long-term outcomes	1 RCT	No effects on WOMAC pain, function, and other outcomes (insufficient evidence)
Key Question 2 Adverse Events		
Non-serious adverse events	40 RCTs, 1 single arm trial	No systematic non-serious AEs with the exception of minor GI complaints among individuals following low-calorie diets (Low-moderate evidence)
Serious adverse events	13 RCTs	No systematic findings of SAEs by intervention type (Low-moderate evidence)

Abbreviations: BWB=behavioral weight management; CI=confidence intervals; MCID=minimum clinically important difference; MCII=minimum clinically important improvement; MD=mean difference; N/A=not applicable; NMES=neuromuscular electrical stimulation; N/R=not reported; NRS=Numeric Rating Scale; PCST=pain coping skills training; QoL=quality of life; RCT=randomized controlled trial; RoB=risk of bias; SF=short form; SMD=standardized mean difference; ST=strength training; TENS=transcutaneous electrical nerve stimulation; TUG=timed up and go; VAS=visual analog scale; WBV=whole-body vibration; WOMAC=Western Ontario McMaster Osteoarthritis Index

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Abbreviations / Acronyms

BWM	behavioral weight management
CI	confidence intervals
MCID	minimum clinically important difference
MCII	minimum clinically important improvement;
MD	mean difference
N/A	not applicable
NMES	neuromuscular electrical stimulation
N/R	not reported
NRS	Numeric Rating Scale
PCST	pain coping skills training
QoL	quality of life
RCT	randomized controlled trial
RoB	risk of bias
SF	short form
SMD	standardized mean difference
ST	strength training
TENS	transcutaneous electrical nerve stimulation
TUG	timed up and go
VAS	visual analog scale
WBV	whole-body vibration
WOMAC	Western Ontario McMaster Osteoarthritis Index