TREATMENT OF OSTEOARTHRITIS OF THE KNEE

EVIDENCE-BASED GUIDELINE
2ND EDITION

Adopted by the American Academy of Orthopaedic Surgeons
Board of Directors
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Disclaimer
This clinical practice guideline was developed by an AAOS work group comprised of volunteer physicians and interdisciplinary clinicians as well as staff researchers with expertise in systematic reviews and statistical methods used to evaluate empirical evidence. It is an educational tool that integrates the current scientific literature and the proficiency and sound judgment that physicians typically acquire in clinical practice. The recommendations that make up this guideline are not intended to be absolute as patients vary in how they experience symptoms and respond to treatment interventions. There may be variability between patients in practice and those who participate in clinical trials. Medical care should always be based on a physician's expertise that is individually tailored to the patient's circumstances, preferences and rights.

Disclosure Requirement
In accordance with AAOS policy, all individuals whose names appear as authors or contributors to this clinical practice guideline provided full disclosure of and were vetted for potential conflicts of interest prior to the introductory meeting.

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FDA Clearance
Some drugs or medical devices referenced or described in this clinical practice guideline may not have been cleared by the Food and Drug Administration (FDA) or may have been cleared for a specific use only. The FDA has stated that it is the responsibility of the physician to determine the clearance status of each drug or device prescribed in clinical practice.

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SUMMARY OF RECOMMENDATIONS

This summary of the AAOS clinical practice guideline, "Treatment of Osteoarthritis of the Knee" contains a list of the evidence based treatment recommendations and includes only less invasive alternatives to knee replacement. Discussion of how and why each recommendation was developed and the evidence report are contained in the full guideline at www.aaos.org/guidelines. Readers are urged to consult the full guideline for the comprehensive evaluation of the available scientific studies. The recommendations were established using methods of evidence-based medicine that rigorously control for bias, enhance transparency, and promote reproducibility.

The summary of recommendations is not intended to stand alone. Medical care should always be based on a physician's expert judgment and the patient's circumstances, values, preferences and rights. For treatment procedures to provide benefit, mutual collaboration with shared decision-making between patient and physician/allied healthcare provider is essential.

Conservative Treatments: Recommendations 1-6

RECOMMENDATION 1

We recommend that patients with symptomatic osteoarthritis of the knee participate in self-management programs, strengthening, low-impact aerobic exercises, and neuromuscular education; and engage in physical activity consistent with national guidelines.

Strength of Recommendation: Strong

Description: Evidence is based on two or more "High" strength studies with consistent findings for recommending for or against the intervention. A **Strong** recommendation means that the benefits of the recommended approach clearly exceed the potential harm and/or that the quality of the supporting evidence is high.

Implications: Practitioners should follow a **Strong** recommendation unless a clear and compelling rationale for an alternative approach is present.

RECOMMENDATION 2

We suggest weight loss for patients with symptomatic osteoarthritis of the knee and a BMI $\geq$ 25.

Strength of Recommendation: Moderate

Description: Evidence from two or more "Moderate" strength studies with consistent findings, or evidence from a single "High" quality study for recommending for or against the intervention. A **Moderate** recommendation means that the benefits exceed the potential harm (or that the potential harm clearly exceeds the benefits in the case of a negative recommendation), but the quality/applicability of the supporting evidence is not as strong.

Implications: Practitioners should generally follow a **Moderate** recommendation but remain alert to new information and be sensitive to patient preferences.

RECOMMENDATION 3A

We cannot recommend using acupuncture in patients with symptomatic osteoarthritis of the knee.

Strength of Recommendation: Strong

Description: Evidence is based on two or more "High" strength studies with consistent findings for recommending for or against the intervention. A **Strong** recommendation means that the quality of the supporting evidence is high. A harms analysis on this recommendation was not performed.

Implications: Practitioners should follow a **Strong** recommendation unless a clear and compelling rationale for an alternative approach is present.

RECOMMENDATION 3B

We are unable to recommend for or against the use of physical agents (including electrotherapeutic modalities) in patients with symptomatic osteoarthritis of the knee.

Strength of Recommendation: Inconclusive

Description: Evidence from a single low quality study or conflicting findings that do not allow a recommendation for or against the intervention. An **Inconclusive** recommendation means that there is a lack of compelling evidence that has resulted in an unclear balance between benefits and potential harm.

Implications: Practitioners should feel little constraint in following a recommendation labeled as **Inconclusive,** exercise clinical judgment, and be alert for emerging evidence that clarifies or helps to determine the balance between benefits and potential harm. Patient preference should have a substantial influencing role.

RECOMMENDATION 3C

We are unable to recommend for or against manual therapy in patients with symptomatic osteoarthritis of the knee.

Strength of Recommendation: Inconclusive

Description: Evidence from a single low quality study or conflicting findings that do not allow a recommendation for or against the intervention. An **Inconclusive** recommendation means that there is a lack of compelling evidence that has resulted in an unclear balance between benefits and potential harm.

Implications: Practitioners should feel little constraint in following a recommendation labeled as **Inconclusive,** exercise clinical judgment, and be alert for emerging evidence that clarifies or helps to determine the balance between benefits and potential harm. Patient preference should have a substantial influencing role.

RECOMMENDATION 4

We are unable to recommend for or against the use of a valgus directing force brace (medial compartment unloader) for patients with symptomatic osteoarthritis of the knee.

Strength of Recommendation: Inconclusive

Description: Evidence from a single low quality study or conflicting findings that do not allow a recommendation for or against the intervention. An **Inconclusive** recommendation means that there is a lack of compelling evidence that has resulted in an unclear balance between benefits and potential harm.

Implications: Practitioners should feel little constraint in following a recommendation labeled as **Inconclusive,** exercise clinical judgment, and be alert for emerging evidence that clarifies or helps to determine the balance between benefits and potential harm. Patient preference should have a substantial influencing role.

RECOMMENDATION 5

We cannot suggest that lateral wedge insoles be used for patients with symptomatic medial compartment osteoarthritis of the knee.

Strength of Recommendation: Moderate

Description: Evidence from two or more "Moderate" strength studies with consistent findings, or evidence from a single "High" quality study for recommending for or against the intervention. A **Moderate** recommendation means that the benefits exceed the potential harm (or that the potential harm clearly exceeds the benefits in the case of a negative recommendation), but the quality/applicability of the supporting evidence is not as strong.

Implications: Practitioners should generally follow a **Moderate** recommendation but remain alert to new information and be sensitive to patient preferences.

RECOMMENDATION 6

We cannot recommend using glucosamine and chondroitin for patients with symptomatic osteoarthritis of the knee.

Strength of Recommendation: Strong

Description: Evidence is based on two or more "High" strength studies with consistent findings for recommending for or against the intervention. A **Strong** recommendation means that the quality of the supporting evidence is high. A harms analysis on this recommendation was not performed.

Implications: Practitioners should follow a **Strong** recommendation unless a clear and compelling rationale for an alternative approach is present.

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Pharmacologic Treatments: Recommendation 7

RECOMMENDATION 7A

We recommend nonsteroidal anti-inflammatory drugs (NSAIDs; oral or topical) or Tramadol for patients with symptomatic osteoarthritis of the knee.

Strength of Recommendation: Strong

Description: Evidence is based on two or more "High" strength studies with consistent findings for recommending for or against the intervention. A **Strong** recommendation means that the quality of the supporting evidence is high. A harms analysis on this recommendation was not performed.

Implications: Practitioners should follow a **Strong** recommendation unless a clear and compelling rationale for an alternative approach is present.

RECOMMENDATION 7B

We are unable to recommend for or against the use of acetaminophen, opioids, or pain patches for patients with symptomatic osteoarthritis of the knee.

Strength of Recommendation: Inconclusive

Description: Evidence from a single low quality study or conflicting findings that do not allow a recommendation for or against the intervention. An **Inconclusive** recommendation means that there is a lack of compelling evidence that has resulted in an unclear balance between benefits and potential harm.

Implications: Practitioners should feel little constraint in following a recommendation labeled as **Inconclusive,** exercise clinical judgment, and be alert for emerging evidence that clarifies or helps to determine the balance between benefits and potential harm. Patient preference should have a substantial influencing role.

Procedural Treatments: Recommendations 8-11

RECOMMENDATION 8

We are unable to recommend for or against the use of intraarticular (IA) corticosteroids for patients with symptomatic osteoarthritis of the knee.

Strength of Recommendation: Inconclusive

Description: Evidence from a single low quality study or conflicting findings that do not allow a recommendation for or against the intervention. An **Inconclusive** recommendation means that there is a lack of compelling evidence that has resulted in an unclear balance between benefits and potential harm.

Implications: Practitioners should feel little constraint in following a recommendation labeled as **Inconclusive,** exercise clinical judgment, and be alert for emerging evidence that clarifies or helps to determine the balance between benefits and potential harm. Patient preference should have a substantial influencing role.

RECOMMENDATION 9

We cannot recommend using hyaluronic acid for patients with symptomatic osteoarthritis of the knee.

Strength of Recommendation: Strong

Description: Evidence is based on two or more “High” strength studies with consistent findings for recommending for or against the intervention. A **Strong** recommendation means that the quality of the supporting evidence is high. A harms analysis on this recommendation was not performed.

Implications: Practitioners should follow a **Strong** recommendation unless a clear and compelling rationale for an alternative approach is present.

RECOMMENDATION 10

We are unable to recommend for or against growth factor injections and/or platelet rich plasma for patients with symptomatic osteoarthritis of the knee.

Strength of Recommendation: Inconclusive

Description: Evidence from a single low quality study or conflicting findings that do not allow a recommendation for or against the intervention. An **Inconclusive** recommendation means that there is a lack of compelling evidence that has resulted in an unclear balance between benefits and potential harm.

Implications: Practitioners should feel little constraint in following a recommendation labeled as **Inconclusive,** exercise clinical judgment, and be alert for emerging evidence that clarifies or helps to determine the balance between benefits and potential harm. Patient preference should have a substantial influencing role.

RECOMMENDATION 11

We cannot *suggest* that the practitioner use needle lavage for patients with symptomatic osteoarthritis of the knee.

Strength of Recommendation: Moderate

Description: Evidence from two or more "Moderate" strength studies with consistent findings, or evidence from a single "High" quality study for recommending for or against the intervention. A **Moderate** recommendation means that the benefits exceed the potential harm (or that the potential harm clearly exceeds the benefits in the case of a negative recommendation), but the quality/applicability of the supporting evidence is not as strong.

Implications: Practitioners should generally follow a **Moderate** recommendation but remain alert to new information and be sensitive to patient preferences.

Surgical Treatments: Recommendations 12-15

RECOMMENDATION 12

We cannot recommend performing arthroscopy with lavage and/or debridement in patients with a primary diagnosis of symptomatic osteoarthritis of the knee.

Strength of Recommendation: Strong

Description: Evidence is based on two or more "High" strength studies with consistent findings for recommending for or against the intervention. A **Strong** recommendation means that the quality of the supporting evidence is high. A harms analysis on this recommendation was not performed.

Implications: Practitioners should follow a **Strong** recommendation unless a clear and compelling rationale for an alternative approach is present.

RECOMMENDATION 13

We are unable to recommend for or against arthroscopic partial meniscectomy in patients with osteoarthritis of the knee with a torn meniscus.

Strength of Recommendation: Inconclusive

Description: Evidence from a single low quality study or conflicting findings that do not allow a recommendation for or against the intervention. An **Inconclusive** recommendation means that there is a lack of compelling evidence that has resulted in an unclear balance between benefits and potential harm.

Implications: Practitioners should feel little constraint in following a recommendation labeled as **Inconclusive,** exercise clinical judgment, and be alert for emerging evidence that clarifies or helps to determine the balance between benefits and potential harm. Patient preference should have a substantial influencing role.

RECOMMENDATION 14

The practitioner might perform a valgus producing proximal tibial osteotomy in patients with symptomatic medial compartment osteoarthritis of the knee.

Strength of Recommendation: Limited

Description: Evidence from two or more "Low" strength studies with consistent findings, or evidence from a single Moderate quality study recommending for or against the intervention or diagnostic. A **Limited** recommendation means that the quality of the supporting evidence is unconvincing, or that well-conducted studies show little clear advantage to one approach over another.

Implications: Practitioners should exercise clinical judgment when following a recommendation classified as **Limited**, and should be alert to emerging evidence that might counter the current findings. Patient preference should have a substantial influencing role.

RECOMMENDATION 15

In the absence of reliable evidence, it is the opinion of the work group not to use the free-floating (un-fixed) interpositional device in patients with symptomatic medial compartment osteoarthritis of the knee.

Strength of Recommendation: Consensus

Description: The supporting evidence is lacking and requires the work group to make a recommendation based on expert opinion by considering the known potential harm and benefits associated with the treatment. A **Consensus** recommendation means that expert opinion supports the guideline recommendation even though there is no available empirical evidence that meets the inclusion criteria of the guideline's systematic review.

Implications: Practitioners should be flexible in deciding whether to follow a recommendation classified as **Consensus,** although they may give it preference over alternatives. Patient preference should have a substantial influencing role.

INTRODUCTION

OVERVIEW

This clinical practice guideline is based on a systematic review of published studies examining the nonarthroplasty treatment of knee osteoarthritis in adults. It provides recommendations that will help practitioners to integrate the current evidence and clinical practice, and it highlights gaps in the literature in need of future research.

This guideline is intended to be used by appropriately trained physicians and clinicians who manage the treatment of osteoarthritis of the knee. It also serves as an information resource for developers and applied users of clinical practice guidelines.

GOALS AND RATIONALE

The purpose of this clinical practice guideline is to evaluate the current best evidence associated with treatment. Evidence-based medicine (EBM) standards advocate for use of empirical evidence by physicians in their clinical decision making. To assist with access to the large resources of information, a systematic review of the literature in publication between April 2010 and May 2012 has been conducted. It highlights where there is good evidence, where evidence is lacking, and what topics future research will need to target in order to help facilitate evidence-based decision making in the treatment of patients with osteoarthritis of the knee. AAOS staff methodologists assisted the physician/clinician work group in evaluating the existing literature so that they could formulate the following recommendations based on a rigorous systematic process.

Musculoskeletal care is provided in many different settings and by a variety of providers. We created this guideline as an educational tool to guide qualified physicians and clinicians in making treatment decisions that improve the quality and efficacy of care. This guideline should not be construed as including all possible methods of care or excluding acceptable interventions similarly directed at obtaining favorable outcomes. The final decision to use a specific procedure must be made after assessing all concerns presented by the patient and consideration of locality-specific resources.

INTENDED USERS

This guideline is intended to be used by orthopaedic surgeons and other healthcare providers managing patients with osteoarthritis of the knee. It serves as an information resource for medical practitioners. In general, individual practicing physicians and clinicians do not have the resources required to complete a project of comparable scope and duration involving the evaluation of an extensive literature base. The AAOS intends for this guideline to assist treatment providers not only in making clinical decisions with their patients, but also in describing to patients and their loved ones why a selected intervention represents the best available course of treatment.

This guideline is not intended for use as a benefits determination document. It does not cover allocation of resources, business and ethical considerations, and other factors needed to determine the material value of orthopaedic care.

Users of this guideline may also want to consider appropriate use criteria (AUC) related to the treatment of osteoarthritis of the knee. The focus of AUC that the AAOS began developing in 2012 is to determine the appropriateness of clinical practice guidelines for the heterogeneous patient population routinely seen in practice. The best available scientific evidence is synthesized with collective expert opinion on topics where gold standard randomized clinical trials are not available or are inadequately detailed for identifying distinct patient types. When there is evidence corroborated by consensus that expected benefits substantially outweigh potential risks exclusive of cost, a procedure is determined to be appropriate.

Similar to other areas of medicine, evidence for the effectiveness of orthopaedic services is not always identifiable. An important distinction to make is that if available data is lacking or evidence is absent, a recommendation is not assumed to be ineffective. When the AAOS cannot recommend for or against an intervention, available data do not provide empirically-based direction on what course of action is best. If data are absent, medical necessity should prevail especially where the disease, disorder, or condition in question can result in loss of life or limb (which is one reason some recommendations incorporate expert opinion).

The AAOS believes evidence-based medicine is an integral component of treatment decisions and that the best results are predicated on reciprocal communication between the patient and physician and an individualized regimen where risks are minimized and benefits are maximized. Medical expertise that is informed by research and takes into account all possible options increases the likelihood that patients will recover effectively.

PATIENT POPULATION

This guideline is intended for use with adults (ages 19 years and older) who have been diagnosed by a physician with osteoarthritis of the knee and are undergoing treatment.

SCOPE

The scope of this guideline includes nonpharmacologic and pharmacologic interventions for symptomatic osteoarthritis of the knee as well as operative procedures less invasive than knee replacement (arthroplasty). It does not provide recommendations for patients diagnosed with rheumatoid arthritis, osteoarthritis of other joints, or other inflammatory arthropathies.

ETIOLOGY

Osteoarthritis results from an imbalance between breakdown and repair of the tissues in the synovial joint organ and occurs as a result of multiple risk factors including trauma, overuse, and genetic predisposition.

INCIDENCE AND PREVALENCE

The incidence of knee osteoarthritis in the United States is estimated at 240 persons per 100,000 per year.

BURDEN OF DISEASE

Osteoarthritis (of any joint) was the primary diagnosis that led to 11.3 million ambulatory care visits in 2009. It was estimated that 9.9 million adults had symptomatic osteoarthritis of the knee in 2010.

Risk factors of the condition increase with age, especially in women. Anywhere from 6%-13% in men and 7%-19% in women over 45 years of age have osteoarthritis of the knee, suggesting that the risk in women is 45% higher than in men. Genetics, large body mass, certain occupations, repetitive knee bending or heavy lifting, and hereditary vulnerability are other factors that increase one's risk of developing the disease.

EMOTIONAL AND PHYSICAL IMPACT

Older adults with self-reported osteoarthritis visit their physicians more frequently and experience greater functional limitations than others in the same age group. The aging of the baby boomers, rise in rates of obesity, and greater emphasis on staying active among the elderly population suggest that the emotional and physical impact of knee osteoarthritis will continue to be widespread.

POTENTIAL BENEFITS, HARM, AND CONTRAINDICATIONS

Individuals with osteoarthritis of the knee often complain of joint pain, stiffness, and difficulty with purposeful movement. The aim of treatment is to provide pain relief and improve the patient's functioning. Most interventions are associated with some potential for adverse outcomes, especially if invasive or operative. Contraindications vary widely by procedure. Reducing risks improves treatment efficacy and is accomplished through collaboration between patient and physician.

DIFFERENCES BETWEEN THE PRESENT AND PREVIOUS GUIDELINES

This updated clinical practice guideline replaces the first edition that was completed in 2008, "Treatment of Osteoarthritis of the Knee (Non-Arthroplasty)."

There have been changes in the methods used to develop the current guideline including new processes for preventing bias that are outlined in the section, "Preventing Bias in an AAOS Clinical Practice Guideline." We incorporated network meta-analysis to compare pharmaceuticals of interest not evaluated in the published sources, and we have implemented more rigorous methods for evaluating quality and applicability (i.e. generalizability) of included studies.

This update considered the literature that we previously examined as well as the empirical evidence published since the 2008 guideline. Changes in article selection criteria necessitated exclusion of some studies that were included in the first edition. The key differences are explained below.

First, the inclusion of only original research and elimination of secondary analyses explained the major differences in recommendation strengths between the previous and present guidelines. Systematic reviews of the Osteoarthritis Research Society

International[1,2] and Agency for Healthcare Research and Quality (AHRQ) [3] were not included in this revised guideline since they comprised secondary analyses. Similarly, the Annual Reports of the Australian Orthopaedic Association Joint Replacement Registry (2004-2007) were excluded after they no longer met inclusion criteria.

Eliminating systematic reviews as described above resulted in the need to develop a consensus recommendation in place of an evidence-graded recommendation because the previous supporting evidence no longer met inclusion criteria for this guideline.

A requisite four week follow up period and minimum study sample of 30 patients (increased from ten) were the other essential modifications to the selection criteria that changed the database. The complete listing of inclusion criteria for this guideline is detailed in the section, "Study Selection Criteria," (beginning on page 13).

PREVENTING BIAS IN AN AAOS CLINICAL PRACTICE GUIDELINE

Clinical practice guidelines (CPGs) are sometimes met with skepticism because of perceived lack of objectivity. Shaneyfelt and Centor assert that most current guidelines have strayed from those originally intended by the Institute of Medicine (IOM)[4] and that the IOM has been critical of CPG development processes because of questionable adherence to quality standards.[5] The AAOS understands that only high-quality guidelines are credible, and we go to great lengths to ensure the integrity of our evidence analyses. The purpose of this section is to describe the Academy's process. Additional details of how we eliminate bias also appear in the methods section.

The AAOS addresses bias beginning with the selection of work group members. Applicants with financial conflicts of interest (COI) related to the guideline topic cannot participate if the conflict occurred within one year of the start date of the guideline's development or if an immediate family member has, or has had, a relevant financial conflict.

Financial COIs are not the only source of bias that can hamper the systematic development of a guideline. The IOM has noted that long time service on government committees or with private insurers, authorship of articles on guideline-related subjects, and one's personal experiences likewise can cause diminished objectivity.[6]

The AAOS establishes a guideline development team free of COIs. The individuals who conduct the literature searches, evaluate the strength of the included studies, and synthesize the data are vetted prior to formalizing their participation (see Appendix I for a list of the work group members and methodologists involved in the assembly of this guideline). Hirsh and Guyatt[7] assert that involving conflict-free participants is crucial.

Our use of methodologists changes the traditional role of the clinicians involved in guideline development. The members of an AAOS work group serve as the content experts. One of their primary tasks is to frame the scope and provide structure for the systematic review by developing preliminary recommendations (see below for further information). Another task is to develop the selection criteria of studies. The AAOS medical librarian conducts a comprehensive literature search based on the key phrases. Suggestions to include specific articles are not accepted at this time to reduce the subjectivity of ad hoc recommendations.

Research analysts identify the full articles to be recalled and determine whether the inclusion criteria are met for each study. The clinician work group receives a detailed listing of the recalled articles with the reasons for inclusion or exclusion noted, and they make criteria-based modifications that they view as necessary. The purpose of this step is to promote the integrity of the guideline's data set. Differences in perspectives at this stage are reconciled according to what is most clinically and methodologically appropriate. Articles that become included as a result of this step in the literature review are integrated into the data base as part of the empirical evidence.

The methodologists then appraise the quality and applicability[1] of each included study. This step entails coding answers to a series of research-design based questions from which final ratings are aggregated. Determination of the quality and generalizability criteria preceding guideline and recommendation topics selection and the use of an automated coding scheme to quantify scientific merit of each study removes virtually all subjectivity from these ratings. Greater rigor is employed over other evidence grading systems. The definitions of each study grade are operationalized to eliminate the possibility of bias that would likely arise with appraisals that are otherwise not replicable. (See Appendix VI for a complete description.) There are more than 50 grading systems[8] and few among them report the use of adequate safeguards to prevent bias even when rating the highest level of evidence.[6]

The AAOS system is somewhat stringent compared to the GRADE system[9] when it comes to the final determination about the scientific strength of a study. Good interrater reliability is maintained by involving a second reviewer who independently appraises a sampling of 10% of the evidence base. The GRADE system allows the investigator to identify "other sources of bias." Although eliminating bias is essential to appropriately evaluating evidence strength, determinations that occur retrospectively allow for possible *post hoc* criticisms of a study and would potentially diminish the a priori orientation and objectivity of the development of the guideline. The AAOS believes that an emphasis on eliminating bias is prudent and needs to be managed systematically.

The AAOS system, unlike GRADE, also specifically addresses the issue of statistical power (i.e. number of patients enrolled). Low statistical power is a common problem in the medical literature[10] that increases the likelihood of making false negative conclusions. We regard low power studies as very low quality, and do not consider them when formulating a final recommendation.[2]

Similar to the GRADE system, the AAOS will include observational studies after performing evidence syntheses to determine if they constitute the best that is available. We rely on using the best available evidence for substantive value over lower strength findings since higher strength results are less likely to be contradicted in future studies.

When including non-randomized controlled studies, prospective case series that meet a number of other quality-related criteria constitute evidence as is the case in the GRADE system. However, retrospective case series are not incorporated in our systematic reviews under any circumstances. The latter do not establish empirically testable comparisons or relationships a priori, are not based on systematic assignment of patients to treatment groups, and do not appropriately control for measurement bias. Including only prospective case series studies is consistent with our a priori orientation in the evidence grading system used by the AAOS.

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[1] Here we use "quality" as synonymous with "risk of bias" since the same methods are used to evaluate them. Similarly, we use the terms "applicability" and "generalizability" as synonyms.

[2] We include low power studies in meta-analyses since one purpose is to overcome the low power of individual studies.

Also unlike the GRADE system, the AAOS will base recommendations on expert opinion when they concern necessary routine services for which the empirical evidence is lacking or when they are directed at preventing loss of limb or life. A consensus-based recommendation is issued only when the service in question has virtually no associated harm and is of low cost (e.g. a history and physical) or when the absence of direction could have catastrophic consequences. To prevent potential bias in recommendations based on expert opinion, we have established specific rules governing their use.

METHODS

The work group met for the introductory meeting on April 25, 2010 to establish preliminary recommendations and search terms for the guideline's systematic review. A two-day final meeting convened on August 25-26, 2012 where members voted on final recommendations following a review of the evidence, wrote the rationales, and approved the methodological contents of the guideline.

FORMULATING PRELIMINARY RECOMMENDATIONS

Based on their expert views of what works best, with whom, and under what circumstances, the work group's preliminary recommendations establishes the focus of the systematic review and determines the contents for the final conclusions. All preliminary recommendations are worded in the affirmative direction.

Modifications to the preliminary recommendations are not permitted between the introductory and final work group meetings. Only editing in accordance with the best available evidence and AAOS rules for wording recommendations based on evidence strengths are adopted. (See below for a discussion on language construction.) Modifications that require new literature searches or are not evidence-based are also not permitted.

FULL DISCLOSURE INFORMATION

The work group's preliminary recommendations are represented in this guideline and the empirical studies that the analysts examined are cited. The AAOS has always striven for total transparency in the guideline development process.

STUDY SELECTION CRITERIA

We develop *a priori* article inclusion criteria that are our "rules of evidence" for the systematic review and meta-analyses. Articles that did not have the selection characteristics were not eligible to be included as evidence for purposes of this guideline.

To be included an article had to meet the following selection criteria:

- Study was of osteoarthritis of the knee
- Study reported on 80% of the patient population of interest
- Article provided full report of a clinical study
- Retrospective non-comparative case series, medical records review, meeting abstracts, historical articles, editorials, letters, and commentaries were ***excluded***
- Case series studies that gave patients the treatment of interest AND another treatment were ***excluded***
- Case series studies that had non-consecutive enrollment of patients were ***excluded***
- Controlled trials in which patients were not stochastically assigned to groups AND in which there was heterogeneity in patient characteristics or outcomes at baseline AND where the authors did not statistically adjust for these differences when analyzing the results were ***excluded***
- All studies of "Very Limited" evidence strength were ***excluded***

- Composite measures or outcomes were ***excluded*** even if they were patient-oriented
- Case series studies were ***excluded*** if no baseline values were reported
- Study was published in a peer-reviewed journal
- Study had a sample of 30 or more patients per treatment group
- Study was of humans
- Study was published in English
- Study was published during or after 1966
- Study results were presented quantitatively
- Study treatment follow up period was at least 4 weeks
- At least 80% of the enrolled study population were 19 years of age or older
- For any included study that used "paper-and-pencil" outcome measures (e.g. SF-36), only those that were validated were included [unless the outcome was identified *a priori* by the work group in the critical outcomes Delphi round]
- "Paper and pencil" outcomes reported by a single group of investigators (i.e. a single study) were excluded
- Study was in vitro
- Study was not performed on cadavers

When a study's time period was not the same as those examined by the work group (i.e. 0-2 weeks, 2-6 weeks, etc.), assignment was made based on mean duration. If a range rather than the mean was provided, the upper end dictated the duration category. For example, time periods of 0-4 weeks was categorized into "2-6 weeks" (when applicable) as established by the work group.

We did not incorporate systematic reviews, meta-analyses, or other guidelines not specified by the AAOS work group to avoid including studies that did not meet our own criteria for selection. Rather, we recalled individual studies if the abstracts suggested that they might constitute evidence for one of our recommendations and also searched the bibliographies of published systematic reviews for any additional studies that potentially supplemented our evaluation.

BEST EVIDENCE SYNTHESIS

When determining the best available evidence, we first include the highest-strength studies available for the outcomes examined. If there are two or more high-strength studies, the recommendation grade is strong. In this case, moderate- and low- strength evidence do not influence the grade of the recommendation. If there is one high- or at least two moderate- strength studies, the recommendation grade is moderate. If there is one moderate- or at least two low- strength studies, the recommendation grade is limited. Inconclusive recommendation grades are assigned when there is one low-strength study, no evidence, or contradictory findings. In this case, the rules for using expert opinion are not applicable so consensus recommendations are not appropriate. Consensus based recommendations are established only when the strength of the evidence would otherwise be inconclusive and the rules for consensus recommendations apply. See the section on Consensus Recommendations in the guideline (page 21).

OUTCOMES CONSIDERED

The work group identifies the critical outcomes that the recommendations are to be based on prior to the literature search. Measures necessary to determine whether or not medical treatment is effective are deemed critical and are listed in the evidence summary tables immediately following each recommendation. As an example, for Recommendation 12 the critical outcomes were:

- Pain
- Functional status
- Disability
- Other arthritis-related symptoms

Please see "Appendix III: Determining Critical Outcomes" for a detailed description of the AAOS process. Other important, although noncritical, outcomes reported by authors are evaluated as well. We analyzed 149 unique outcomes of which six were critical.

LITERATURE SEARCHES

We begin the systematic review with a comprehensive search of the literature. Articles we consider were published prior to May 2012 in four electronic databases; PubMed, EMBASE, CINAHL, and The Cochrane Central Register of Controlled Trials. The medical librarian conducts the search using key terms determined from the work group's preliminary recommendations.

We supplement the electronic search with a manual search of the bibliographies of all retrieved publications, recent systematic reviews, and other review articles for potentially relevant citations. Recalled articles are evaluated for possible inclusion based on the study selection criteria and are summarized for the work group who assist with reconciling possible errors and omissions.

The study attrition diagram in Appendix IV provides a detailed description of the numbers of identified abstracts and recalled and selected studies that were evaluated in the systematic review of this guideline. The search strategies used to identify the abstracts are contained in Appendix V.

APPRAISING EVIDENCE QUALITY AND APPLICABILITY

QUALITY

As noted earlier, we judge quality based on *a priori* research questions and use an automated numerical scoring process to arrive at final ratings. Extensive measures are taken to determine quality ratings so that they are free of bias.

We evaluate the quality of evidence separately for each outcome reported in every study using research design domains suggested by GRADE work group members and others.[9,11] The GRADE evidence appraisal system is used in the Cochrane Collaboration[12] and has been developed for studies evaluating matched control groups. We incorporate a coding scheme adaptable to all research designs that involves incremental increases for:

- Prospective design (evaluation of a priori hypotheses)
- Adequate statistical power
- Stochastic random assignment of patients to comparison groups
- Sufficient blinding to mitigate against a placebo effect
- Comparability of the patient groups at the beginning of the study
- Delivery of treatment in a manner where observed differences between the comparison groups could reasonably be attributed to the treatment
- Validated outcome measures
- Absence of investigator bias

Each of the above quality domains is rated for possible flaws based on up to four indicator questions that define them. See Appendix VI for a discussion of the AAOS appraisal system. Domains are considered "flawed" if one indicator is coded "No" or at least two defining questions are "Unclear." The Statistical Power domain is considered flawed if sample size is too small to detect at least a small effect size of 0.2.

If there are flawed domains then the evidence quality is downgraded according to the reductions shown in Table 1. As an example, the evidence reported in a randomized controlled trial (RCT) for any given outcome is rated as "High" quality if none of the domains are flawed. If one to two domains are flawed, the rating is reduced to "Moderate." If three or four domains are flawed, the quality of evidence is downgraded to "Low." The quality of evidence is reduced to "Very Low" if five or more domains are flawed. As indicated above, very low quality evidence is not included in this AAOS guideline.

Table 1. Relationship between Quality and Domain Scores for Treatment Studies

Number of Domains With No More Than One "Unclear" Answer	Strength of Evidence
0	High
1-2	Moderate
3-4	Low
>5	Very Low

The following flaws are so detrimental that we appraise the evidence as "Very Low" quality regardless of the computed domain scores.

- Non-consecutive enrollment of patients in a case series
- Case series involving the administration of multiple treatments
- Heterogeneity in outcome measurement
- Low statistical power

Quality is one of two dimensions that determines the strength of the final recommendations.

APPLICABILITY

We rate the applicability (also referred to as "generalizability" or "external validity") of each outcome reported in the studies. As with quality, applicability ratings are based on pre-established indicators that are coded and scored algorithmically. Applicability is rated as "High," "Moderate," or "Low," based on the number of domains that are flawed. A study is rated "High" if none of the domains are flawed, "Low" if all of the domains are flawed, and "Moderate" in all other cases. See Appendix VI for a additional discussion of the AAOS appraisal system

Table 2. Relationship between Applicability and Domain Scores for Treatment Studies

Number of Flawed Domains	Applicability
0	High
1, 2, 3	Moderate
4	Low

Our applicability appraisal system is derived from the PRECIS instrument[21] originally intended for randomized controlled trials but also appropriate for other types of research design. It is comprised of 10 questions that are divided into four domains. The defining characteristics and domains are presented in Table 3.

Table 3. Brief Description of the PRECIS Questions and Domains

Question	Domain
All Types of Patients Enrolled	Participants
Flexible Instructions to Practitioners	Interventions and Expertise
Full Range of Experimental Practitioners	Interventions and Expertise
Usual Practice Control	Interventions and Expertise
Full Range of Control Practitioners	Interventions and Expertise
No Formal Follow-up	Interventions and Expertise
Usual and Meaningful Outcome	Interventions and Expertise
Compliance Not Measured	Compliance and Adherence
No Measure of Practitioner Adherence	Compliance and Adherence
All Patients in Analysis	Analysis

MINIMUM CLINICALLY IMPORTANT IMPROVEMENT

Without consideration of clinical significance to patients, analysis of statistical significance is limited. The latter provides information about sample size and does not quantify the size of the effect that differentiates the treatment groups. Whenever the data is available, we identified minimum clinically important improvement (MCII) treatment effects in addition to statistical significance. The MCII reflects the smallest clinical change that is important to patients and recognizes that there are some treatment-related statistically significant improvements that are too small to be relevant. We incorporated terminology based on Armitage et al.[13] that is outlined in Table 4. See Appendix XIV for a visual presentation of the descriptive terms.

Table 4. Descriptive Terms for Results with MCII

Descriptive Term	Condition for Use
Clinically Significant	Statistically significant and lower confidence limit > MCII
Possibly Clinically Significant	Statistically significant and confidence intervals contain the MCII
Not Clinically Significant	Statistically significant and upper confidence limit < MCII
True Negative Finding	Not statistically significant and upper confidence limit < MCII
Inconclusive Finding	Not statistically significant but confidence intervals contain the MCII

When MCII calculations from the specific guideline patient population are not available, we use thresholds from the most closely related population for which published data exists. Although possible variability between diseases and subjectivity in what patients view as improvement can cause discrepancies, calculations of the MCII based on closely related populations function as a reasonable proxy for evaluating meaningful effects.

The values we used for MCIIs are derived from the published literature. We used the effect sizes reported by Angst et al. to compute the MCII of pain (0.39) and function (0.37) for the WOMAC instrument[14] and calculated effect sizes reported in their data to compute the MCIIs of stiffness (0.39) and total score (0.40).

We also used data from the same study to calculate the effect sizes for the MCIIs of the Short Form-36 (SF-36) bodily pain (0.47), physical function (0.17), and role physical (0.26) composite scores.[15] We used data reported by Tubach et al. to calculate the effect sizes for the MCIIs of the Visual Analog Scale (VAS) pain (1.23) and global assessment (1.0) subscale scores. [16] For all calculated MCIIs, we standardized the effect sizes of the applicable instruments by dividing the minimum clinically important difference from baseline to follow-up by the standard deviation of the mean baseline score.

GRADE OF RECOMMENDATION

The recommendation grades are based on the strengths of evidence and express the confidence one can have in the final recommendations. Grades reflect how likely it is current findings will be replicated in future studies. They are assigned as “Strong,” “Moderate,” or “Limited.”

We base evidence grades on the quality and applicability ratings, whether or not the studies report critical outcomes, and potential harm to patients. More specifically, we begin by setting the strength as equal to the quality of available evidence. High quality evidence is preliminarily rated as “Strong,” moderate quality as “Moderate,” and low quality as “Limited.”The ratings are downgraded if the evidence is: 1) of “Low” applicability; 2) inconsistent (comprised of studies with discrepant findings or a high

degree of heterogeneity in the meta- or network meta- analyses); 3) based on only one study; or, 4) lacking "critical" outcomes. Preliminary recommendation grades are adjusted upward if the evidence is of "High" applicability or if the intervention is associated with decreased likelihood of catastrophic harm (i.e. possible loss of life or limb). In the present guideline, reducing potential harm is the reason that the evidence strength of one recommendation was raised.

DEFINING THE STRENGTH OF THE RECOMMENDATIONS

Judging the strength of evidence is only one step in the process of arriving at the final grade of a guideline recommendation. The overall strength is also based on clinical appropriateness, volume of the evidence, benefit versus potential harm to the patient's well-being, magnitude of treatment effects, and available data on critical outcomes.

It is highly unlikely that future evidence will overturn a recommendation supported by numerous high strength randomized controlled trials that show a large treatment effect. There is a greater likelihood for future evidence to contradict recommendations that are based on a small number of case series. Since RCTs tend to have higher scientific merit, they are usually associated with higher evidence strengths than case series studies.

When determining strength, AAOS staff first assigns a preliminary grade for each recommendation that reflects the quality and applicability ratings as well as volume of the evidence. Work group members then modify the preliminary recommendation strengths using the 'Form for Assigning Strength of Recommendation (Interventions)' shown in Appendix VI. Table 6 on the following page describes the possible grades, definitions, and implications that can be assigned to recommendations.

WORDING OF THE FINAL RECOMMENDATIONS

To prevent bias in the way recommendations are worded, the AAOS uses specific predetermined language stems that are governed by the evidence strengths. The format of guideline language is shown in Table 5.

Table 5. AAOS Guideline Language

Guideline Language Stem	Grade
We ***recommend***	Strong
We ***suggest***	Moderate
The practitioner ***might***	Limited
We are ***unable to recommend for or against***	Inconclusive
In the absence of reliable evidence, the ***opinion*** of this work group is*	Consensus*

*Consensus recommendations are made only if specific criteria are met (see below).

Table 6. Recommendation Strengths, Descriptions, and Clinical Implications

Evidence Rating	Description of Evidence Strength	Implication for Practice
Strong	Evidence is based on two or more "High" strength studies with consistent findings in support of recommending for or against the intervention. A **Strong** (positive) recommendation means that the benefits of the recommended approach clearly exceed the potential harm, and/or that the strength of the supporting evidence is high. A **Strong** (negative) recommendation means that the quality of the supporting evidence is high. A harms analysis on this recommendation was not performed.	Practitioners should follow a **Strong** recommendation unless a clear and compelling rationale for an alternative approach is present.
Moderate	Evidence from two or more "Moderate" strength studies with consistent results, or evidence from a single "High" strength study recommending for or against the intervention. A **Moderate** recommendation means that the benefits exceed the potential harm (or that the potential harm exceeds the benefits in the case of a negative recommendation), but the quality/applicability of the supporting evidence is not as strong.	Practitioners should generally follow a **Moderate** recommendation but remain alert to new information and be sensitive to patient preferences.
Limited	Evidence from two or more "Low" strength studies with consistent results, or evidence from a single Moderate strength study recommending for or against the intervention. A **Limited** recommendation means that the strength of the supporting evidence is unconvincing, or that well-conducted studies show little clear advantage to one approach over another.	Practitioners should exercise clinical judgment when following a recommendation classified as **Limited**, and should be alert to emerging evidence that might negate the current findings. Patient preference should have a substantial influencing role.
Inconclusive	Evidence from a single low strength study or otherwise conflicting evidence that does not allow a recommendation to be made for or against the intervention. An **Inconclusive** recommendation means that there is a lack of compelling evidence that has resulted in an unclear balance between benefits and potential harm.	Practitioners should feel little constraint in following a recommendation labeled as **Inconclusive,** exercise clinical judgment, and be alert for emerging evidence that clarifies or helps to determine the balance between benefits and potential harm. Patient preference should have a substantial influencing role.
Consensus	The supporting evidence is lacking and requires the work group to make a recommendation based on expert opinion by considering the known potential harm and benefits associated with the treatment. A **Consensus** recommendation means that expert opinion supports the guideline recommendation even though there is no available empirical evidence that meets the inclusion criteria in the systematic review.	Practitioners should be flexible in deciding whether to follow a recommendation classified as **Consensus,** although they may give it preference over alternatives. Patient preference should have a substantial influencing role.

CONSENSUS RECOMMENDATIONS

Consensus recommendations are based on expert opinion. While they are prudent in certain instances, their liberal use can cause a source of bias. When the AAOS uses consensus-based recommendations, we follow the procedures described by the U.S. Preventative Services Task Force (USPSTF).[17] In our view, there are only two circumstances that warrant their use. The first is in the case of procedures that have virtually no associated harm, are of relatively low cost, and reflect routine clinical care. The second pertains to medical interventions that potentially prevent loss of life or limb.

In making consensus-based recommendations, work group members consider:

- Preventable burden of disease
- Applications in current practice
- Potential harm that could result from providing a medical service
- Relative difference in costs of a recommended service over alternatives

The AAOS employs additional rules to manage the potential bias that may influence consensus recommendations. First, the rationale cannot contain references to studies that are not a part of the systematic review. Excluded articles are not viewed as evidence. Second, the final recommendation must use the language shown in Table 5 that eliminates stating "we recommend," "we suggest," or "the practitioner might" to avoid confusion with the evidence-based recommendations. Third, the rationale must address any apparent discrepancies in logic with other recommendations. For example, if a guideline does not endorse an intervention in some instances but the work group has nevertheless issued a consensus-based recommendation, the rationale must explain the reason for the descrepancy in decisions.

When a recommendation is equivocal (i.e., when the recommendation reads "we are unable to recommend for or against"), the explanation why cannot contain an implied recommendation. For example, in the case of a new device, drug, or procedure, the work group may not incorporate such statements as, "Although treatment X *appears to be promising*, there is currently insufficient evidence to recommend for or against its use." The italicized phrase implies effectiveness in treatment X when "not being able to recommend for or against" implies that effectiveness remains undetermined.

VOTING ON THE RECOMMENDATIONS

The recommendations and their strengths are voted on using the nominal group technique. We present the details in Appendix VIII. Voting is conducted by secret ballot; work group members are blinded to the responses of the other members. If there is significant disagreement, negotiation takes place and is followed by up to an additional three rounds of voting. If the disagreements cannot be resolved, the applicable recommendation is not adopted. Lack of agreement is a reason some grades might be labeled "Inconclusive."

Formal vote by work group members was used to approve all of the recommendations. Only the work group chair is required to approve the rationales with the editing support of staff unless the evidence grade is consensus. However, the rationales for this guideline

were approved by the entire work group. All components of consensus recommendations require formal vote.

STATISTICAL METHODS

NETWORK META-ANALYSIS

During evidence appraisal of this guideline Bayesian network meta-analyses (also known as mixed treatment comparisons analysis) of randomized controlled trials were preformed to ascertain the comparative effectiveness of analgesic treatments not directly compared in the literature, as explained below. For all interventions connected in one network by pairwise relationships, if there is no direct evidence about two analgesics but they are each compared to the same reference treatment then their relative effectiveness can be estimated based on their computable effects with the common comparator. Both direct and indirect comparisons contribute to the totality of evidence for selecting the best choices of treatment. The mixed treatment comparisons analysis follows methodology described by Lu and Ades[18] using Winbugs version 1.4.

Network meta-analysis assumes that randomization within the individual trials is maintained. Additionally, it is appropriate when interactions and covariates that affect trial AB have similar effects on trial AC, and the same indirect effect BC could be obtained as if it had been evaluated as a true direct effect (i.e. third arm of the RCT). Breaking randomization and permitting effect modifying heterogeneity leads to biased estimates of the indirect comparisons. Consistency, the second important assumption, helps to produce interpretable results along with the similarity requisite. Similarity is required of the treatment effects among studies; consistency addresses the potential for significant variability between the direct and indirect comparisons.

Network meta-analysis requires statistical consistency between the direct and indirect pairwise effects. We use the "back calculation" method as described by Dias et al.[19] summarized as follows. Indirect effect BC is calculated as the difference between direct effects AB and AC and evaluated against the direct effect estimation for BC. The z-statistic for the difference between the direct and indirect effects of BC is compared to a standard normal distribution to test the null hypothesis evaluating consistency. If statistical significance is found, then the model is interpreted as having questionable reliability and is excluded from the data analysis. The results of the tests of statistical consistency between the direct and indirect comparisons of the pairs of analgesics examined in this guideline indicated that the consistency assumption was met; the output summary can be found in Appendix XIII.

Network meta-analysis is based on multiple pairwise comparisons across at least three RCTs that connect at least three interventions where there is at least one closed loop (i.e. common comparator; direct comparison). It is an extension of traditional meta-analysis that incorporates a process where the outcome of a given comparison can affect the next outcome requiring the convergence of Markov chains that is based on this type of sampling. A total of k-1 parameters are estimated that allow for multiple pairwise comparisons across a range of k distributions. The results are assessed by examination of trace plots that graphically display the values a parameter took during the runtime of the

chain. In general, for each network model we performed 100,000 iterations of which the first 50,000 were discarded as "burn in" pre-convergence iterations. Occasionally models required 100,000 burn-in pre-convergence iterations, which resulted in a total of 150,000 iterations.

PLACEBO DATA REGRESSION ANALYSIS

INCLUSION CRITERIA

As part of the studies included in the full guideline, articles that met inclusion criteria for a supplementary osteoarthritis of the knee placebo project were also recalled. Selection criteria included:

- Studies written in English
- Placebo-controlled randomized controlled trial study design evaluating treatment for knee osteoarthritis
- ≥ 80% of participants have osteoarthritis of the knee (or the results for those with knee osteoarthritis reported separately)
- Study reported patient-oriented outcomes (i.e. pain, function, global assessment)
- Study reported sufficient data from the placebo group to perform statistical analysis: baseline and follow-up measures or change from baseline measures, including measures of dispersion (95% confidence interval, standard deviation, or standard error)
- Withdrawal rate of placebo group <20% (measured at each treatment follow up duration)

Because of differences in inclusion criteria between the placebo data project and the full guideline, some articles were included only in the placebo study while others were a part of both. As an example, sample size ≥ 30 was not a selection criterion for the regression analysis but it was for the full guideline.

We searched placebo controlled trials relevant to all the recommendations for the following outcomes: WOMAC pain, stiffness, function, and total subscales, VAS pain, SF-36 role- physical and mental subscales, and the Lequesne Index. The only data available examined the treatment efficacy of osteotomy using the VAS; so only placebo controlled trials that measured change in VAS pain following osteotomy were incorporated.

STATISTICAL ANALYSIS

Data from 48 articles were extracted to predict differences between baseline and treatment scores in the experimental and placebo groups of two case series designed studies. Prais-Winsten regression analysis was conducted using STATA's XTP CSE command used specifically with panel data affected by heteroskedasticity and autocorrelation. Since each observation represented study-level averages of VAS pain scores, the regression was weighted by size of the study samples.

The initial regression model predicted change in VAS pain using pretreatment score, age, percent female, follow up duration in weeks, multicenter study (0 = yes, 1 = no), and allowance for concomitant treatment (0 = no,1 = yes) as independent variables. Blinding was not used as a predictor variable because patients were masked to the treatment assignments in all but one of the studies.

RESULTS

Baseline VAS pain score, age, and duration of treatment follow up were the only statistically significant covariates retained in the final model. For every one point increase in baseline VAS pain score, follow up VAS pain decreased by .32 millimeters ($p < .001$). A study population with baseline VAS pain score = 70 showed more improvement than one with baseline score = 60.

There were negative coefficients that reflected regression to the mean effects. Regression to the mean refers to the tendency for outlying values to become less extreme as large positive values decrease and extreme negative ones increase.

Placebo treatments had a larger effect on study populations of older adults. For every one year increase in age, post treatment VAS pain score decreased by .30 millimeters ($p < .001$). Similarly, VAS pain scores were significantly associated with duration of treatment follow up time. For every one additional week of treatment, VAS pain scores decreased by .123 millimeters ($p < .001$).

The final regression model was:

$$\Delta\text{VAS pain} = 25.83 - .32(\text{baseline VAS score}) - 30(\text{mean age}) - .123(\text{duration})$$

NEW TO META-ANALYSIS IN THIS GUIDELINE: MINIMAL IMPORTANT DIFFERENCE (MID) UNITS

In following the Cochrane Collaboration method of systematic reviews we compute standardized mean differences otherwise referred to as effect sizes, that are reported essentially in standard deviation units. The calculation describes the average change between the treatment and control groups taking into account the degree of dispersion within each of the two groups. Wider variation indicates that patients in both groups report improvements as well as no improvements. Treatment effects are adjusted mathematically to reflect this lower relative responsiveness.

The calculations of MCII that we used were validated based on patients with knee osteoarthritis whose final outcome of treatment was, “good, satisfactory effect with occasional episodes of pain or stiffness.” Final response to treatment anchored by baseline value was calculated for each patient. Our determinations of clinical significance required patients in the studies included in this guideline to achieve a change score comparable to that achieved by 75% of patients reporting good outcomes in the population (which amounted to about half of one likert rating on a five-point likert scale). Knowing the threshold that identifies successfully treated patients, it was possible for us to discern clinically effective from suboptimal treatment effects.

One lesson learned in clinical practice guideline development is that while meta-analysis effectively pools the individual effect sizes by assigning greater weight to studies with less variability and lesser weight to effects where dispersion is higher, there is still heterogeneity in the treatment effects that diminishes their data analytic interpretation and the output does not easily resonate with clinicians to whom they are meant to be relevant.

Since it is the AAOS' intent to develop guidelines for the benefit of patients and healthcare providers, we have incorporated the use of MID units. When reported statistically, effect sizes are interpreted as:

Effect Size	Interpretation
.20	Small
.50	Moderate
.80	Large

Since theses values of are limited usefulness to clinicians, we have also conducted meta-analysis in MID units instead of standard deviation units. Instead of dividing the mean difference between groups of each study by its standard deviation, we divided each mean difference by the MID. The MID is the smallest difference in outcome score that informed patients or proxies perceive as important when considering benefit and potential harm and that would lead the patient or clinician to consider a change in the course of treatment (Guyatt et al.). An MID of one-half of a likert rating on a five-point scale (i.e. equal to our MCII) is comparable to many empirical derivations of the MID [presented by Dr. Guyatt at the *FDA: Minimum Clinically Important Difference (MCID): Defining Outcome Metrics for Orthopaedic Devices* meeting held on November 27 – 28, 2012].

By interpreting effect sizes in MID units, it is possible to assess whether or not an appreciable number of patients achieve clinically important benefits in the outcomes. Degrees of possible efficacy follow a normal distribution so increasingly smaller effects below one MID unit reflect decreasingly lower likelihoods. In this guideline, when the overall treatment effect in meta-analysis was below .5 MID units, we concluded that there was a low likelihood an appreciable number of patients achieved clinically important benefits in the outcomes.

PEER REVIEW

Following the final meeting, the guideline draft undergoes peer review for additional input from external content experts. Written comments are provided on the structured review form (see Appendix IX). All peer reviewers are required to disclose their conflicts of interest.

To guide who participates, the work group identifies specialty societies at the introductory meeting. O*rganizations*, not *individuals*, are specified.

The specialty societies are solicited for nominations of individual peer reviewers approximately six weeks before the final meeting. The peer review period is announced

as it approaches and others interested are able to volunteer to review the draft. The chair of the AAOS committee on Evidence Based Quality and Value reviews the draft of the guideline prior to dissemination.

Some specialty societies (both orthopaedic and non-orthopaedic) ask their evidence-based practice (EBP) committee to provide review of the guideline. The organization is responsible for coordinating the distribution of our materials and consolidating their comments onto one form. The chair of the external EBP committees provides disclosure of their conflicts of interest (COI) and manages the potential conflicts of their members.

Again, the AAOS asks for comments to be assembled into a single response form by the specialty society and for the individual submitting the review to provide disclosure of potentially conflicting interests. The peer review stage gives external stakeholders an opportunity to provide evidence-based direction for modifications that they believe have been overlooked. **Since the draft is subject to revisions until its approval by the AAOS Board of Directors as the final step in the guideline development process, confidentiality of all working drafts is essential.**

The clinical practice guidelines manager drafts the initial responses to comments that address methodology. These responses are then reviewed by the work group chair and vice-chair, who respond to questions concerning clinical practice and techniques. The director of the Department of Research and Scientific Affairs provides input as well. All comments received and the initial drafts of the responses are also reviewed by all members of the work group. All changes to a recommendation as a result of peer review are based on the evidence and undergoes majority vote by the work group members via teleconference. Final revisions are summarized in a detailed report that is made part of the guideline document throughout the remainder of the review and approval processes.

The AAOS believes in the importance of demonstrating responsiveness to input received during the peer review process and welcomes the critiques of external specialty societies. Following final approval of the guideline, all individual responses are posted on our website http://www.aaos.org/research/guidelines/guide.asp with a point-by-point reply to each non-editorial comment. Reviewers who wish to remain anonymous notify the AAOS to have their names de-identified; their comments, our responses, and their COI disclosures are still posted.

Review of the *Treatment of Osteoarthritis of the Knee* guideline was requested of 19 organizations and 18 external content experts were nominated to represent them. Sixteen individuals returned comments on the structured review form (see Appendix X).

PUBLIC COMMENT

After modifying the draft in response to peer reviewers' input, the guideline is circulated for a 30-day public comment period. Public commentators consist of members of the AAOS Board of Directors (BOD), Council on Research and Quality (CORQ), Board of Councilors (BOC), and Board of Specialty Societies (BOS). The guideline draft is customarily sent to the AAOS BOD and CORQ for requested commentary whereas members of the BOC and BOS are solicited in advance for their interest and receive

materials upon request. Additionally, a copy of this guideline is placed online (in a dropbox) and notices are sent to all members of the BOC and BOS instructing them on access during the Public Comment period.

If warranted and based on evidence, the guideline draft is modified in response to the public comments by the AAOS clinical practice guidelines unit and work group members. Changes that are made are summarized, and those who provide comment are informed of the revisions that result from their review. As indicated above and similar to peer review modifications, changes following the public comment period must be based on the evidence. They are detailed in a summary sheet that accompanies the document throughout the final approval process.

During the public comment period, 42 stakeholders returned the structured review form commenting on the clinical practice guideline (see Appendix X).

THE AAOS GUIDELINE APPROVAL PROCESS

The work group submits the final guideline for approval by the Committee on Evidence Based Quality and Value, Council on Research and Quality, and Board of Directors. These decision-making bodies are described in Appendix II and are not designated to modify the contents. Their charge is to approve or reject its publication by majority vote.

REVISION PLANS

This guideline represents a cross-sectional view of the current literature and may become outdated as additional information becomes available. Future editions will be developed in accordance with new evidence, changing practice, rapidly emerging treatment options, and advances in technology. The *Treatment of Osteoarthritis of the Knee 2nd Edition* guideline will be updated or withdrawn in five years in accordance with the standards of the National Guideline Clearinghouse.

GUIDELINE DISSEMINATION PLANS

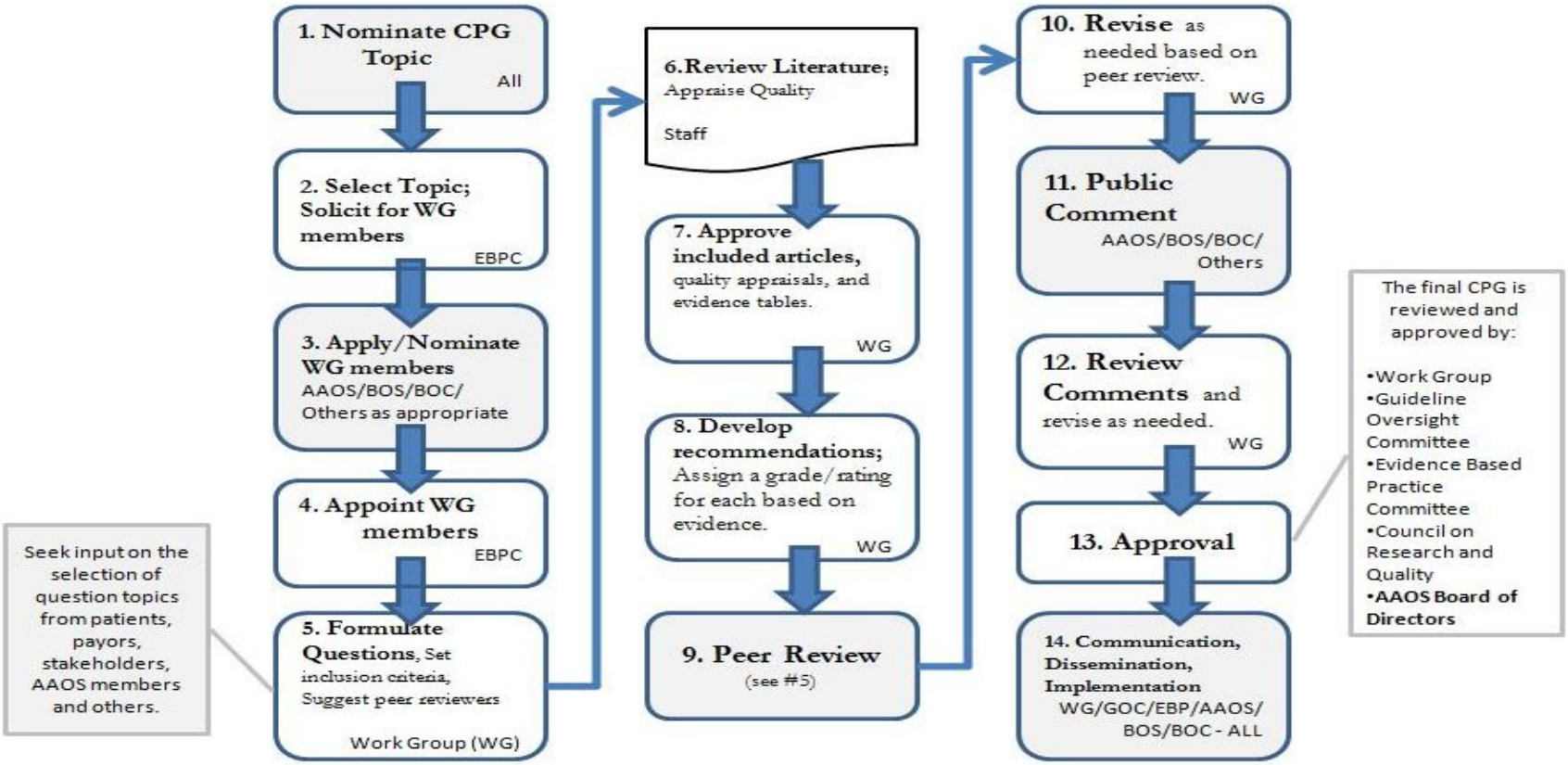
The primary purpose of this guideline is to provide interested readers with comprehensive documentation about our recommendations and the process followed to develop them. All guidelines are available at http://www.aaos.org/research/guidelines/guide.asp.

Shorter versions of the guideline are available in other venues. Publication of a guideline is typically announced during an Academy press release, and published in articles authored by the work group in the Journal of the American Academy of Orthopaedic Surgeons and AAOS *Now*. Most guidelines are also showcased at the AAOS Annual Meeting on Academy Row and as part of the Committee Scientific Exhibits.

Selected guidelines are disseminated by webinar, website, radio, briefings and continuing education. Examples include an online module for the Orthopaedic Knowledge Online website, radio media tours, media briefings, and AAOS' continuing medical education (CME) curriculum and Resource Center.

Other dissemination efforts outside of the AAOS include submission to the National Guideline Clearinghouse and to the Guidelines International Network database, as well as distribution at the annual meetings of other medical specialty societies.

Figure 1. AAOS Clinical Practice Guidelines Development Process



AAOS CLINICAL GUIDELINE ON TREATING OSTEOARTHRITIS OF THE KNEE
GUIDELINE RECOMMENDATIONS

RECOMMENDATION 1
We recommend that patients with symptomatic osteoarthritis of the knee participate in self-management programs, strengthening, low-impact aerobic exercises, and neuromuscular education; and engage in physical activity consistent with national guidelines.

Strength of Recommendation: Strong

Description: Evidence is based on two or more "High" strength studies with consistent findings for recommending for or against the intervention. A **Strong** recommendation means that the benefits of the recommended approach clearly exceed the potential harm and/or that the quality of the supporting evidence is high.

Implications: Practitioners should follow a **Strong** recommendation unless a clear and compelling rationale for an alternative approach is present.

RATIONALE
This recommendation is rated strong because of seven high-strength studies of which five showed beneficial outcomes. The exercise interventions were predominantly conducted under supervision, most often by a physical therapist. The self-management interventions were led by various healthcare providers including rheumatologists, nurses, physical and occupational therapists, and health educators. The evidence supports the use of self-management programs in primary care patients with knee osteoarthritis. One of the studies used an existing evidence-based program, the Arthritis Self-Management Program (ASMP), which was modified to include an exercise component.[20] In a high-strength study by Coleman et al.,[21] patients in a 6-week self-management program demonstrated statistically significant and possibly minimum clinically important improvements in WOMAC Pain, Stiffness, Function, and Total scores at eight weeks as compared to wait-listed controls. The program in that study was based on the same theoretical framework as the ASMP, but included content that was specifically tailored to patients with knee osteoarthritis.

Studies in this review reported improvements in 29 of 37 outcomes favoring strength training over a control (usual care, education, or no treatment). Statistically significant and clinically important improvements were reported for VAS Pain, WOMAC Pain, and WOMAC Function scores.

In addition, 7 of 23 outcomes indicated statistically significant improvements with strengthening exercises, when performed as part of a physical therapy treatment program, versus control. [22-24] Three of the seven outcomes were clinically significant and one was possibly clinically significant. One study reported statistically significant and possibly clinically significant improvement in WOMAC Total score following a combination of knee exercise and manual physical therapy as compared to subtherapeutic ultrasound (control).[25]

Studies also addressed the type and setting for strength training. Long-term outcomes did not vary among isometric, isotonic, or isokinetic exercises.[26] Both weight-bearing and nonweight-bearing exercises were superior to control in improving physical function, however, the results were conflicting when the exercises were compared to each other.[27] High-resistance strength training led to significantly faster walk times on spongy surfaces as compared to low-resistance training[28]. Ebnezar et al.[29-31] compared a combination of yoga and physical therapy to physical therapy alone. All eight outcomes were statistically and clinically significant favoring the combined treatment group measured by WOMAC Function and the SF-36 Physical Function and Bodily Pain subscales. Aquatic therapy was also deemed a suitable alternative to land-based strengthening exercises.[32] Of the three studies that investigated exercise in the home setting, the highest strength study favored home exercise versus no exercise in reducing patients' global pain rating; however, this finding did not meet the minimum clinically important improvement threshold.[33]

Three studies the effects of aerobic walking versus health education and one compared it to usual care in adults with osteoarthritis of the knee. There were statistically significant improvements with aerobic exercise in all but one of the performance-based functional tasks as compared to the education group. In the study by Kovar et al.,[34] favorable outcomes were reported by the supervised walking group rather than usual care with statistically significant improvements in 6-minute walking distance and the Arthritis Impact Measurement Scale (AIMS) Physical Activity and Pain subscales.

For neuromuscular education, three of four outcomes were statistically significant favoring combined kinesthesia, balance, and strength training exercises versus strength training alone. A high-strength study by Fitzgerald et al.[35] applied an effective treatment for anterior cruciate ligament injury to patients with osteoarthritis of the knee; they found that standard exercise combined with agility and perturbation therapy was not more effective than standard exercise therapy alone. Five of five outcomes were statistically significant for proprioception training. Lin et al.[36] randomized 108 patients to nonweight-bearing proprioception training, nonweight-bearing strength training, and non treatment groups. Both proprioception and strength training were significantly more effective in improving WOMAC Pain and Function scores than no treatment.

A number of fitness-related organizations have disseminated guidelines for physical activity. They generally emphasize the importance of aerobic conditioning and muscle- and bone- strengthening, regular activity, and balance exercises for older adults. In 2008, the federal government for the first time published national guidelines. Here is the link to the US Department of Health and Human Service's physical activity guidelines: http://www.health.gov/paguidelines/guidelines/default.aspx.

SUPPORTING EVIDENCE

QUALITY

Relevant Tables: Table 7 Table 22-Table 38

There were nine studies that compared strength training to a control group. Seven of the studies were moderate quality and the remaining two were of low and high quality. Studies by Topp et al.[37] , Huang et al.[26], Jan et al[28]. and Bennell et al.[38] were flawed in the blinding and investigator bias domains. The Shakoor et al.[39] study had investigator bias, but was sufficiently blinded. Topp et al.,[37] Maurer et al.,[40] Azad et al.[41] and Shakoor et al.[39] were flawed in group assignment and group comparability. The Jan et al.[28]study was flawed in the group comparability domain. The Lin et al.[36] study was of high quality and was only flawed by lack of patient blinding. Huang et al.[26] compared isokinetic, isotonic, and isometric strength training. All of the outcomes were of moderate quality. The study was flawed in the blinding and investigator bias domains.

Ettinger et al.[42] compared aerobic exercise and strength training to education programs. Their moderate quality study had uncertain group comparability, as well as flaws in the group assignment and blinding domains.

Lin et al.[36] compared proprioceptive training and strength training to no exercise measuring five outcomes. Their high quality study was only flawed by lack of patient blinding.

Three studies of low, moderate and high quality compared physical therapy to control on six outcomes. Fransen et al.[22] (moderate quality) and Borjesson et al.[21] (low quality) were flawed in group assignment, blinding, and investigator bias. The study by Borjesson et al. was also flawed in group comparability. The high quality Bennell et al.[23] study was not flawed in any domain.

Deyle et al.[25] compared combined exercise and physical therapy to placebo (non therapeutic intensity ultrasound) and was flawed in the group assignment, treatment integrity, and investigator bias domains

Diracoglu et al.[43] compared kinesthesia plus strength training to a control group that received only strength training. All five outcomes that they evaluated were of moderate quality. There were flaws in the group assignment and investigator bias domains.

Teixeira et al.[44] and Fitzgerald et al.[35] compared combined agility and perturbation exercise to standard exercise therapy. Teixeira et al.[44] conducted a low quality retrospective study that was flawed in the hypothesis, group assignment and blinding domains. The Fitzgerald et al. study was of high quality; its only flaw was investigator bias.

Yip et al.[45] studied the efficacy of self-management programs combined with an exercise component. Their moderate quality study was flawed in the group comparability, group assignment, and investigator bias domains. Kovar et al.[34] compared a supervised walking program to usual care; their study was flawed in the same three domains.

Three studies compared aerobic exercise to education. Two studies were assigned low quality ratings. The study by Ettinger et al.[42] was of moderate quality and has been described in a previous paragraph. Focht et al.[46] did not establish a prospective hypothesis

and was flawed in the group assignment, blinding, and investigator bias domains. The study by Rejeski et al.[47] (also of low quality) was determined to have the same flaws.

Home-based exercise programs were evaluated in two high[33;48] and one moderate[49] quality studies. One high quality study[33] compared a home-based exercise program to a group that received no intervention. Its only flaw was that evaluators were not blinded to treatment allocation. The other high[48] and the one moderate[49] quality studies compared hospital-based to home-based exercise programs. Group assignment and group comparability were flawed in the moderate quality study. Potential investigator bias was the only flaw in the high quality study.

A study by Jan et al.[27] of moderate quality compared weight bearing to nonweight-bearing exercise. Although it was sufficiently blinded, was free of investigator bias, used valid measurements, and had treatment integrity, the group assignment and group comparability domains were flawed.

Six outcomes were included from a study by Silva et al.[32] that compared water and land-based exercise treatments. The study was flawed in the group assignment and investigator bias domains, producing a moderate quality rating.

The study by Coleman et al.[21] compared a self-management education program to waitlist control. There were no flaws in the quality domains. Allen et al.[50] compared telephone based self-management to attention control and usual care. In the comparison to attention control, there was uncertain group comparability at baseline and lack of allocation concealment. In the comparison to usual care, the same limitations occurred and the blinding domain was also flawed.

Hurley et al.[51] studied the effect of an integrated exercise, self-management and coping strategies education program in comparison to usual care. This moderate quality study was flawed in the group assignment, group comparability and treatment integrity domains.

Three studies compared yoga plus physiotherapy to a control group that received physiotherapy only. One study by Ebnezar et al.[29] was of high quality, and the other two by Ebnezar et al.[30,31] were low quality studies. The only flaw in the high quality study was possible investigator bias. The two low quality studies were retrospective and were flawed in the blinding, group assignment and group comparability domains.

Ravaud et al.[52] compared a standardized structured physician consultation program to usual care. Their moderate quality study was flawed in the treatment integrity and investigator bias domains.

APPLICABILITY

Relevant Tables: Table 7 Table 22-Table 38

In all the included studies except the one by Bennell et al.[38] there was uncertainty if the treatment administration and those who delivered them represented typical clinical practice. In 27 out of 34 studies, participants may not have been representative of the general patient population. In all but six studies, patient compliance and adherence to the treatment regimens were representative. Thirty out of 34 studies included a sufficient percentage of enrolled patients in the final analysis.

FINAL STRENGTH OF EVIDENCE

Every included study was of moderate applicability. The strength of evidence ratings remained unchanged from the quality ratings for all outcomes.

Table 7. Quality and Applicability Summary: Strength Training Versus Control

Study	Outcome	Duration	Quality	Applicability	Strength of Evidence
Bennell (2010)	WOMAC Function	12 weeks	Moderate	Moderate	Moderate
Bennell (2010)	WOMAC Pain	12 weeks	Moderate	Moderate	Moderate
Bennell (2010)	Stair climb	12 weeks	Moderate	Moderate	Moderate
Bennell (2010)	Number of steps	12 weeks	Moderate	Moderate	Moderate
Huang (2003)	VAS Pain	8 weeks	Moderate	Moderate	Moderate
Huang (2003)	VAS Pain	8 weeks	Moderate	Moderate	Moderate
Huang (2003)	VAS Pain	8 weeks	Moderate	Moderate	Moderate
Huang (2003)	VAS Pain	1 year	Moderate	Moderate	Moderate
Huang (2003)	VAS Pain	1 year	Moderate	Moderate	Moderate
Huang (2003)	VAS Pain	1 year	Moderate	Moderate	Moderate
Huang (2003)	Walk speed m/minute	8 weeks	Moderate	Moderate	Moderate
Huang (2003)	Walk speed m/minute	1 year	Moderate	Moderate	Moderate
Huang (2003)	Lequesne index	8 weeks	Moderate	Moderate	Moderate
Huang (2003)	Lequesne index	1 year	Moderate	Moderate	Moderate
Jan (2008)	Level ground walk time	8 weeks	Moderate	Moderate	Moderate
Jan (2008)	Spongy surface walk time	8 weeks	Moderate	Moderate	Moderate
Jan (2008)	Spongy surface walk time	8 weeks	Moderate	Moderate	Moderate
Jan (2008)	Stair climb	8 weeks	Moderate	Moderate	Moderate
Jan (2008)	Stair climb	8 weeks	Moderate	Moderate	Moderate
Jan (2008)	Figure 8 walk time	8 weeks	Moderate	Moderate	Moderate
Jan (2008)	Figure 8 walk time	8 weeks	Moderate	Moderate	Moderate
Jan (2008)	Level ground walk time	8 weeks	Moderate	Moderate	Moderate
Jan (2008)	WOMAC Pain	8 weeks	Moderate	Moderate	Moderate

Study	Outcome	Duration	Quality	Applicability	Strength of Evidence
Lin (2009)	Level ground walk time	8 weeks	High	Moderate	High
Lin (2009)	Stair walk time	8 weeks	High	Moderate	High
Lin (2009)	Spongy surface walk time	8 weeks	High	Moderate	High
Lin (2009)	WOMAC Pain	8 weeks	High	Moderate	High
Maurer (1999)	WOMAC Pain	8 weeks	Moderate	Moderate	Moderate
Maurer(1999)	WOMAC Total	8 weeks	Moderate	Moderate	Moderate
Topp (2002)*	WOMAC Pain	16 weeks	Low	Moderate	Low
Azad (2011)	WOMAC Total	4 weeks	Moderate	Moderate	Moderate
Azad (2011)	WOMAC Total	5 weeks	Moderate	Moderate	Moderate
Azad (2011)	WOMAC Total	6 weeks	Moderate	Moderate	Moderate
Shakoor (2010)	WOMAC Total	139 weeks	Moderate	Moderate	Moderate
Shakoor (2010)	WOMAC Total	139 weeks	Moderate	Moderate	Moderate
Shakoor (2010)	WOMAC Total	139 weeks	Moderate	Moderate	Moderate

Table 8 Quality and Applicability Summary: Isokinetic Versus Isotonic Versus Isometric Strength Training

Study	Outcome	Duration	Quality	Applicability	Strength of Evidence
Ettinger (1997)	Time to get in and out of car	18 weeks	Moderate	Moderate	Moderate
Ettinger (1997)	Lift and carry task	18 weeks	Moderate	Moderate	Moderate
Ettinger (1997)	6-minute walk distance	18 weeks	Moderate	Moderate	Moderate

Table 9. Quality and Applicability Summary: High Versus Low Resistance Strength Training

Study	Outcome	Duration	Quality	Applicability	Strength of Evidence
Jan (2008)	Stair climb	8 weeks	Moderate	Moderate	Moderate
Jan (2008)	Figure 8 walk time	8 weeks	Moderate	Moderate	Moderate
Jan (2008)	Level ground walk time	8 weeks	Moderate	Moderate	Moderate
Jan (2008)	Spongy surface walk time	8 weeks	Moderate	Moderate	Moderate

Table 10. Quality and Applicability Summary: Isokinetic Versus Isotonic Versus Isometric Strength Training

Study	Outcome	Duration	Quality	Applicability	Strength of Evidence
Huang (2003)	VAS Pain	8 weeks	Moderate	Moderate	Moderate
Huang (2003)	VAS Pain	8 weeks	Moderate	Moderate	Moderate
Huang (2003)	VAS Pain	8 weeks	Moderate	Moderate	Moderate
Huang (2003)	VAS Pain	1 year	Moderate	Moderate	Moderate
Huang (2003)	VAS Pain	1 year	Moderate	Moderate	Moderate
Huang (2003)	VAS Pain	1 year	Moderate	Moderate	Moderate

Table 11. Quality and Applicability Summary: Proprioception Versus Control

Study	Outcome	Duration	Quality	Applicability	Strength of Evidence
Lin (2009)	Level ground walk time	8 weeks	High	Moderate	High
Lin (2009)	Stair walk time	8 weeks	High	Moderate	High
Lin (2009)	Spongy surface walk time	8 weeks	High	Moderate	High
Lin (2009)	WOMAC Pain	8 weeks	High	Moderate	High
Lin (2009)	WOMAC Function	8 weeks	High	Moderate	High

Table 12. Quality and Applicability Summary: Physical Therapy Versus Control

Study	Outcome	Duration	Quality	Applicability	Strength of Evidence
Fransen (2007)	WOMAC Pain	8 weeks	Moderate	Moderate	Moderate
Fransen (2007)	SF-Mental Function	8 weeks	Moderate	Moderate	Moderate
Fransen (2007)	SF-36 Physical	8 weeks	Moderate	Moderate	Moderate
Fransen (2007)	WOMAC Function	8 weeks	Moderate	Moderate	Moderate
Borjesson (1996)	Steps/seconds	5 weeks	Low	Moderate	Low

Study	Outcome	Duration	Quality	Applicability	Strength of Evidence
Borjesson (1996)	Stride length	5 weeks	Low	Moderate	Low
Bennell (2005)	VAS Pain On Movement	12	High	Moderate	High
Bennell (2005)	VAS Pain On Movement	24	High	Moderate	High
Bennell (2005)	WOMAC Pain	12	High	Moderate	High
Bennell (2005)	WOMAC Pain	24	High	Moderate	High
Bennell (2005)	WOMAC Function	12	High	Moderate	High
Bennell (2005)	WOMAC Function	24	High	Moderate	High
Bennell (2005)	Knee Pain Scale Severity	12	High	Moderate	High
Bennell (2005)	Knee Pain Scale Severity	24	High	Moderate	High
Bennell (2005)	Knee Pain Scale Frequency	12	High	Moderate	High
Bennell (2005)	Knee Pain Scale Frequency	24	High	Moderate	High
Bennell (2005)	SF-36 Physical Role	12	High	Moderate	High
Bennell (2005)	SF-36 Physical Role	24	High	Moderate	High
Bennell (2005)	Assessment of Quality of Life index	12	High	Moderate	High
Bennell (2005)	Assessment of Quality of Life index	24	High	Moderate	High
Bennell (2005)	Number of Steps	12	High	Moderate	High
Bennell (2005)	Number of Steps	24	High	Moderate	High
Bennell (2005)	VAS Pain On Movement	12	High	Moderate	High
Bennell (2005)	VAS Pain On Movement	24	High	Moderate	High
Borjesson (1996)	Meters walked per minute	5 weeks	Low	Moderate	Low
Deyle (2000)	WOMAC Total	8 weeks	Moderate	Moderate	Moderate
Deyle (2000)	6-minute walk distance	4 weeks	Moderate	Moderate	Moderate
Deyle (2000)	6-minute walk distance	8 weeks	Moderate	Moderate	Moderate

Table 13. Quality and Applicability Summary: Kinesthesia Plus Strengthening Versus Strengthening Only

Study	Outcome	Duration	Quality	Applicability	Strength of Evidence
Diracoglu (2005)	SF-36 Physical Function	8 weeks	Moderate	Moderate	Moderate
Diracoglu (2005)	SF-36 Role Physical	8 weeks	Moderate	Moderate	Moderate
Diracoglu (2005)	SF-36 Vitality	8 weeks	Moderate	Moderate	Moderate
Diracoglu (2005)	WOMAC Function	8 weeks	Moderate	Moderate	Moderate
Diracoglu (2005)	10m walk	8 weeks	Moderate	Moderate	Moderate

Table 14. Quality and Applicability Summary: Agility Plus Perturbation Versus Standard Exercise Therapy

Study	Outcome	Duration	Quality	Applicability	Strength of Evidence
Fitzgerald (2011)	WOMAC Total	52	High	Moderate	High
Fitzgerald (2011)	WOMAC Function	52	High	Moderate	High
Fitzgerald (2011)	Knee pain (numerical rating scale)	52	High	Moderate	High
Fitzgerald (2011)	Global rating of change	52	High	Moderate	High
Fitzgerald (2011)	Get up and go test	52	High	Moderate	High
Texeira (2011)	When going down stairs?	8	Low	Moderate	Low
Texeira (2011)	When going up stairs?	8	Low	Moderate	Low
Texeira (2011)	Getting up from sitting position	8	Low	Moderate	Low
Texeira (2011)	While standing?	8	Low	Moderate	Low
Texeira (2011)	While bending to the floor?	8	Low	Moderate	Low
Texeira (2011)	When walking on a flat surface?	8	Low	Moderate	Low
Texeira (2011)	While getting in/out of car?	8	Low	Moderate	Low
Texeira (2011)	While going shopping?	8	Low	Moderate	Low

Texeira (2011)	When putting on socks/stockings?	8	Low	Moderate	Low
Texeira (2011)	While getting out of bed?	8	Low	Moderate	Low
Texeira (2011)	When taking off socks/stockings	8	Low	Moderate	Low
Texeira (2011)	While lying in bed?	8	Low	Moderate	Low
Texeira (2011)	When getting in/out of bath?	8	Low	Moderate	Low
Texeira (2011)	While sitting?	8	Low	Moderate	Low

Table 15. Quality and Applicability Summary: Self-Management Plus Exercise Versus Exercise Alone

Study	Outcome	Duration	Quality	Applicability	Strength of Evidence
Yip (2007)	Arthritis Self-Efficacy Pain	16 weeks	Moderate	Moderate	Moderate
Yip (2007)	VAS Pain	16 weeks	Moderate	Moderate	Moderate
Yip (2007)	Hours of light exercise	16 weeks	Moderate	Moderate	Moderate
Yip (2007)	Health Assessment Questionnaire	16 weeks	Moderate	Moderate	Moderate

Table 16. Quality and Applicability Summary: Aerobic Exercise Versus Education

Study	Outcome	Duration	Quality	Applicability	Strength of Evidence
Rejeski (2002)	SF-36 Mental Health	18 months	Low	Moderate	Low
Ettinger (1997)	Lift and carry task time(s)	18 weeks	Moderate	Moderate	Moderate
Ettinger (1997)	Stair climb	18 weeks	Moderate	Moderate	Moderate
Ettinger (1997)	Time to get in/out of car	18 weeks	Moderate	Moderate	Moderate
Ettinger (1997)	Walk distance	18 weeks	Moderate	Moderate	Moderate
Focht (2005)	Stair climb time	18 months	Low	Moderate	Low

Table 17. Quality and Applicability Summary: Home-Based Exercise, Self-Management, and Coping Strategies Versus Usual Care

Study	Outcome	Duration (Weeks)	Quality	Applicability	Strength of Evidence
Hurley (2007)	WOMAC Function	26	Moderate	Moderate	Moderate
Hurley (2007)	WOMAC Pain	26	Moderate	Moderate	Moderate
Hurley (2007)	WOMAC Total	26	Moderate	Moderate	Moderate
Hurley (2007)	Functional Performance time(s)	26	Moderate	Moderate	Moderate
Hurley (2007)	Exercise Health Beliefs Self-Efficacy Subscale	26	Moderate	Moderate	Moderate
Hurley (2007)	Exercise Health Beliefs Total	26	Moderate	Moderate	Moderate
Hurley (2007)	Hospital Anxiety and Depression Scale Depression Subscale	26	Moderate	Moderate	Moderate
Hurley (2007)	Hospital Anxiety and Depression Scale Anxiety Subscale	26	Moderate	Moderate	Moderate
Hurley (2007)	MACTAR	26	Moderate	Moderate	Moderate
Hurley (2007)	EQ-5D	26	Moderate	Moderate	Moderate
Coleman (2012)	WOMAC Pain	8	High	Moderate	High
Coleman (2012)	WOMAC Pain	26	High	Moderate	High
Coleman (2012)	WOMAC Stiffness	8	High	Moderate	High
Coleman (2012)	WOMAC Stiffness	26	High	Moderate	High
Coleman (2012)	WOMAC Function	8	High	Moderate	High
Coleman (2012)	WOMAC Function	26	High	Moderate	High
Coleman (2012)	WOMAC Total	8	High	Moderate	High

Study	Outcome	Duration (Weeks)	Quality	Applicability	Strength of Evidence
Coleman (2012)	WOMAC Total	26	High	Moderate	High
Coleman (2012)	SF-36 Physical Function	26	High	Moderate	High
Coleman (2012)	SF-36 Role Physical	26	High	Moderate	High
Coleman (2012)	SF-36 Body Pain	26	High	Moderate	High
Coleman (2012)	SF-36 General Health	26	High	Moderate	High
Coleman (2012)	SF-36 Vitality	26	High	Moderate	High
Coleman (2012)	SF-36 Social Function	26	High	Moderate	High
Coleman (2012)	SF-36 Role Emotional	26	High	Moderate	High
Coleman (2012)	SF-36 Mental Health	26	High	Moderate	High
Coleman (2012)	SF-36 Physical Function	8	High	Moderate	High
Coleman (2012)	SF-36 Role Physical	8	High	Moderate	High
Coleman (2012)	SF-36 Body Pain	8	High	Moderate	High
Coleman (2012)	SF-36 General Health	8	High	Moderate	High
Coleman (2012)	SF-36 Vitality	8	High	Moderate	High
Coleman (2012)	SF-36 Social Function	8	High	Moderate	High
Coleman (2012)	SF-36 Role Emotional	8	High	Moderate	High
Coleman (2012)	SF-36 Mental Health	8	High	Moderate	High
Allen (2010)	AIMS2 Pain	52	Moderate	Moderate	Moderate
Allen (2010)	AIMS2 Function	52	Moderate	Moderate	Moderate
Allen (2010)	AIMS2 Walking and Bending	52	Moderate	Moderate	Moderate
Allen (2010)	AIMS2 Mobility	52	Moderate	Moderate	Moderate
Allen (2010)	AIMS2 Affect	52	Moderate	Moderate	Moderate

Study	Outcome	Duration (Weeks)	Quality	Applicability	Strength of Evidence
Allen (2010)	Arthritis Self-Efficacy Scale	52	Moderate	Moderate	Moderate
Allen (2010)	VAS Pain	52	Moderate	Moderate	Moderate
O'Reilly (1999)	Global pain score	26	High	Moderate	High
O'Reilly (1999)	VAS walking	26	High	Moderate	High
O'Reilly (1999)	VAS stairs	26	High	Moderate	High
O'Reilly (1999)	SF-36 Physical Function	26	High	Moderate	High
O'Reilly (1999)	SF-36 Mental Health	26	High	Moderate	High
O'Reilly (1999)	Energy	26	High	Moderate	High
O'Reilly (1999)	Health perception	26	High	Moderate	High
O'Reilly (1999)	Role limitation physical	26	High	Moderate	High
O'Reilly (1999)	Role limitation emotional	26	High	Moderate	High
McCarthy (2004)	WOMAC Pain	52	High	Moderate	High
McCarthy (2004)	WOMAC Stiffness	26	High	Moderate	High
McCarthy (2004)	WOMAC Stiffness	52	High	Moderate	High
McCarthy (2004)	VAS Pain	26	High	Moderate	High
McCarthy (2004)	VAS Pain	52	High	Moderate	High
McCarthy (2004)	WOMAC Pain	26	High	Moderate	High
Tunay (2010)	Left knee VAS Rest	6	Moderate	Moderate	Moderate
Tunay (2010)	Left knee VAS Activity	6	Moderate	Moderate	Moderate
Tunay (2010)	Left knee VAS Night	6	Moderate	Moderate	Moderate
Tunay (2010)	Right knee VAS Rest	6	Moderate	Moderate	Moderate
Tunay (2010)	Right knee VAS Activity	6	Moderate	Moderate	Moderate

Study	Outcome	Duration (Weeks)	Quality	Applicability	Strength of Evidence
Tunay (2010)	Right knee VAS Night	6	Moderate	Moderate	Moderate
Tunay (2010)	Proprioception	6	Moderate	Moderate	Moderate
Tunay (2010)	WOMAC Total	6	Moderate	Moderate	Moderate
Tunay (2010)	TUG (sec)	6	Moderate	Moderate	Moderate

Table 18. Quality and Applicability Summary: Water Versus Land-Based Exercises

Study	Outcome	Duration	Quality	Applicability	Strength of Evidence
Silva (2008)	VAS Pain	8 weeks	Moderate	Moderate	Moderate
Silva (2008)	VAS Pain after 50 foot walk	8 weeks	Moderate	Moderate	Moderate
Silva (2008)	VAS Pain after 50 foot walk	8 weeks	Moderate	Moderate	Moderate
Silva (2008)	VAS Pain before 50 foot walk	8 weeks	Moderate	Moderate	Moderate
Silva (2008)	VAS Pain before 50 foot walk	8 weeks	Moderate	Moderate	Moderate
Silva (2008)	Lequesne index	8 weeks	Moderate	Moderate	Moderate

Table 19. Quality and Applicability Summary: Supervised Walking Versus Usual Care

Study	Outcome	Duration	Quality	Applicability	Strength of Evidence
Kovar (1992)	AIMS Arthritis Pain	8 weeks	Moderate	Moderate	Moderate
Kovar (1992)	6 minute walk distance	8 weeks	Moderate	Moderate	Moderate
Kovar (1992)	AIMS Arthritis Impact	8 weeks	Moderate	Moderate	Moderate
Kovar (1992)	AIMS Medications Use	8 weeks	Moderate	Moderate	Moderate
Kovar (1992)	AIMS Physical Activity	8 weeks	Moderate	Moderate	Moderate
Kovar (1992)	AIMS Arthritis Pain	8 weeks	Moderate	Moderate	Moderate

Table 20. Quality and Applicability Summary: Yoga Plus Physiotherapy Versus Physiotherapy Only

Study	Outcome	Duration	Quality	Applicability	Strength of Evidence
Ebnezar (2012)	SF-36 Physical Functioning	13	Low	Moderate	Low
Ebnezar (2012)	SF-36 Role Limitations	13	Low	Moderate	Low
Ebnezar (2012)	SF-36 Emotional Problems	13	Low	Moderate	Low
Ebnezar (2012)	SF-36 Energy/Fatigue	13	Low	Moderate	Low
Ebnezar (2012)	SF-36 Emotional Well-Being	13	Low	Moderate	Low
Ebnezar (2012)	SF-36 Social Function	13	Low	Moderate	Low
Ebnezar (2012)	SF-36 Pain	13	Low	Moderate	Low
Ebnezar (2012)	SF-36 General Health	13	Low	Moderate	Low
Ebnezar (2012)	Resting pain	13	Low	Moderate	Low
Ebnezar (2012)	Early morning stiffness	13	Low	Moderate	Low
Ebnezar (2011)	Walking pain	13	High	Moderate	High
Ebnezar (2011)	WOMAC Function	13	High	Moderate	High
Ebnezar (2011)	Walking time	13	High	Moderate	High

Table 21. Quality and Applicability Summary: Standardized Consultation Versus Usual Care

Study	Outcome	Duration	Quality	Applicability	Strength of Evidence
Ravaud (2009)	SF-12 Mental Function improvement	16 weeks	Moderate	Moderate	Moderate
Ravaud (2009)	SF-12 Physical Function improvement	16 weeks	Moderate	Moderate	Moderate
Ravaud (2009)	WOMAC Function improvement	16 weeks	Moderate	Moderate	Moderate

RESULTS

Relevant Tables: Figure 2-Figure 11, Table 39-Table 67, Figure 12

The results of statistical testing for the comparison of strength training to control (usual care, education, or no treatment) can be found below (Figure 2). Twenty-nine out of 37 outcomes were statistically significant in favor of strength training.

There were three critical outcomes: VAS Pain, WOMAC Pain and WOMAC Function. A total of ten measurements comprised these outcomes and eight showed statistically significant benefits from strength training. Four of the statistically significant critical outcomes were clinically significant, and three were possibly clinically significant.

For VAS Pain, two out of four outcomes were clinically significant showing benefit in strength training. The other two outcomes were possibly clinically significant. Three out of five WOMAC Pain outcomes were statistically significant in favor of strength training. One was clinically significant and another was possibly clinically significant. Clinical importance was unknown for the significant WOMAC Pain outcome in the Topp et al. study because the article did not provide sufficient data to determine it. Also, one WOMAC Function outcome was clinically significant.

A meta-analysis of four studies was computed comparing strength training to control groups in pain outcome. Three of the studies used the visual analogue versions of the WOMAC Pain subscale, and the fourth used the VAS pain scale. The treatment group reported significantly less pain than the control group (see Figure 12). Clinical significance could not be determined since nonidentical pain measures were used in the meta-analysis.

One strength training study investigated treatment effect on WOMAC Function at eight weeks. This study found a clinically significant improvement reported by the strength training group.

VAS pain was evaluated in a study that compared isokinetic, isotonic and isometric strength training. At eight weeks there was a possibly clinically significant treatment effect suggesting isometric strength training was superior to isotonic training. However, at 52 weeks, patients in the isotonic group had lower VAS pain scores than isometric patients although the effect was not clinically significant. VAS pain was significantly lower in the isotonic group than the isokinetic group at week eight, but this difference was not statistically significant at the 52nd week. Isokinetic was significantly more effective at 8 and 52 weeks than isometric strength training although the effect was not clinically significant.

Jan et al.[28]examined the effect of high versus low resistance strength training and found that the high resistance strength training group had a significantly faster spongy surface walk time. The treatment effect was not statistically significant for the timed stair climb or level ground and figure-8 walk times.

Seven out of 23 outcomes showed statistically significant improvement from physical therapy over the control group. Seven of 18 critical outcomes significantly favored physical therapy. Of the seven significant outcomes, three were clinically significant and one was possibly clinically significant. Functional performance tasks, such as number of steps walked per second, stride length, and meters walked per minute were not statistically significant. Additionally, all three outcomes in the study by Deyle et al.[25] were statistically significant endorsing combined manual physical therapy and exercise over the placebo treatment. Finally, only the timed walk outcome out of seven measures was statistically significant in comparisons of home and center based physiotherapy.

Coleman et al.[21] compared a class-based self-management program to waitlist control. Fourteen of 24 outcomes were statistically significant in favor of the treatment group. Pain and function were the critical outcomes. Ten out of 18 functional outcomes and one out of two pain outcomes were significantly improved in the self-management group compared to the control group.

Allen et al.[50]compared a telephone-based self-management program to an attention control group and usual care. The treatment group received written and audio osteoarthritis self-management materials as well as monthly phone calls from a health educator. The health educator discussed self-management strategies and helped the patient develop goal-oriented action plans. The attention control group received general health education materials and phone calls that were not specifically related to osteoarthritis. Compared to the attention control group, osteoarthritis self-management patients reported significantly better VAS pain, AIMS-2 pain, AIMS-2 walking and bending and Arthritis Self-Efficacy scale scores. AIMS-2 function, mobility, and affect scores did not differ statistically. VAS pain scores were lower for patients in the osteoarthritis telephone self-management group than for those who received usual care. However, the AIMS-2 subscales and Arthritis Self-Efficacy scores were not statistically improved over usual care.

One study[27] compared weight bearing and non-weight bearing exercise to a control group using self reported function and functional performance outcomes. Both exercise treatment groups were associated with significantly better scores than the control group. The results comparing weight bearing and non-weight bearing exercise were inconsistent. Patients in the non-weight bearing group were able to climb stairs significantly faster than those in the weight bearing group. However, the weight bearing group produced significantly faster walk times on a spongy surface. All other outcomes did not show statistically significant differences between the two groups.

Three out of four outcomes were statistically significant for combined kinesthesia, balance, and strength training compared to strength training alone in the control group. Two out of three self reported functional outcomes were higher for the treatment group. Ten meter walk times were significantly faster in the kinesthesia plus balance group.

Exercise combined with agility and perturbation therapy was not found to be significantly more effective than exercise therapy alone. Out of 22 outcomes in the Fitzgerald et al. and Teixeira et al. studies, only one was statistically significant for the treatment group.

There was one self reported functional outcome examining the effect of aerobic exercise. Rejeski et al. reported that the exercise group did not have significantly better SF-36 Mental Health scores. However, the aerobic exercise group performed better on all functional tasks except timed stair climb.

Kovar et al.[34] compared a supervised walking program and education to routine care. AIMS Pain and physical activity were significantly better in the walking group than in the control group. AIMS-arthritis impact was not statistically significant, but six minute walking distances were significantly longer for patients in the treatment group.

O'Reilly et al.[33]compared the effect of a home-based exercise program to no intervention. VAS overall pain, VAS pain on walking, VAS pain climbing stairs, and WOMAC function were all statistically significant in favor of the treatment. The improvement in WOMAC function was possibly clinically important. However, the lower confidence limit of each VAS measure was lower than the MCII, meaning home-based exercise did not result in a clinically significant improvement in self reported pain relative to the control group. The study also measured the treatment effects using each subscale of the SF-36 (we excluded SF-36 physical function and bodily pain because they were not sufficiently powered). Each subscale was not significantly different between the treatment and control groups.

McCarthy et al.[48]and Tunay et al.[49]compared home-based and classroom format exercise programs. The former found that supplementing home-based programs with in-class ones resulted in significant improvements in pain and stiffness for patients compared to those who participated in home-based exercise only. The Tunay et al. study, however, did not find hospital-based proprioception and strengthening programs to be more effective than those conducted at home; except when they measured VAS activity score of the left knee.

One study compared the efficacy of water-based exercise programs to land-based programs. The treatment effect for VAS pain before and after walking was not statistically significant at nine weeks, but was significant at 18 weeks. However, the effect was not clinically important. Overall VAS pain and Lequesne index scores were not significantly different for water- and land- based exercise programs.

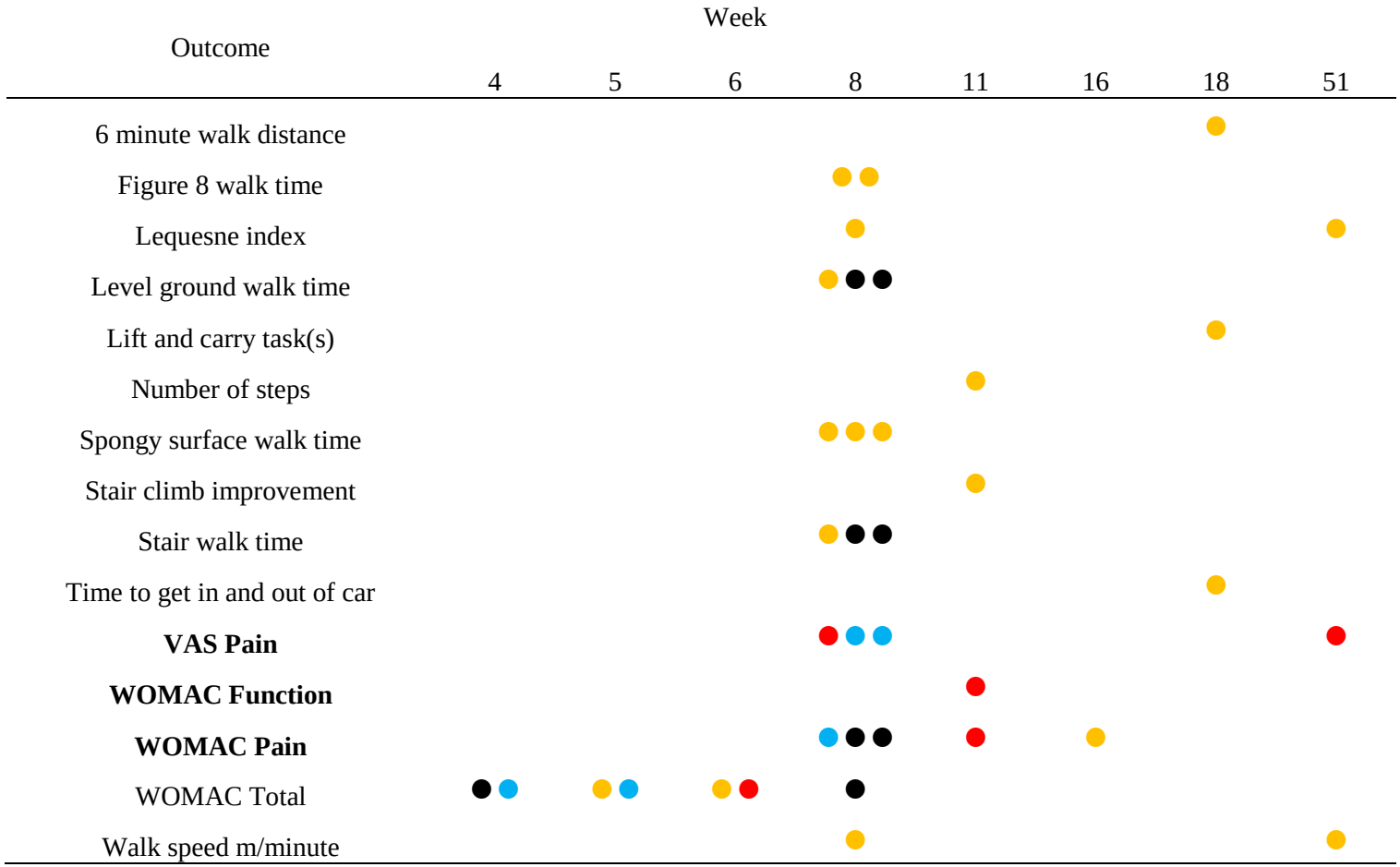
Yip et al.[45] compared self-management plus exercise to usual care. Both pain outcomes were significantly lower in the treatment group. However, the difference in VAS pain was not clinically important. There was not a statistically significant difference in Health Assessment Questionnaire scores, but the treatment group reported significantly higher Arthritis Self-Efficacy Other Symptoms Scores, and spent a greater number of hours exercising per week.

Figure 8 contains the summary of results for the effect of a standardized structured physician consultation program that focused on educating the patient in osteoarthritis treatment, exercises, and weight loss. Three critical outcomes are presented: SF-12 Mental function, SF-12 Physical Function and WOMAC Function. While the effect of education on mental function was clinically significant, the other two critical outcomes were not statistically significant.

Hurley et al.[51] studied found that a program integrating exercise with self-management and coping strategies education resulted in statistically significant improvements over the control group in seven out of ten outcomes. The treatment effects for WOMAC Pain function and total scores were possibly clinically important.

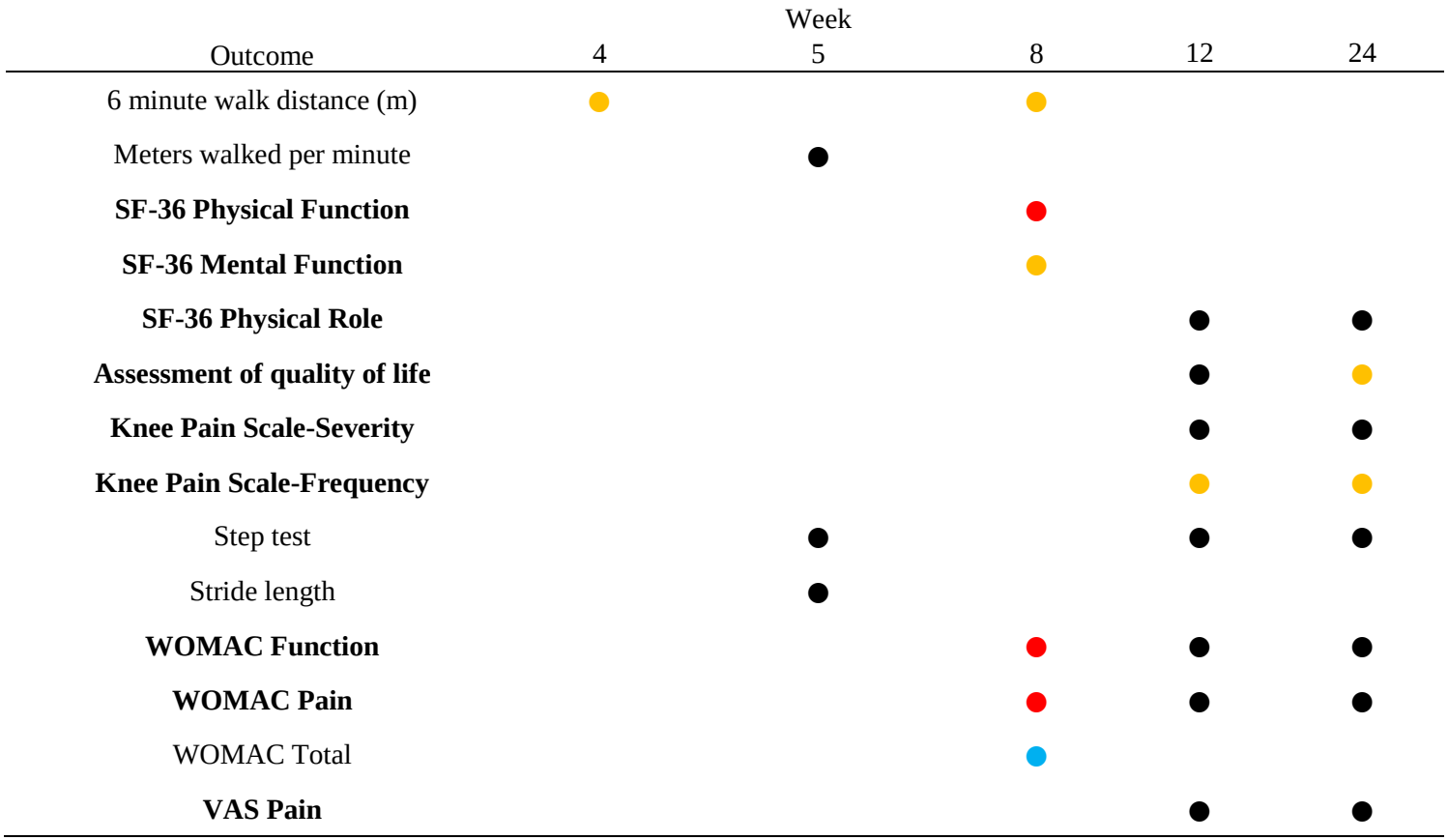
Ebnezar et al.[29-31] compared a group undergoing yoga and physiotherapy to a control group that only received physiotherapy. All eight outcomes were significantly higher in the treatment group. The treatment effects for WOMAC function, SF-36 physical function and pain were clinically significant.

Figure 2. Results Summary: Strength Training Versus Control



Key: ●=Not Significant; ●=Statistically Significant; ●=Possibly Clinically Important; ●=Clinically Significant

Figure 3. Results Summary: Physical Therapy



Key: ●=Not Significant; ●=Statistically Significant; ●=Possibly Clinically Important; ●=Clinically Significant

Symbols with bold lettering indicate a critical outcome.

Figure 4. Results Summary: Proprioception Versus Control

	Outcome	Week 8
Proprioceptive Training	WOMAC Pain	🔴
	Walk time- level ground	🟡
	WOMAC Function	🔴
	Spongy surface walk time	🟡
	Stair climb walk time	🟡

Key: 🟡=Statistically significant; 🔴 =Clinically significant

Figure 5. Results Summary: Agility and Perturbation Training Plus Usual Exercise Versus Exercise Only

Outcome	Week 8	52
WOMAC Total		●
WOMAC Function		●
Knee pain (numerical rating scale)		●
Global rating of change		●
Get up and go test		●
WOMAC Function Subscale: Get up and go test	●	
WOMAC Function Subscale: When walking down the stairs?	●	
WOMAC Function Subscale: When going up stairs?	●	
WOMAC Function Subscale: Getting up from sitting position	●	
WOMAC Function Subscale: While standing?	●	
WOMAC Function Subscale: While bending to the floor?	●	
WOMAC Function Subscale: When walking on a flat surface?	●	
WOMAC Function Subscale: While getting In/out of car?	●	
WOMAC Function Subscale: While going shopping?	●	
WOMAC Function Subscale: When putting on socks/stockings?	●	
WOMAC Function Subscale: While getting out of bed?	●	
WOMAC Function Subscale: When taking off socks/stockings?	●	
WOMAC Function Subscale: While lying in bed?	●	
WOMAC Function Subscale: When getting in/out of bath?	●	
WOMAC Function Subscale: While sitting?	●	
WOMAC Function Subscale: When getting on/off toilet?	●	
WOMAC Function Subscale: Doing heavy household chores?	●	
WOMAC Function Subscale: Doing light household chores?	●	

Key: ● =Not Significant; ● =Statistically Significant

Figure 6. Results Summary: Kinesthesia Versus Control

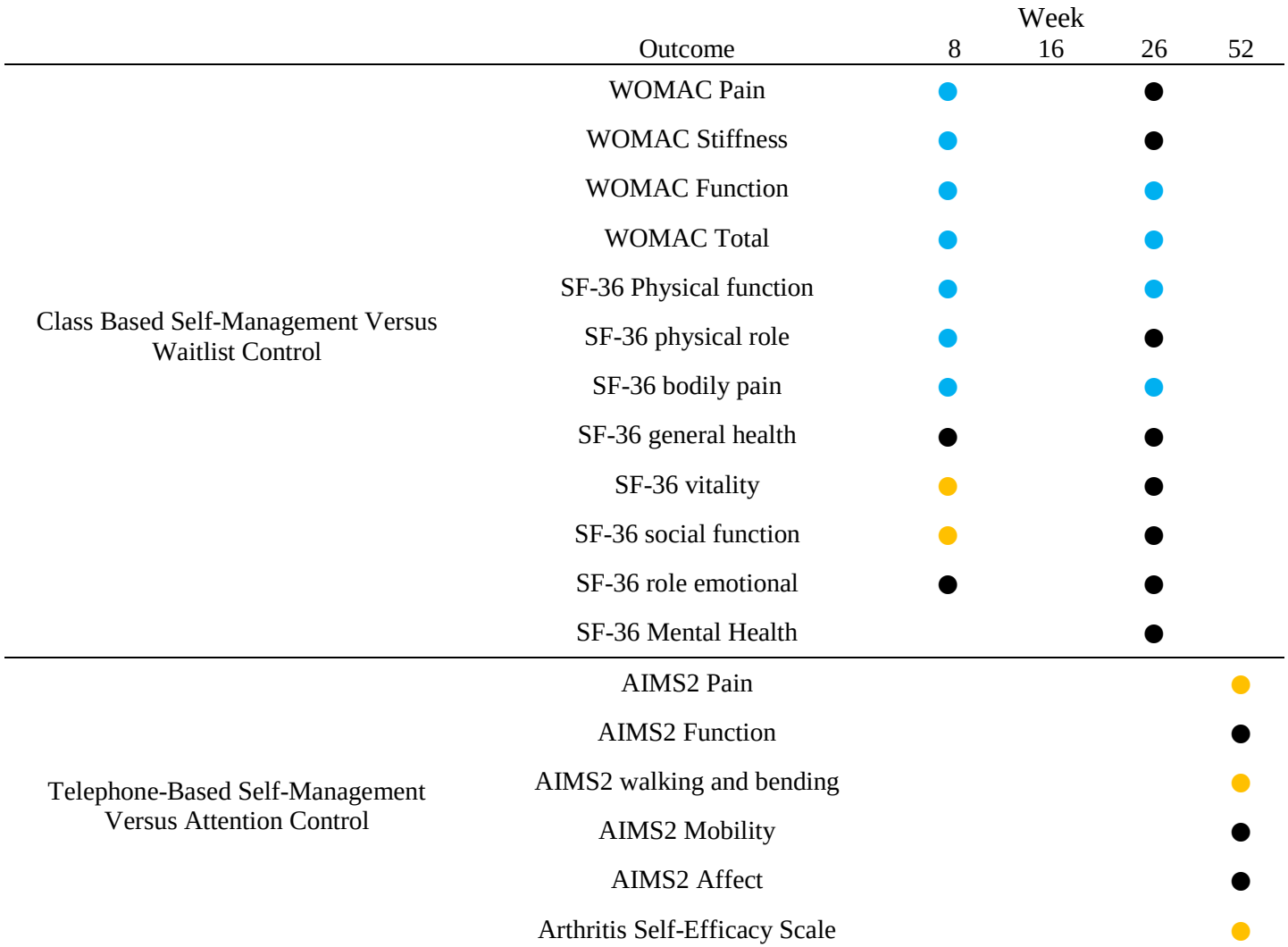
Key: ●=Not Significant; ●=Statistically Significant; ●=Clinically Significant

Figure 7. Results Summary: Exercise Versus Control

		Week					
	Outcome	4	5	6	8	18	78
Aerobic Exercise	SF-36 Mental Health						●
	Lift and carry task time(s)					●	
	Stair climb					●	
	Time to get in and out of car					●	
	Walk distance					●	
	Stair climb time						●
Supervised Walking	AIMS Arthritis Pain				●		
	AIMS Physical Activity				●		
	AIMS Arthritis Impact				●		
	6 minute walk distance				●		
	AIMS Medications Use				●		

Key: ● = Not Significant; ● = Statistically Significant

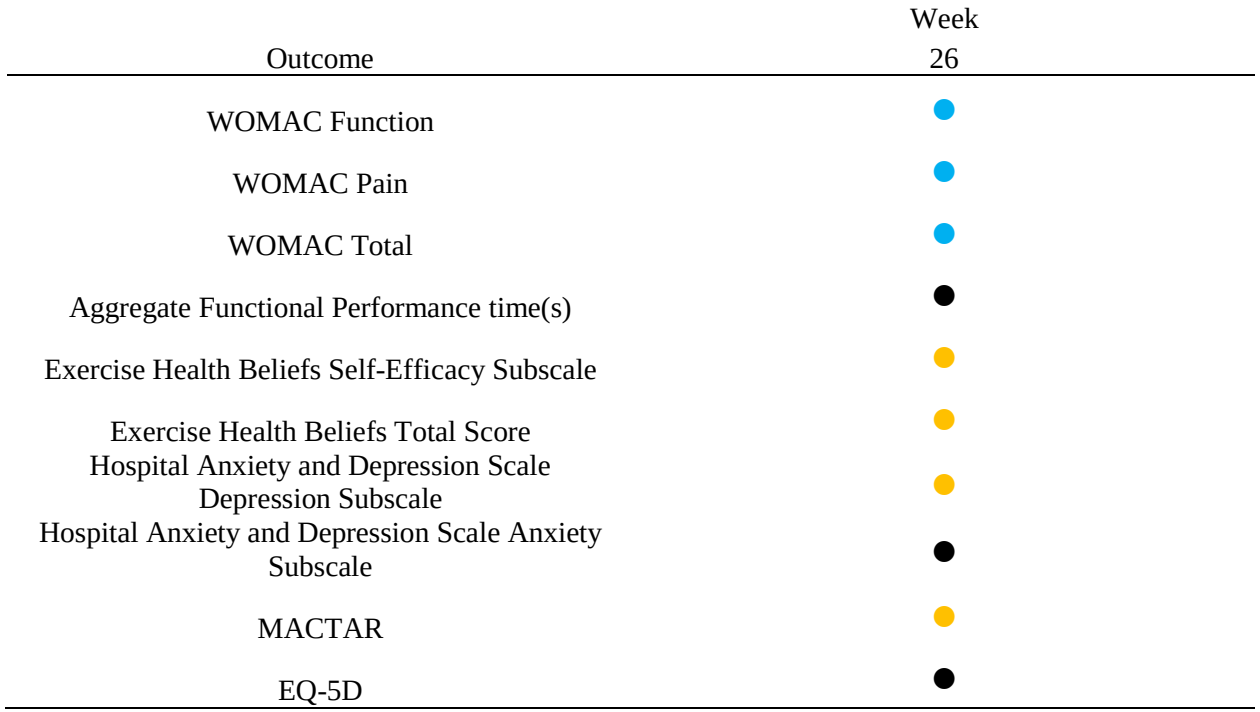
Figure 8. Self-Management and Structured Consultation Versus Control



	VAS Pain	🟡
Telephone-Based Self-Management Versus Usual Care	AIMS2 Pain	⚫
	AIMS2 Function	⚫
	AIMS2 walking and bending	⚫
	AIMS2 Mobility	⚫
	AIMS2 Affect	⚫
	Arthritis Self-Efficacy Scale	⚫
	VAS Pain	🟡
Self-Management Plus Exercise Versus Usual Care	Health Assessment Questionnaire improvement	⚫
	Arthritis Self-Efficacy: Other Symptoms improvement	🟡
	Hours of light exercise improvement	🟡
	Arthritis Self-Efficacy: Pain Score improvement	🟡
	VAS Pain improvement	⚪
Structured Consultation Versus Control: Function	SF-12 Mental Function improvement	🟡
	SF-12 Physical Function improvement	⚫
	WOMAC Function improvement	⚫

Key: ⚫=Not Significant; 🔵= Possibly Clinically Important; 🟡= Statistically Significant; ⚪= Statistically Significant But Not Clinically Important

Figure 9. Results Summary: Integrated Exercise, Self-Management, and Coping Strategies Versus Usual Care



Key: ●=Not Significant; ●=Statistically Significant; ●=Statistically Significant But Not Clinically Important

Figure 10. Results Summary: Water Versus Land-Based Exercise

Outcome	Week 9	Week 18
VAS Pain		●
VAS Pain after 50 foot walk	●	●
VAS Pain before 50 foot walk	●	●
Lequesne index		●

Key: ● =Not Significant; ● = Statistically Significant But Not Clinically Important

Figure 11. Results Summary: Yoga Versus Control

Outcome	Week 13
Physical functioning	🔴
Role limitations	🟡
Emotional problems	🟡
Energy/fatigue	🟡
Emotional well-being	🟡
Social function	🟡
Pain	🔴
General health	🟡
WOMAC Function	🔴
Walking pain	🟡
Resting pain	🟡
Timed walk	🟡
Early morning stiffness	🟡

Key: 🟡 = Statistically Significant 🔴 = Clinically Important

EVIDENCE TABLES AND FIGURES

QUALITY AND APPLICABILITY

Table 22. Quality and Applicability: Strength Training Versus Control

●: Domain free of flaws

○: Domain flaws present

◐:Moderate power

Study	*Outcome*	*Duration (Weeks)*	Prospective	Power	Group Assignment	Blinding	Group Comparability	Treatment Integrity	Measurement	Investigator Bias	*Quality*	Participants	Intervention and Expertise	Compliance and Adherence	Analysis	*Applicability Study*
Azad (2011)	WOMAC Total	4	●	●	○	●	○	●	●	●	**Moderate**	○	○	●	○	**Moderate**
Azad (2011)	WOMAC Total	5	●	●	○	●	○	●	●	●	**Moderate**	○	○	●	○	**Moderate**
Azad (2011)	WOMAC Total	6	●	●	○	●	○	●	●	●	**Moderate**	○	○	●	○	**Moderate**
Bennell (2010)	Number of steps	12	●	●	●	○	●	●	●	○	**Moderate**	●	○	●	●	**Moderate**
Bennell (2010)	WOMAC Function improvement	12	●	●	●	○	●	●	●	○	**Moderate**	●	○	●	●	**Moderate**
Bennell (2010)	WOMAC Pain improvement	12	●	●	●	○	●	●	●	○	**Moderate**	●	○	●	●	**Moderate**
Bennell (2010)	Stair climb improvement	12	●	●	●	○	●	●	●	○	**Moderate**	●	○	●	●	**Moderate**

●: Domain free of flaws

○: Domain flaws present

◐:Moderate power

Study	*Outcome*	*Duration (Weeks)*	**Prospective**	**Power**	**Group Assignment**	**Blinding**	**Group Comparability**	**Treatment Integrity**	**Measurement**	**Investigator Bias**	*Quality*	**Participants**	**Intervention and Expertise**	**Compliance and Adherence**	**Analysis**	*Applicability Study*
Huang (2003)	VAS Pain	8	●	●	●	○	●	●	●	○	**Moderate**	○	○	●	●	**Moderate**
Huang (2003)	VAS Pain	8	●	●	●	○	●	●	●	○	**Moderate**	○	○	●	●	**Moderate**
Huang (2003)	VAS Pain	8	●	●	●	○	●	●	●	○	**Moderate**	○	○	●	●	**Moderate**
Huang (2003)	VAS Pain	52	●	●	●	○	●	●	●	○	**Moderate**	○	○	●	●	**Moderate**
Huang (2003)	VAS Pain	52	●	●	●	○	●	●	●	○	**Moderate**	○	○	●	●	**Moderate**
Huang (2003)	VAS Pain	52	●	●	●	○	●	●	●	○	**Moderate**	○	○	●	●	**Moderate**
Huang (2003)	Walk speed m/minute	8	●	●	●	○	●	●	●	○	**Moderate**	○	○	●	●	**Moderate**
Huang (2003)	Walk speed m/minute	52	●	●	●	○	●	●	●	○	**Moderate**	○	○	●	●	**Moderate**
Huang (2003)	Lequesne index	8	●	●	●	○	●	●	●	○	**Moderate**	○	○	●	●	**Moderate**

●: Domain free of flaws

○: Domain flaws present

◐:Moderate power

Study	*Outcome*	*Duration (Weeks)*	**Prospective**	**Power**	**Group Assignment**	**Blinding**	**Group Comparability**	**Treatment Integrity**	**Measurement**	**Investigator Bias**	*Quality*	**Participants**	**Intervention and Expertise**	**Compliance and Adherence**	**Analysis**	*Applicability Study*
Huang (2003)	Lequesne index	52	●	●	●	○	●	●	●	○	**Moderate**	○	○	●	●	**Moderate**
Jan (2008)	Stair climb	8	●	◐	○	○	●	●	●	○	**Moderate**	○	○	●	●	**Moderate**
Jan (2008)	Stair climb	8	●	◐	○	○	●	●	●	○	**Moderate**	○	○	●	●	**Moderate**
Jan (2008)	WOMAC Pain	8	●	○	○	○	●	●	●	○	**Moderate**	○	○	●	●	**Moderate**
Jan (2008)	Figure 8 walk time	8	●	●	○	○	●	●	●	○	**Moderate**	○	○	●	●	**Moderate**
Jan (2008)	Figure 8 walk time	8	●	●	○	○	●	●	●	○	**Moderate**	○	○	●	●	**Moderate**
Jan (2008)	Level ground walk time	8	●	◐	○	○	●	●	●	○	**Moderate**	○	○	●	●	**Moderate**
Jan (2008)	Level ground walk time	8	●	◐	○	○	●	●	●	○	**Moderate**	○	○	●	●	**Moderate**
Jan (2008)	Spongy surface walk time	8	●	●	○	○	●	●	●	○	**Moderate**	○	○	●	●	**Moderate**

●: Domain free of flaws

○: Domain flaws present

◐:Moderate power

Study	*Outcome*	*Duration (Weeks)*	**Prospective**	**Power**	**Group Assignment**	**Blinding**	**Group Comparability**	**Treatment Integrity**	**Measurement**	**Investigator Bias**	*Quality*	**Participants**	**Intervention and Expertise**	**Compliance and Adherence**	**Analysis**	*Applicability Study*
Jan (2008)	Spongy surface walk time	8	●	●	○	○	●	●	●	○	**Moderate**	○	○	●	●	**Moderate**
Lin (2009)	WOMAC Pain	8	●	●	●	○	●	●	●	●	**High**	●	○	●	●	**Moderate**
Lin (2009)	Level ground walk time	8	●	●	●	○	●	●	●	●	**High**	●	○	●	●	**Moderate**
Lin (2009)	Stair walk time	8	●	●	●	○	●	●	●	●	**High**	●	○	●	●	**Moderate**
Lin (2009)	Spongy surface walk time	8	●	●	●	○	●	●	●	●	**High**	●	○	●	●	**Moderate**
Topp (2002)	WOMAC Pain	16	●	●	○	○	○	●	●	○	**Low**	○	○	●	●	**Moderate**
Topp (2002)	WOMAC Pain	16	●	●	○	○	○	●	●	○	**Low**	○	○	●	●	**Moderate**
Maurer (1999)	WOMAC Pain	8	●	◐	○	●	○	●	●	●	**Moderate**	○	○	●	●	**Moderate**
Maurer (1999)	WOMAC Total	8	●	◐	○	●	○	●	●	●	**Moderate**	○	○	●	●	**Moderate**

●: Domain free of flaws

○: Domain flaws present

◐:Moderate power

Study	*Outcome*	*Duration (Weeks)*	**Prospective**	**Power**	**Group Assignment**	**Blinding**	**Group Comparability**	**Treatment Integrity**	**Measurement**	**Investigator Bias**	*Quality*	**Participants**	**Intervention and Expertise**	**Compliance and Adherence**	**Analysis**	*Applicability Study*
Shakoor (2010)	WOMAC Total	139	●	●	○	●	○	●	●	○	**Moderate**	●	○	●	●	**Moderate**
Shakoor (2010)	WOMAC Total	139	●	●	○	●	○	●	●	○	**Moderate**	●	○	●	●	**Moderate**
Shakoor (2010)	WOMAC Total	139	●	●	○	●	○	●	●	○	**Moderate**	●	○	●	●	**Moderate**

Table 23. Quality and Applicability: High Versus Low Resistance Training

●: Domain free of flaws
○: Domain flaws present
◐: Moderate power

Study	*Outcome*	*Duration (Weeks)*	Prospective	Power	Group Assignment	Blinding	Group Comparability	Treatment Integrity	Measurement	Investigator Bias	*Quality*	Participants	Intervention and Expertise	Compliance and Adherence	Analysis	*Applicability Study*
Jan (2008)	WOMAC Pain	8	●	○	○	●	●	●	●	○	**Moderate**	○	○	●	●	**Moderate**
Jan (2008)	Stair climb	8	●	◐	○	●	●	●	●	○	**Moderate**	○	○	●	●	**Moderate**
Jan (2008)	Figure 8 walk time	8	●	◐	○	●	●	●	●	○	**Moderate**	○	○	●	●	**Moderate**
Jan (2008)	Level ground walk time	8	●	◐	○	●	●	●	●	○	**Moderate**	○	○	●	●	**Moderate**
Jan (2008)	Spongy surface walk time	8	●	●	○	●	●	●	●	○	**Moderate**	○	○	●	●	**Moderate**

Table 24. Quality and Applicability: Isokinetic Versus Isotonic Versus Isometric Strength Training

●: Domain free of flaws

○: Domain flaws present

◐: Moderate power

Study	*Outcome*	*Duration (Weeks)*	**Prospective**	**Power**	**Group Assignment**	**Blinding**	**Group Comparability**	**Treatment Integrity**	**Measurement**	**Investigator Bias**	*Quality*	**Participants**	**Intervention and Expertise**	**Compliance and Adherence**	**Analysis**	*Applicability Study*
Huang (2003)	VAS Pain	8	●	●	●	○	●	●	●	○	**Moderate**	○	○	●	●	**Moderate**
Huang (2003)	VAS Pain	8	●	●	●	○	●	●	●	○	**Moderate**	○	○	●	●	**Moderate**
Huang (2003)	VAS Pain	8	●	●	●	○	●	●	●	○	**Moderate**	○	○	●	●	**Moderate**
Huang (2003)	VAS Pain	52	●	●	●	○	●	●	●	○	**Moderate**	○	○	●	●	**Moderate**
Huang (2003)	VAS Pain	52	●	●	●	○	●	●	●	○	**Moderate**	○	○	●	●	**Moderate**
Huang (2003)	VAS Pain	52	●	●	●	○	●	●	●	○	**Moderate**	○	○	●	●	**Moderate**

Table 25. Quality and Applicability: Strength Training Versus Education

●: Domain free of flaws

○: Domain flaws present

◐: Moderate power

Study	*Outcome*	*Duration (Weeks)*	**Prospective**	**Power**	**Group Assignment**	**Blinding**	**Group Comparability**	**Treatment Integrity**	**Measurement**	**Investigator Bias**	*Quality*	**Participants**	**Intervention and Expertise**	**Compliance and Adherence**	**Analysis**	*Applicability Study*
Ettinger (1997)	Time to get in and out of car	18	●	●	○	○	○	●	●	●	**Moderate**	○	○	○	●	**Moderate**
Ettinger (1997)	Lift and Carry Task	18	●	●	○	○	○	●	●	●	**Moderate**	○	○	○	●	**Moderate**
Ettinger (1997)	6 minute walk distance	18	●	●	○	○	○	●	●	●	**Moderate**	○	○	○	●	**Moderate**

Table 26. Quality and Applicability: Proprioceptive Versus Control

●: Domain free of flaws

○: Domain flaws present

◐: Moderate power

Study	*Outcome*	*Duration (Weeks)*	**Prospective**	**Power**	**Group Assignment**	**Blinding**	**Group Comparability**	**Treatment Integrity**	**Measurement**	**Investigator Bias**	*Quality*	**Participants**	**Intervention and Expertise**	**Compliance and Adherence**	**Analysis**	*Applicability Study*
Lin (2009)	WOMAC Pain	8	●	●	●	○	●	●	●	●	**High**	●	○	●	●	**Moderate**
Lin (2009)	Walk time-level ground	8	●	●	●	○	●	●	●	●	**High**	●	○	●	●	**Moderate**
Lin (2009)	WOMAC Function	8	●	●	●	○	●	●	●	●	**High**	●	○	●	●	**Moderate**
Lin (2009)	Spongy surface walk time	8	●	●	●	○	●	●	●	●	**High**	●	○	●	●	**Moderate**
Lin (2009)	Stair climb walk time	8	●	●	●	○	●	●	●	●	**High**	●	○	●	●	**Moderate**

Table 27. Quality and Applicability: Physical Therapy Versus Control

●: Domain free of flaws

○: Domain flaws present

◐: Moderate power

Study	*Outcome*	*Duration (Weeks)*	**Prospective**	**Power**	**Group Assignment**	**Blinding**	**Group Comparability**	**Treatment Integrity**	**Measurement**	**Investigator Bias**	*Quality*	**Participants**	**Intervention and Expertise**	**Compliance and Adherence**	**Analysis**	*Applicability Study*
Fransen (2007)	WOMAC Pain improvement	8	●	●	○	○	●	●	●	○	**Moderate**	○	○	●	●	**Moderate**
Fransen (2007)	SF-Mental Function	8	●	◐	○	○	●	●	●	○	**Moderate**	○	○	●	●	**Moderate**
Fransen (2007)	SF-36 Physical	8	●	●	○	○	●	●	●	○	**Moderate**	○	○	●	●	**Moderate**
Fransen (2007)	WOMAC Function improvement	8	●	●	○	○	●	●	●	○	**Moderate**	○	○	●	●	**Moderate**
Borjesson (1996)	Stride length	5	●	◐	○	○	○	●	●	○	**Low**	●	○	●	●	**Moderate**
Borjesson (1996)	Number of steps walked/second	5	●	◐	○	○	○	●	●	○	**Low**	●	○	●	●	**Moderate**
Borjesson (1996)	Meters walked per minute	5	●	◐	○	○	○	●	●	○	**Low**	●	○	●	●	**Moderate**
Deyle (2000)	WOMAC Total	8	●	●	○	●	○	●	●	○	**Moderate**	○	○	●	○	**Moderate**

●: Domain free of flaws

○: Domain flaws present

◐: Moderate power

Study	*Outcome*	*Duration (Weeks)*	**Prospective**	**Power**	**Group Assignment**	**Blinding**	**Group Comparability**	**Treatment Integrity**	**Measurement**	**Investigator Bias**	*Quality*	**Participants**	**Intervention and Expertise**	**Compliance and Adherence**	**Analysis**	*Applicability Study*
Deyle (2000)	WOMAC Total	4	●	◐	○	●	○	●	●	○	**Moderate**	○	○	●	○	**Moderate**
Bennell (2005)	VAS Pain On Movement	12	●	●	●	●	●	●	●	●	**High**	○	○	●	●	**Moderate**
Bennell (2005)	VAS Pain On Movement	24	●	●	●	●	●	●	●	●	**High**	○	○	○	●	**Moderate**
Bennell (2005)	WOMAC Pain	12	●	●	●	●	●	●	●	●	**High**	○	○	●	●	**Moderate**
Bennell (2005)	WOMAC Pain	24	●	●	●	●	●	●	●	●	**High**	○	○	●	●	**Moderate**
Bennell (2005)	WOMAC Function	12	●	●	●	●	●	●	●	●	**High**	●	○	○	●	**Moderate**
Bennell (2005)	WOMAC Function	24	●	●	●	●	●	●	●	●	**High**	○	○	○	●	**Moderate**
Bennell (2005)	Knee Pain Scale Severity	12	●	◐	●	●	●	●	●	●	**High**	●	○	●	●	**Moderate**
Bennell (2005)	Knee Pain Scale Severity	24	●	◐	●	●	●	●	●	●	**High**	○	○	●	●	**Moderate**

●: Domain free of flaws

○: Domain flaws present

◐: Moderate power

Study	*Outcome*	*Duration (Weeks)*	**Prospective**	**Power**	**Group Assignment**	**Blinding**	**Group Comparability**	**Treatment Integrity**	**Measurement**	**Investigator Bias**	*Quality*	**Participants**	**Intervention and Expertise**	**Compliance and Adherence**	**Analysis**	*Applicability Study*
Bennell (2005)	Knee Pain Scale Frequency	12	●	●	●	●	●	●	●	●	**High**	○	○	●	●	**Moderate**
Bennell (2005)	Knee Pain Scale Frequency	24	●	●	●	●	●	●	●	●	**High**	○	○	○	●	**Moderate**
Bennell (2005)	SF-36 Physical Role	12	●	◐	●	●	●	●	●	●	**High**	○	○	●	●	**Moderate**
Bennell (2005)	SF-36 Physical Role	24	●	◐	●	●	●	●	●	●	**High**	○	○	●	●	**Moderate**
Bennell (2005)	Assessment of Quality of Life index	12	●	◐	●	●	●	●	●	●	**High**	●	○	○	●	**Moderate**
Bennell (2005)	Assessment of Quality of Life index	24	●	●	●	●	●	●	●	●	**High**	○	○	○	●	**Moderate**
Bennell (2005)	Step test (number of steps) improvement	12	●	◐	●	●	●	●	●	●	**High**	●	○	●	●	**Moderate**
Bennell (2005)	Step test (number of steps) improvement	24	●	◐	●	●	●	●	●	●	**High**	○	○	●	●	**Moderate**
Bennell (2005)	VAS Pain On Movement	12	●	●	●	●	●	●	●	●	**High**	○	○	●	●	**Moderate**

●: Domain free of flaws

○: Domain flaws present

◐: Moderate power

Study	*Outcome*	*Duration (Weeks)*	**Prospective**	**Power**	**Group Assignment**	**Blinding**	**Group Comparability**	**Treatment Integrity**	**Measurement**	**Investigator Bias**	*Quality*	**Participants**	**Intervention and Expertise**	**Compliance and Adherence**	**Analysis**	*Applicability Study*
Bennell (2005)	VAS Pain On Movement	24	●	●	●	●	●	●	●	●	**High**	○	○	○	●	**Moderate**
Deyle (2000)	WOMAC Total	8	●	◐	○	●	○	●	●	○	**Moderate**	○	○	●	○	**Moderate**

Table 28. Quality and Applicability: Kinesthesia Plus Strengthening Versus Strengthening Alone

●: Domain free of flaws

○: Domain flaws present

◐: Moderate power

Study	*Outcome*	*Duration (Weeks)*	**Prospective**	**Power**	**Group Assignment**	**Blinding**	**Group Comparability**	**Treatment Integrity**	**Measurement**	**Investigator Bias**	*Quality*	**Participants**	**Intervention and Expertise**	**Compliance and Adherence**	**Analysis**	*Applicability Study*
Diracoglu (2005)	SF-36 Physical	8	●	●	○	●	●	●	●	○	**Moderate**	●	○	●	○	**Moderate**
Diracoglu (2005)	SF-36 Role Limitations	8	●	◐	○	●	●	●	●	○	**Moderate**	●	○	●	○	**Moderate**
Diracoglu (2005)	SF-36 Vitality	8	●	●	○	●	●	●	●	○	**Moderate**	●	○	●	○	**Moderate**
Diracoglu (2005)	10m walk	8	●	●	○	●	●	●	●	○	**Moderate**	●	○	●	○	**Moderate**

Table 29. Quality and Applicability: Agility Plus Perturbation Versus Standard Exercise Therapy

●: Domain free of flaws

○: Domain flaws present

◐: Moderate power

Study	*Outcome*	*Duration (Weeks)*	**Prospective**	**Power**	**Group Assignment**	**Blinding**	**Group Comparability**	**Treatment Integrity**	**Measurement**	**Investigator Bias**	*Quality*	**Participants**	**Intervention and Expertise**	**Compliance and Adherence**	**Analysis**	*Applicability Study*
Fitzgerald (2011)	WOMAC Total	52	●	●	●	●	●	●	●	●	**High**	○	○	●	●	**Moderate**
Fitzgerald (2011)	WOMAC Function	52	●	●	●	●	●	●	●	●	**High**	○	○	●	●	**Moderate**
Fitzgerald (2011)	Knee pain (numerical rating scale)	52	●	◐	●	●	●	●	●	●	**High**	○	○	●	●	**Moderate**
Fitzgerald (2011)	Global Rating of Change	52	●	◐	●	●	●	●	●	●	**High**	○	○	●	●	**Moderate**
Fitzgerald (2011)	Get Up and Go Test	52	●	◐	●	●	●	●	●	●	**High**	○	○	●	●	**Moderate**
Texeira (2011)	When down the stairs?	8	○	◐	○	○	●	●	●	○	**Low**	○	○	●	●	**Moderate**
Texeira (2011)	When going up stairs?	8	○	◐	○	○	●	●	●	○	**Low**	○	○	●	●	**Moderate**
Texeira (2011)	Getting up from sitting position?	8	○	◐	○	○	●	●	●	○	**Low**	○	○	●	●	**Moderate**

●: Domain free of flaws

○: Domain flaws present

◐: Moderate power

Study	*Outcome*	*Duration (Weeks)*	**Prospective**	**Power**	**Group Assignment**	**Blinding**	**Group Comparability**	**Treatment Integrity**	**Measurement**	**Investigator Bias**	*Quality*	**Participants**	**Intervention and Expertise**	**Compliance and Adherence**	**Analysis**	*Applicability Study*
Texeira (2011)	While standing?	8	○	◐	○	○	●	●	●	○	**Low**	○	○	●	●	**Moderate**
Texeira (2011)	While bending to the floor?	8	○	◐	○	○	●	●	●	○	**Low**	○	○	●	●	**Moderate**
Texeira (2011)	When walking on a flat surface?	8	○	◐	○	○	●	●	●	○	**Low**	○	○	●	●	**Moderate**
Texeira (2011)	While getting in/out of car?	8	○	◐	○	○	●	●	●	○	**Low**	○	○	●	●	**Moderate**
Texeira (2011)	While going shopping?	8	○	◐	○	○	●	●	●	○	**Low**	○	○	●	●	**Moderate**
Texeira (2011)	When putting on socks/stockings?	8	○	◐	○	○	●	●	●	○	**Low**	○	○	●	●	**Moderate**
Texeira (2011)	While getting out of bed?	8	○	◐	○	○	●	●	●	○	**Low**	○	○	●	●	**Moderate**
Texeira (2011)	When taking off socks/stockings?	8	○	◐	○	○	●	●	●	○	**Low**	○	○	●	●	**Moderate**
Texeira (2011)	While lying in bed?	8	○	◐	○	○	●	●	●	○	**Low**	○	○	●	●	**Moderate**

●: Domain free of flaws

○: Domain flaws present

◐: Moderate power

Study	*Outcome*	*Duration (Weeks)*	**Prospective**	**Power**	**Group Assignment**	**Blinding**	**Group Comparability**	**Treatment Integrity**	**Measurement**	**Investigator Bias**	*Quality*	**Participants**	**Intervention and Expertise**	**Compliance and Adherence**	**Analysis**	*Applicability Study*
Texeira (2011)	When getting in/out of bath?	8	○	◐	○	○	●	●	●	○	**Low**	○	○	●	●	**Moderate**
Texeira (2011)	While sitting?	8	○	◐	○	○	●	●	●	○	**Low**	○	○	●	●	**Moderate**
Texeira (2011)	When getting on/off toilet?	8	○	◐	○	○	●	●	●	○	**Low**	○	○	●	●	**Moderate**
Texeira (2011)	While doing heavy household chores?	8	○	◐	○	○	●	●	●	○	**Low**	○	○	●	●	**Moderate**
Texeira (2011)	While doing light household chores?	8	○	◐	○	○	●	●	●	○	**Low**	○	○	●	●	**Moderate**

Table 30. Quality and Applicability: Self-Management Versus Control

●: Domain free of flaws

○: Domain flaws present

◐: Moderate power

Study	*Outcome*	*Duration (Weeks)*	**Prospective**	**Power**	**Group Assignment**	**Blinding**	**Group Comparability**	**Treatment Integrity**	**Measurement**	**Investigator Bias**	*Quality*	**Participants**	**Intervention and Expertise**	**Compliance and Adherence**	**Analysis**	*Applicability Study*
Yip (2007)	Arthritis Self-Efficacy Pain Score improvement	16	●	●	○	●	○	●	●	○	**Moderate**	●	○	●	●	**Moderate**
Yip (2007)	VAS Pain improvement	16	●	●	○	●	○	●	●	○	**Moderate**	●	○	●	●	**Moderate**
Yip (2007)	Hours of light exercise improvement	16	●	●	○	●	○	●	●	○	**Moderate**	●	○	●	●	**Moderate**
Yip (2007)	Health Assessment Questionnaire improvement	16	●	◐	○	●	○	●	●	○	**Moderate**	●	○	●	●	**Moderate**
Coleman (2012)	WOMAC Pain	8	●	●	●	●	●	●	●	●	**High**	○	○	●	●	**Moderate**
Coleman (2012)	WOMAC Pain	26	●	●	●	●	●	●	●	●	**High**	○	○	●	●	**Moderate**
Coleman (2012)	WOMAC Stiffness	8	●	●	●	●	●	●	●	●	**High**	○	○	●	●	**Moderate**

●: Domain free of flaws

○: Domain flaws present

◐: Moderate power

Study	*Outcome*	*Duration (Weeks)*	**Prospective**	**Power**	**Group Assignment**	**Blinding**	**Group Comparability**	**Treatment Integrity**	**Measurement**	**Investigator Bias**	*Quality*	**Participants**	**Intervention and Expertise**	**Compliance and Adherence**	**Analysis**	*Applicability Study*
Coleman (2012)	WOMAC Stiffness	26	●	●	●	●	●	●	●	●	**High**	○	○	●	●	**Moderate**
Coleman (2012)	WOMAC Function	8	●	●	●	●	●	●	●	●	**High**	○	○	●	●	**Moderate**
Coleman (2012)	WOMAC Function	26	●	●	●	●	●	●	●	●	**High**	○	○	●	●	**Moderate**
Coleman (2012)	WOMAC Total	8	●	●	●	●	●	●	●	●	**High**	○	○	●	●	**Moderate**
Coleman (2012)	WOMAC Total	26	●	●	●	●	●	●	●	●	**High**	○	○	●	●	**Moderate**
Coleman (2012)	SF-36 Physical Function	26	●	●	●	●	●	●	●	●	**High**	○	○	●	●	**Moderate**
Coleman (2012)	SF-36 Role Physical	26	●	◐	●	●	●	●	●	●	**High**	○	○	●	●	**Moderate**
Coleman (2012)	SF-36 Body Pain	26	●	●	●	●	●	●	●	●	**High**	○	○	●	●	**Moderate**

●: Domain free of flaws

○: Domain flaws present

◐: Moderate power

Study	*Outcome*	*Duration (Weeks)*	**Prospective**	**Power**	**Group Assignment**	**Blinding**	**Group Comparability**	**Treatment Integrity**	**Measurement**	**Investigator Bias**	*Quality*	**Participants**	**Intervention and Expertise**	**Compliance and Adherence**	**Analysis**	*Applicability Study*
Coleman (2012)	SF-36 General Health	26	●	◐	●	●	●	●	●	●	**High**	○	○	●	●	**Moderate**
Coleman (2012)	SF-36 Vitality	26	●	◐	●	●	●	●	●	●	**High**	○	○	●	●	**Moderate**
Coleman (2012)	SF-36 Social Function	26	●	◐	●	●	●	●	●	●	**High**	○	○	●	●	**Moderate**
Coleman (2012)	SF-36 Role Emotional	26	●	◐	●	●	●	●	●	●	**High**	○	○	●	●	**Moderate**
Coleman (2012)	SF-36 Mental Health	26	●	◐	●	●	●	●	●	●	**High**	○	○	●	●	**Moderate**
Coleman (2012)	SF-36 Physical Function	8	●	●	●	●	●	●	●	●	**High**	○	○	●	●	**Moderate**
Coleman (2012)	SF-36 Role Physical	8	●	●	●	●	●	●	●	●	**High**	○	○	●	●	**Moderate**
Coleman (2012)	SF-36 Body Pain	8	●	●	●	●	●	●	●	●	**High**	○	○	●	●	**Moderate**

●: Domain free of flaws

○: Domain flaws present

◐: Moderate power

Study	*Outcome*	*Duration (Weeks)*	**Prospective**	**Power**	**Group Assignment**	**Blinding**	**Group Comparability**	**Treatment Integrity**	**Measurement**	**Investigator Bias**	*Quality*	**Participants**	**Intervention and Expertise**	**Compliance and Adherence**	**Analysis**	*Applicability Study*
Coleman (2012)	SF-36 General Health	8	●	◐	●	●	●	●	●	●	**High**	○	○	●	●	**Moderate**
Coleman (2012)	SF-36 Vitality	8	●	●	●	●	●	●	●	●	**High**	○	○	●	●	**Moderate**
Coleman (2012)	SF-36 Social Function	8	●	●	●	●	●	●	●	●	**High**	○	○	●	●	**Moderate**
Coleman (2012)	SF-36 Role Emotional	8	●	◐	●	●	●	●	●	●	**High**	○	○	●	●	**Moderate**
Coleman (2012)	SF-36 Mental Health	8	●	◐	●	●	●	●	●	●	**High**	○	○	●	●	**Moderate**
Allen (2010)	AIMS2 Pain	52	●	●	○	●	○	●	●	●	**Moderate**	○	●	●	●	**Moderate**
Allen (2010)	AIMS2 Function	52	●	●	○	●	○	●	●	●	**Moderate**	○	●	●	●	**Moderate**
Allen (2010)	AIMS2 Walking and Bending	52	●	●	○	●	○	●	●	●	**Moderate**	○	●	●	●	**Moderate**

●: Domain free of flaws

○: Domain flaws present

◐: Moderate power

Study	*Outcome*	*Duration (Weeks)*	**Prospective**	**Power**	**Group Assignment**	**Blinding**	**Group Comparability**	**Treatment Integrity**	**Measurement**	**Investigator Bias**	*Quality*	**Participants**	**Intervention and Expertise**	**Compliance and Adherence**	**Analysis**	*Applicability Study*
Allen (2010)	AIMS2 Mobility	52	●	●	○	●	○	●	●	●	**Moderate**	○	●	●	●	**Moderate**
Allen (2010)	AIMS2 Affect	52	●	●	○	●	○	●	●	●	**Moderate**	○	●	●	●	**Moderate**
Allen (2010)	Arthritis Self-Efficacy Scale	52	●	●	○	●	○	●	●	●	**Moderate**	○	●	●	●	**Moderate**
Allen (2010)	VAS Pain	52	●	●	○	●	○	●	●	●	**Moderate**	○	●	●	●	**Moderate**
Allen (2010)	AIMS2 Pain	52	●	●	○	○	○	●	●	●	**Moderate**	○	●	●	●	**Moderate**
Allen (2010)	AIMS2 Function	52	●	●	○	○	○	●	●	●	**Moderate**	○	●	●	●	**Moderate**
Allen (2010)	AIMS2 Walking and Bending	52	●	●	○	○	○	●	●	●	**Moderate**	○	●	●	●	**Moderate**
Allen (2010)	AIMS2 Mobility	52	●	●	○	○	○	●	●	●	**Moderate**	○	●	●	●	**Moderate**

●: Domain free of flaws

○: Domain flaws present

◐: Moderate power

Study	*Outcome*	*Duration (Weeks)*	**Prospective**	**Power**	**Group Assignment**	**Blinding**	**Group Comparability**	**Treatment Integrity**	**Measurement**	**Investigator Bias**	*Quality*	**Participants**	**Intervention and Expertise**	**Compliance and Adherence**	**Analysis**	*Applicability Study*
Allen (2010)	AIMS2 Affect	52	●	●	○	○	○	●	●	●	**Moderate**	○	●	●	●	**Moderate**
Allen (2010)	Arthritis Self-Efficacy Scale	52	●	◐	●	○	○	●	●	●	**Moderate**	○	●	●	●	**Moderate**
Allen (2010)	VAS Pain	52	●	●	●	○	○	●	●	●	**Moderate**	○	●	●	●	**Moderate**

Table 31. Quality and Applicability: Supervised Walking Versus Control

●: Domain free of flaws

○: Domain flaws present

◐: Moderate power

Study	*Outcome*	*Duration (Weeks)*	**Prospective**	**Power**	**Group Assignment**	**Blinding**	**Group Comparability**	**Treatment Integrity**	**Measurement**	**Investigator Bias**	*Quality*	**Participants**	**Intervention and Expertise**	**Compliance and Adherence**	**Analysis**	*Applicability Study*
Kovar (1992)	AIMS Arthritis Pain	8	●	●	○	●	○	●	●	○	**Moderate**	○	○	●	○	**Moderate**
Kovar (1992)	6 minute walk distance	8	●	●	○	●	○	●	●	○	**Moderate**	○	○	●	○	**Moderate**
Kovar (1992)	AIMS Arthritis Impact	8	●	◐	○	●	○	●	●	○	**Moderate**	○	○	●	○	**Moderate**
Kovar (1992)	AIMS Medications Use	8	●	◐	○	●	○	●	●	○	**Moderate**	○	○	●	○	**Moderate**
Kovar (1992)	AIMS Physical Activity	8	●	●	○	●	○	●	●	○	**Moderate**	○	○	●	○	**Moderate**

Table 32. Quality and Applicability: Water Versus Land-Based Exercise

●: Domain free of flaws

○: Domain flaws present

◐: Moderate power

Study	*Outcome*	*Duration (Weeks)*	**Prospective**	**Power**	**Group Assignment**	**Blinding**	**Group Comparability**	**Treatment Integrity**	**Measurement**	**Investigator Bias**	*Quality*	**Participants**	**Intervention and Expertise**	**Compliance and Adherence**	**Analysis**	*Applicability Study*
Silva (2008)	VAS Pain	18	●	●	○	●	●	●	●	○	**Moderate**	○	○	●	●	**Moderate**
Silva (2008)	VAS Pain after 50 foot walk	9	●	●	○	●	●	●	●	○	**Moderate**	○	○	●	●	**Moderate**
Silva (2008)	VAS Pain after 50 foot walk	18	●	●	○	●	●	●	●	○	**Moderate**	○	○	●	●	**Moderate**
Silva (2008)	VAS Pain before 50 foot walk	9	●	●	○	●	●	●	●	○	**Moderate**	○	○	●	●	**Moderate**
Silva (2008)	VAS Pain before 50 foot walk	18	●	●	○	●	●	●	●	○	**Moderate**	○	○	●	●	**Moderate**
Silva (2008)	Lequesne index	18	●	◐	○	●	●	●	●	○	**Moderate**	○	○	●	●	**Moderate**

Table 33. Quality and Applicability: Aerobic Exercise Versus Education

●: Domain free of flaws

○: Domain flaws present

◐: Moderate power

Study	*Outcome*	*Duration (Weeks)*	**Prospective**	**Power**	**Group Assignment**	**Blinding**	**Group Comparability**	**Treatment Integrity**	**Measurement**	**Investigator Bias**	*Quality*	**Participants**	**Intervention and Expertise**	**Compliance and Adherence**	**Analysis**	*Applicability Study*
Rejeski (2002)	SF-36 Mental Health	78	○	◐	○	○	●	●	●	○	**Low**	○	○	●	●	**Moderate**
Rejeski (2002)	SF-36 Physical Component Score	78	○	○	○	○	●	●	●	○	**Low**	○	○	●	●	**Moderate**
Ettinger (1997)	Lift and carry task time(s)	18	●	●	○	○	○	●	●	●	**Moderate**	○	○	○	●	**Moderate**
Ettinger (1997)	Stair climb	18	●	◐	○	○	○	●	●	●	**Moderate**	○	○	○	●	**Moderate**
Ettinger (1997)	Time to get in and out of car	18	●	●	○	○	○	●	●	●	**Moderate**	○	○	○	●	**Moderate**
Ettinger (1997)	Walk distance	18	●	●	○	○	○	●	●	●	**Moderate**	○	○	○	●	**Moderate**
Focht (2005)	Stair climb time	78	○	◐	○	○	●	●	●	○	**Low**	○	○	●	●	**Moderate**

●: Domain free of flaws

○: Domain flaws present

◐: Moderate power

Study	*Outcome*	*Duration (Weeks)*	**Prospective**	**Power**	**Group Assignment**	**Blinding**	**Group Comparability**	**Treatment Integrity**	**Measurement**	**Investigator Bias**	*Quality*	**Participants**	**Intervention and Expertise**	**Compliance and Adherence**	**Analysis**	*Applicability Study*
Yip (2007)	Arthritis Self-Efficacy Pain Score improvement	16	●	●	○	●	○	●	●	○	**Moderate**	●	○	●	●	**Moderate**
Yip (2007)	VAS Pain improvement	16	●	●	○	●	○	●	●	○	**Moderate**	●	○	●	●	**Moderate**
Yip (2007)	Hours of light exercise improvement	16	●	●	○	●	○	●	●	○	**Moderate**	●	○	●	●	**Moderate**
Yip (2007)	Health Assessment Questionnaire improvement	16	●	◐	○	●	○	●	●	○	**Moderate**	●	○	●	●	**Moderate**

Table 34. Quality and Applicability: Weight Bearing and Non-Weight Bearing Exercise Programs

●: Domain free of flaws

○: Domain flaws present

◐: Moderate power

Study	*Outcome*	*Duration (Weeks)*	**Prospective**	**Power**	**Group Assignment**	**Blinding**	**Group Comparability**	**Treatment Integrity**	**Measurement**	**Investigator Bias**	*Quality*	**Participants**	**Intervention and Expertise**	**Compliance and Adherence**	**Analysis**	*Applicability Study*
Jan (2009)	WOMAC Function	8 weeks	●	●	○	●	○	●	●	●	**Moderate**	○	○	●	●	**Moderate**
Jan (2009)	Level ground walking time(s)	8 weeks	●	●	○	●	○	●	●	●	**Moderate**	○	○	●	●	**Moderate**
Jan (2009)	Stair climb time	8 weeks	●	●	○	●	○	●	●	●	**Moderate**	○	○	●	●	**Moderate**
Jan (2009)	Figure 8 walking time	8 weeks	●	●	○	●	○	●	●	●	**Moderate**	○	○	●	●	**Moderate**
Jan (2009)	Sponge walk time	8 weeks	●	●	○	●	○	●	●	●	**Moderate**	○	○	●	●	**Moderate**
Jan (2009)	WOMAC Function	8 weeks	●	●	○	●	○	●	●	●	**Moderate**	○	○	●	●	**Moderate**
Jan (2009)	Level ground walking time(s)	8 weeks	●	●	○	●	○	●	●	●	**Moderate**	○	○	●	●	**Moderate**
Jan (2009)	Stair climb time	8 weeks	●	●	○	●	○	●	●	●	**Moderate**	○	○	●	●	**Moderate**

●: Domain free of flaws

○: Domain flaws present

◐: Moderate power

Study	*Outcome*	*Duration (Weeks)*	**Prospective**	**Power**	**Group Assignment**	**Blinding**	**Group Comparability**	**Treatment Integrity**	**Measurement**	**Investigator Bias**	*Quality*	**Participants**	**Intervention and Expertise**	**Compliance and Adherence**	**Analysis**	*Applicability Study*
Jan (2009)	Figure 8 walking time	8 weeks	●	●	○	●	○	●	●	●	**Moderate**	○	○	●	●	**Moderate**
Jan (2009)	Sponge walk time	8 weeks	●	●	○	●	○	●	●	●	**Moderate**	○	○	●	●	**Moderate**
Jan (2009)	Level ground walking time(s)	8 weeks	●	◐	○	●	○	●	●	●	**Moderate**	○	○	●	●	**Moderate**
Jan (2009)	Stair climb time	8 weeks	●	●	○	●	○	●	●	●	**Moderate**	○	○	●	●	**Moderate**
Jan (2009)	Figure 8 walking time	8 weeks	●	◐	○	●	○	●	●	●	**Moderate**	○	○	●	●	**Moderate**
Jan (2009)	Sponge walk time	8 weeks	●	●	○	●	○	●	●	●	**Moderate**	○	○	●	●	**Moderate**

Table 35. Quality and Applicability: Home and Class-Based Exercise Programs

●: Domain free of flaws

○: Domain flaws present

◐: Moderate power

Study	*Outcome*	*Duration (Weeks)*	**Prospective**	**Power**	**Group Assignment**	**Blinding**	**Group Comparability**	**Treatment Integrity**	**Measurement**	**Investigator Bias**	*Quality*	**Participants**	**Intervention and Expertise**	**Compliance and Adherence**	**Analysis**	**Applicability *Study***
O'Reilly (1999)	Global pain score	6 months	●		●	○	●	●	●	●	**High**	○	○	○	●	**Moderate**
O'Reilly (1999)	VAS walking	6 months	●		●	○	●	●	●	●	**High**	○	○	○	●	**Moderate**
O'Reilly (1999)	VAS stairs	6 months	●		●	○	●	●	●	●	**High**	○	○	○	●	**Moderate**
O'Reilly (1999)	Physical function	6 months	●		●	○	●	●	●	●	**High**	○	○	○	●	**Moderate**
O'Reilly (1999)	Mental health	6 months	●		●	○	●	●	●	●	**High**	○	○	○	●	**Moderate**
O'Reilly (1999)	Energy	6 months	●		●	○	●	●	●	●	**High**	○	○	○	●	**Moderate**
O'Reilly (1999)	Health perception	6 months	●		●	○	●	●	●	●	**High**	○	○	○	●	**Moderate**
O'Reilly (1999)	Role limitation physical	6 months	●		●	○	●	●	●	●	**High**	○	○	○	●	**Moderate**

●: Domain free of flaws

○: Domain flaws present

◐: Moderate power

Study	*Outcome*	*Duration (Weeks)*	**Prospective**	**Power**	**Group Assignment**	**Blinding**	**Group Comparability**	**Treatment Integrity**	**Measurement**	**Investigator Bias**	*Quality*	**Participants**	**Intervention and Expertise**	**Compliance and Adherence**	**Analysis**	**Applicability** *Study*
O'Reilly (1999)	Role limitation emotional	6 months	●		●	○	●	●	●	●	**High**	○	○	○	●	**Moderate**
O'Reilly (1999)	Social functioning	6 months	●		●	○	●	●	●	●	**High**	○	○	○	●	**Moderate**
McCarthy (2004)	WOMAC Pain	12-month	●		●	●	●	●	●	○	**High**	●	○	○	●	**Moderate**
McCarthy (2004)	WOMAC Stiffness	6 months	●		●	●	●	●	●	○	**High**	●	○	○	●	**Moderate**
McCarthy (2004)	WOMAC Stiffness	12-month LVCF	●		●	●	●	●	●	○	**High**	●	○	○	●	**Moderate**
McCarthy (2004)	VAS Pain	6 months	●		●	●	●	●	●	○	**High**	●	○	○	●	**Moderate**
McCarthy (2004)	VAS Pain	12 months	●		●	●	●	●	●	○	**High**	●	○	○	●	**Moderate**
McCarthy (2004)	WOMAC Pain	6 months	●		●	●	●	●	●	○	**High**	●	○	○	●	**Moderate**
Tunay (2010)	Left knee VAS Rest	6 weeks	●		○	●	○	●	●	●	**Moderate**	○	○	●	●	**Moderate**

●: Domain free of flaws

○: Domain flaws present

◐: Moderate power

Study	*Outcome*	*Duration (Weeks)*	**Prospective**	**Power**	**Group Assignment**	**Blinding**	**Group Comparability**	**Treatment Integrity**	**Measurement**	**Investigator Bias**	*Quality*	**Participants**	**Intervention and Expertise**	**Compliance and Adherence**	**Analysis**	**Applicability** *Study*
Tunay (2010)	Left knee VAS Activity	6 weeks	●		○	●	○	●	●	●	**Moderate**	○	○	●	●	**Moderate**
Tunay (2010)	Left knee VAS Night	6 weeks	●		○	●	○	●	●	●	**Moderate**	○	○	●	●	**Moderate**
Tunay (2010)	Right knee VAS Rest	6 weeks	●		○	●	○	●	●	●	**Moderate**	○	○	●	●	**Moderate**
Tunay (2010)	Right knee VAS Activity	6 weeks	●		○	●	○	●	●	●	**Moderate**	○	○	●	●	**Moderate**
Tunay (2010)	Right knee VAS Night	6 weeks	●		○	●	○	●	●	●	**Moderate**	○	○	●	●	**Moderate**
Tunay (2010)	Proprioception	6 weeks	●		○	●	○	●	●	●	**Moderate**	○	○	●	●	**Moderate**
Tunay (2010)	WOMAC Total	6 weeks	●		○	●	○	●	●	●	**Moderate**	○	○	●	●	**Moderate**
Tunay (2010)	TUG (sec)	6 weeks	●		○	●	○	●	●	●	**Moderate**	○	○	●	●	**Moderate**

Table 36. Quality and Applicability: Standardized Structured Physician Consultation Program (Education) Versus Control

●: Domain free of flaws

○: Domain flaws present

◐: Moderate power

Study	*Outcome*	*Duration (Weeks)*	**Prospective**	**Power**	**Group Assignment**	**Blinding**	**Group Comparability**	**Treatment Integrity**	**Measurement**	**Investigator Bias**	*Quality*	**Participants**	**Intervention and Expertise**	**Compliance and Adherence**	**Analysis**	*Applicability Study*
Ravaud (2009)	SF-12 Mental Function improvement	16	●	◐	●	●	●	○	●	○	**Moderate**	○	○	●	●	**Moderate**
Ravaud (2009)	SF-12 Physical Function improvement	16	●	◐	●	●	●	○	●	○	**Moderate**	○	○	●	●	**Moderate**
Ravaud (2009)	WOMAC Function improvement	16	●	●	●	●	●	○	●	○	**Moderate**	○	○	●	●	**Moderate**

Table 37. Quality and Applicability: Integrated Exercise, Self-Management, and Coping Strategies Versus Usual Care

●: Domain free of flaws

○: Domain flaws present

◐: Moderate power

Study	*Outcome*	*Duration (Weeks)*	**Prospective**	**Power**	**Group Assignment**	**Blinding**	**Group Comparability**	**Treatment Integrity**	**Measurement**	**Investigator Bias**	*Quality*	**Participants**	**Intervention and Expertise**	**Compliance and Adherence**	**Analysis**	*Applicability Study*
Hurley (2007)	WOMAC Function	26	●	●	○	●	○	○	●	●	**Moderate**	○	○	○	●	**Moderate**
Hurley (2007)	WOMAC Pain	26	●	●	○	●	○	○	●	●	**Moderate**	○	○	○	●	**Moderate**
Hurley (2007)	WOMAC Total	26	●	●	○	●	○	○	●	●	**Moderate**	○	○	○	●	**Moderate**
Hurley (2007)	Aggregate Functional Performance time(s)	26	●	○	○	●	○	○	●	●	**Moderate**	○	○	○	●	**Moderate**
Hurley (2007)	Exercise Health Beliefs Self-Efficacy Subscale	26	●	●	○	●	○	○	●	●	**Moderate**	○	○	○	●	**Moderate**
Hurley (2007)	Exercise Health Beliefs Total Score	26	●	●	○	●	○	○	●	●	**Moderate**	○	○	○	●	**Moderate**
Hurley (2007)	Hospital Anxiety and Depression Scale Depression Subscale	26	●	●	○	●	○	○	●	●	**Moderate**	○	○	○	●	**Moderate**

●: Domain free of flaws

○: Domain flaws present

◐: Moderate power

Study	*Outcome*	*Duration (Weeks)*	**Prospective**	**Power**	**Group Assignment**	**Blinding**	**Group Comparability**	**Treatment Integrity**	**Measurement**	**Investigator Bias**	*Quality*	**Participants**	**Intervention and Expertise**	**Compliance and Adherence**	**Analysis**	*Applicability Study*
Hurley (2007)	Hospital Anxiety and Depression Scale Anxiety subscale	26	●	●	○	●	○	○	●	●	**Moderate**	○	○	○	●	**Moderate**
Hurley (2007)	MACTAR	26	●	●	○	●	○	○	●	●	**Moderate**	○	○	○	●	**Moderate**
Hurley (2007)	EQ-5D	26	●	●	○	●	○	○	●	●	**Moderate**	○	○	○	●	**Moderate**

Table 38. Quality and Applicability: Yoga Plus Physiotherapy Versus Physiotherapy Only

●: Domain free of flaws

○: Domain flaws present

◐: Moderate power

Study	*Outcome*	*Duration (Weeks)*	**Prospective**	**Power**	**Group Assignment**	**Blinding**	**Group Comparability**	**Treatment Integrity**	**Measurement**	**Investigator Bias**	*Quality*	**Participants**	**Intervention and Expertise**	**Compliance and Adherence**	**Analysis**	*Applicability Study*
Ebnezar (2011)	Physical functioning	13	○	●	○	○	○	●	●	○	**Low**	○	○	○	●	**Moderate**
Ebnezar (2011)	Role limitations	13	○	●	○	○	○	●	●	○	**Low**	○	○	○	●	**Moderate**
Ebnezar (2011)	Emotional problems	13	○	●	○	○	○	●	●	○	**Low**	○	○	○	●	**Moderate**
Ebnezar (2011)	Energy/fatigue	13	○	●	○	○	○	●	●	○	**Low**	○	○	○	●	**Moderate**
Ebnezar (2011)	Emotional well-being	13	○	●	○	○	○	●	●	○	**Low**	○	○	○	●	**Moderate**
Ebnezar (2011)	Social function	13	○	●	○	○	○	●	●	○	**Low**	○	○	○	●	**Moderate**
Ebnezar (2011)	Pain	13	○	●	○	○	○	●	●	○	**Low**	○	○	○	●	**Moderate**
Ebnezar (2011)	General health	13	○	●	○	○	○	●	●	○	**Low**	○	○	○	●	**Moderate**

●: Domain free of flaws

○: Domain flaws present

◐: Moderate power

Study	*Outcome*	*Duration (Weeks)*	**Prospective**	**Power**	**Group Assignment**	**Blinding**	**Group Comparability**	**Treatment Integrity**	**Measurement**	**Investigator Bias**	*Quality*	**Participants**	**Intervention and Expertise**	**Compliance and Adherence**	**Analysis**	*Applicability Study*
Ebnezar (2012)	Resting pain	13	○	●	○	○	○	●	●	○	**Low**	○	○	○	●	**Moderate**
Ebnezar (2012)	Early morning stiffness	13	○	●	○	○	○	●	●	○	**Low**	○	○	○	●	**Moderate**
Ebnezar (2012)	Walking pain	13	●	●	●	●	●	●	●	○	**High**	○	○	○	●	**Moderate**
Ebnezar (2012)	WOMAC Function	13	●	●	●	●	●	●	●	○	**High**	○	○	○	●	**Moderate**
Ebnezar (2012)	Walking time	13	●	●	●	●	●	●	●	○	**High**	○	○	○	●	**Moderate**

Table 39. Strength Training Compared to Control: Pain Outcomes

Study	Outcome	N	Sufficient Power	Week	Group 1	Group 2	SMD (Odds Ratio or Raw Mean Difference When Indicated)	Sig	Clinical Importance	Strength of Evidence
Bennell (2010)	WOMAC Pain	89	Yes	12	Hip strengthening	No exercise	.86(.392, 1.33)	Favors hip strengthening	Clinically important	Moderate
Topp (2002)	WOMAC Pain	67	Yes	16	Dynamic strength training	No exercise	Mean difference=1.71	Favors strength training (ST) group	Unclear	Low
Topp (2002)	WOMAC Pain	67	Yes	16	Isometric strength training	No exercise	Mean difference=1.39	Favors ST	Unclear	Low
Jan (2008)	WOMAC Pain	64	No	8	High resistance training	No exercise	-.41(-.91,.08)	No	Inconclusive	Moderate
Lin (2009)	WOMAC Pain	72	Yes	8	Strength training	No exercise	-.96(-.71, -.06)	Favors ST	Possibly clinically significant	High
Huang (2003)	VAS Pain	128	Yes	8	Isotonic strength training	Control	-3.16(-3.69, -2.64)	Favors ST	Clinically important	Moderate
Huang (2003)	VAS Pain	128	Yes	8	Isometric strength training	Control	-1.57(-1.97, -1.17)	Favors ST	Possibly clinically important	Moderate

Study	Outcome	N	Sufficient Power	Week	Group 1	Group 2	SMD (Odds Ratio or Raw Mean Difference When Indicated)	Sig	Clinical Importance	Strength of Evidence
Huang (2003)	VAS Pain	124	Yes	8	Isokinetic strength training	Control	-1.48(-1.88, -1.08)	Favors ST	Possibly clinically important	Moderate
Huang (2003)	VAS Pain	112	Yes	52	Isotonic strength training	Control	-3.01(-3.56, -2.46)	Favors ST	Clinically important	Moderate
Huang (2003)	VAS Pain	124	Yes	52	Isometric strength training	Control	-1.97(-2.42, -1.52)	Favors ST	Clinically important	Moderate
Huang (2003)	VAS Pain	110	Yes	52	Isokinetic strength training	Control	-2.27(-2.75,-1.79)	Favors ST	Clinically important	Moderate
Maurer (1999)	WOMAC Pain	98	Unclear	8	Isokinetic quadriceps exercise	Education	Mean difference=15.09 (p>.05)	NS	Unclear	Moderate

Table 40. Isokinetic Versus Isotonic Versus Isometric Exercise: Pain

Study	Outcome	N	Sufficient Power to Detect MCII	Week	Group 1	Group 2	SMD (Odds Ratio or Raw Mean Difference When Indicated)	Sig	Clinical Importance	Strength of Evidence
Huang (2003)	VAS Pain	120	Yes	8	Isokinetic	Isometric	-.53(-.89,-.16)	Favors isokinetic	Not clinically important	Moderate

Study	Outcome	N	Sufficient Power to Detect MCII	Week	Group 1	Group 2	SMD (Odds Ratio or Raw Mean Difference When Indicated)	Sig	Clinical Importance	Strength of Evidence
Huang (2003)	VAS Pain	120	Yes	8	Isokinetic	Isotonic	.51(15, .87)	Favors isotonic	Not clinically important	Moderate
Huang (2003)	VAS Pain	124	Yes	8	Isometric	Isotonic	1.52(1.12, 1.93)	Favors isometric	Possibly clinically important	Moderate
Huang (2003)	VAS Pain	116	Yes	52	Isometric	Isokinetic	.41(.04, .78)	Favors isokinetic	Not clinically important	Moderate
Huang (2003)	VAS Pain	118	Yes	52	Isometric	Isotonic	.79(.42, 1.17)	Favors isotonic	Not clinically important	Moderate
Huang (2003)	VAS Pain	114	Yes	52	Isokinetic	Isotonic	.31(-.06, .68)	No	Inconclusive	Moderate

Table 41. Strength Training Versus Control: Functional Measure

Study	Outcome	N	Powered for MCII	Week	Group 1	Group 2	SMD (Odds Ratio or Raw Mean Difference When Indicated)	Sig	Clinical Importance	Strength of Evidence
Bennell (2010)	Stair climb improvement	76	Yes	12	Hip strengthening	No exercise	.61(.15, 1.07)	Favors hip strengthening	Unclear	Moderate
Bennell (2010)	Number of steps	76	Yes	12	Hip strengthening	No exercise	.48(.03, .94)	Favors HS	Unclear	Moderate
Jan (2008)	Stair climb	64	Unclear	8	Low resistance exercise	No exercise	-.03(-.52, .46)	No	Unclear	Moderate
Jan (2008)	Stair climb	64	Unclear	8	High resistance exercise	No exercise	-.09(-.59, .40)	No	Unclear	Moderate

Study	Outcome	N	Powered for MCII	Week	Group 1	Group 2	SMD (Odds Ratio or Raw Mean Difference When Indicated)	Sig	Clinical Importance	Strength of Evidence
Huang (2003)	Walk speed m/minute	64	Yes	8	Isotonic strength training	Control	4.21 (3.31, 5.11)	Favors isotonic strength training	Unclear	Moderate
Huang (2003)	Walk speed m/minute	64	Yes	52	Isometric	Control	1.93 (1.33, 2.53)	Favors isometric strength training	Unclear	Moderate
Huang (2003)	Lequesne index	64	Yes	8	Isotonic	Control	-1.32 (-1.86, -0.77)	Favors isotonic strength training	Unclear	Moderate
Huang (2003)	Lequesne index	64	Yes	52	Isometric	Control	-1.38 (-1.93, -0.83)	Favors isometric strength training	Unclear	Moderate
Jan (2008)	Figure 8 walk time	64	Yes	8	Low resistance training	No Exercise	-0.63 (-1.13, -0.12)	Favors LRT	Unclear	Moderate
Jan (2008)	Figure 8 walk time	64	Yes	8	High resistance training	No exercise	-0.71 (-1.21, -0.20)	Favors HRT	Unclear	Moderate
Jan (2008)	Level ground walk time	64	Unclear	8	Low resistance training	No exercise	-0.15 (-0.65, 0.34)	No	Unclear	Moderate
Jan (2008)	Level ground walk time	64	Unclear	8	High resistance training	No exercise	-0.09 (-0.59, 0.40)	No	Unclear	Moderate
Jan (2008)	Spongy surface walk time	64	Yes	8	Low resistance training	No exercise	-0.60 (-1.10, -0.09)	Favors LRT	Unclear	Moderate

Study	Outcome	N	Powered for MCII	Week	Group 1	Group 2	SMD (Odds Ratio or Raw Mean Difference When Indicated)	Sig	Clinical Importance	Strength of Evidence
Jan (2008)	Spongy surface walk time	64	Yes	8	High resistance training	No exercise	-0.70 (-1.21, -0.19)	Favors HRT	Unclear	Moderate
Lin (2009)	Level ground walk time	72	Yes	8	Strength training	No exercise	-0.54 (-1.01, -0.07)	Favors ST	Unclear	High
Lin (2009)	Stair walk time	72	Yes	8	Strength training	No exercise	-1.30 (-1.81, -0.78)	Favors ST	Unclear	High
Lin (2009)	Spongy surface walk time	72	Yes	8	Strength training	No exercise	-0.93 (-1.42, -0.44)	Favors ST	Unclear	High
Bennell (2010)	WOMAC Function	76	Yes	12	Hip strengthening	No exercise	0.86 (0.39, 1.33)	Favors HS	Clinically important	Moderate

Table 42. Strengthening Versus Control: WOMAC Total

Study	Outcome	N	Powered for MCII	Week	Group 1	Group 2	SMD (Odds Ratio or Raw Mean Difference When Indicated)	Sig	Clinical Importance	Strength of Evidence
Azad (2011)	WOMAC Total	68	Yes	4	Quadriceps muscle strengthening plus NSAIDS	NSAIDS only	-0.37 (-0.76, 0.01)	No	Unclear	Moderate
Azad (2011)	WOMAC Total	68	Yes	5	Quadriceps muscle strengthening plus NSAIDS	NSAIDS only	-0.59 (-0.98, -0.20)	Favors quadriceps muscle strengthening plus NSAIDS	Unclear	Moderate
Azad (2011)	WOMAC Total	68	Yes	6	Quadriceps muscle strengthening plus NSAIDS	NSAIDS only	-0.77 (-1.17, -0.38)	Favors quadriceps muscle strengthening plus NSAIDS	Unclear	Moderate
Maurer (1999)	WOMAC Total	98	Unclear	8	Isokinetic quadriceps exercise	Education	Mean Difference=3(p>.05)	NS	Unclear	Moderate
Shakoor (2010)	WOMAC Total	139	Yes	4 weeks	Isometric strengthening plus NSAIDS	NSAIDS only	-0.44 (-0.78, -0.11)	Favors exercise plus NSAIDS	Possibly clinically important	Moderate
Shakoor (2010)	WOMAC Total	139	Yes	5 weeks	Isometric strengthening plus NSAIDS	NSAIDS only	-0.59 (-0.93, -0.25)	Favors exercise plus NSAIDS	Possibly clinically important	Moderate
Shakoor (2010)	WOMAC Total	139	Yes	6 weeks	Isometric strengthening plus NSAIDS	NSAIDS only	-0.74 (-1.09, -0.4)	Favors exercise plus NSAIDS	Clinically significant	Moderate

Table 43. High Versus Low Resistance Training: Function

Study	Outcome	N	Powered for MCII	Week	Group 1	Group 2	SMD (Odds Ratio or Raw Mean Difference When Indicated)	Sig	Clinical Importance	Strength of Evidence
Jan (2008)	Stair climb	68	Unclear	8	High resistance exercise	Low resistance exercise	-.16(-.64, .31)	No	Unclear	Moderate
Jan (2008)	Figure 8 walk time	68	Unclear	8	High resistance training	Low resistance training	-0.40 (-0.88, 0.08)	No	Unclear	Moderate
Jan (2008)	Level ground walk time	68	Unclear	8	High resistance training	Low resistance training	0.30 (-0.17, 0.78)	No	Unclear	Moderate
Jan (2008)	Spongy surface walk time	68	Yes	8	High resistance training	Low resistance training	-0.49 (-0.97, -0.01)	Favors HRT	Unclear	Moderate

Table 44. Resistance Strength Training Versus Health Education

Study	Outcome	N	Powered for MCII	Week	Group 1	Group 2	SMD (Odds Ratio or Raw Mean Difference When Indicated)	Sig	Clinical Importance	Strength of Evidence
Ettinger (1997)	Time to get in and out of car	259	Yes	18	Resistance exercise	Health education	-.55(-.80, -.31)	Favors resistance exercise	Unclear	Moderate
Ettinger (1997)	Lift and carry task	259	Yes	18	Resistance exercise	Health education	-.51(-.75, -.26)	Favors resistance exercise	Unclear	Moderate

Study	Outcome	N	Powered for MCII	Week	Group 1	Group 2	SMD (Odds Ratio or Raw Mean Difference When Indicated)	Sig	Clinical Importance	Strength of Evidence
Ettinger (1997)	6 minute walk distance	259	Yes	18	Resistance exercise	Health Education	.87(.61, 1.12	Favors resistance exercise	Unclear	Moderate

Table 45. Physical Therapy Versus Control: Pain Measures

Study	Outcome	N	Powered for MCII	Week	Group 1	Group 2	SMD (Odds Ratio or Raw Mean Difference When Indicated)	Sig	Clinical Importance	Strength of Evidence
Fransen (2007)	WOMAC Pain improvement	126	Yes	8	Physical therapy	Waitlist control	3.04 (2.51, 3.57)	Favors physical therapy	Clinically important	Moderate
Bennell (2005)	VAS Pain on movement	140	Yes	12 weeks	Physiotherapy	No treatment	-0.1 (-0.43, 0.23)	NS	Inconclusive	High
Bennell (2005)	VAS Pain on movement	140	Yes	24 weeks	Physiotherapy	No treatment	-0.21 (-0.54, 0.12)	NS	Inconclusive	High
Bennell (2005)	WOMAC Pain	140	Yes	12 weeks	Physiotherapy	No treatment	0.03 (-0.3, 0.37)	NS	True negative	High
Bennell (2005)	WOMAC Pain	140	Yes	24 weeks	Physiotherapy	No treatment	-0.12 (-0.45, 0.21)	NS	Inconclusive	High
Bennell (2005)	Knee pain scale severity	140	Unclear	12 weeks	Physiotherapy	No treatment	-0.08 (-0.41, 0.25)	NS	Unclear	High
Bennell (2005)	Knee pain scale severity	140	Unclear	24 weeks	Physiotherapy	No treatment	-0.24 (-0.57, 0.09)	NS	Unclear	High

Study	Outcome	N	Powered for MCII	Week	Group 1	Group 2	SMD (Odds Ratio or Raw Mean Difference When Indicated)	Sig	Clinical Importance	Strength of Evidence
Bennell (2005)	Knee pain scale frequency	140	Yes	12 weeks	Physiotherapy	Placebo	-1.42 (-1.79, -1.05)	Favors physiotherapy	Unclear	High
Bennell (2005)	Knee pain scale frequency	140	Yes	24 weeks	Physiotherapy	Placebo	-0.79 (-1.13, -0.44)	Favors physiotherapy	Unclear	High

Table 46. Physical Therapy Versus Control: Functional Measures

Study	Outcome	N	Sufficient Power	Week	Group 1	Group 2	SMD (Odds Ratio or Raw Mean Difference When Indicated)	Sig	Clinical Importance	Strength of Evidence
Fransen (2007)	SF-36 Mental Function	126	Unclear	8	Physical therapy	Waitlist control	1.13 (0.74, 1.53)	Favors physical therapy	Unclear	Moderate
Bennell (2005)	SF-36 Physical Role	140	Unclear	12 weeks	Physiotherapy	No treatment	-0.03 (-0.36, 0.3)	NS	Unclear	High
Bennell (2005)	SF-36 Physical Role	140	Unclear	24 weeks	Physiotherapy	No treatment	0.04 (-0.29, 0.37)	NS	Unclear	High

Study	Outcome	N	Sufficient Power	Week	Group 1	Group 2	SMD (Odds Ratio or Raw Mean Difference When Indicated)	Sig	Clinical Importance	Strength of Evidence
Bennell (2005)	Assessment of Quality of Life index	140	Unclear	12 weeks	Physiotherapy	No treatment	0.09 (-0.24, 0.42)	NS	Unclear	High
Bennell (2005)	Assessment of Quality of Life index	140	Yes	24 weeks	Physiotherapy	Placebo	0.45 (0.12, 0.79)	Favors physiotherapy	Unclear	High
Bennell (2005)	Step test (number of steps) improvement	140	Unclear	12 weeks	Physiotherapy	No treatment	0.04 (-0.29, 0.37)	NS	Unclear	High
Bennell (2005)	Step test (number of steps) improvement	140	Unclear	24 weeks	Physiotherapy	No treatment	0.1 (-0.23, 0.44)	NS	Unclear	High
Bennell (2005)	WOMAC Function	140	Yes	12 weeks	Physiotherapy	No treatment	0.06 (-0.27, 0.39)	NS	True negative	High
Bennell (2005)	WOMAC Function	140	Yes	24 weeks	Physiotherapy	No treatment	-0.07 (-0.4, 0.26)	NS	Inconclusive	High
Fransen (2007)	SF-36 Physical	126	Yes	8	Physical therapy	Waitlist control	0.80 (0.42, 1.19)	Favors physical therapy	Clinically important	Moderate
Fransen (2007)	WOMAC Function improvement	126	Yes	8	Physical therapy	Waitlist control	1.01 (0.62, 1.40)	Favors physical therapy	Clinically important	Moderate
Borjesson (1996)	Steps/second	68	Unclear	5	Physiotherapy	No treatment	-0.08 (-0.55, 0.40)	No	Unclear	Low

Study	Outcome	N	Sufficient Power	Week	Group 1	Group 2	SMD (Odds Ratio or Raw Mean Difference When Indicated)	Sig	Clinical Importance	Strength of Evidence
Borjesson (1996)	Stride length	68	Unclear	5	Physiotherapy	No treatment	0.06 (-0.41, 0.54)	No	Unclear	Low
Borjesson (1996)	Meters walked per minute	68	Unclear	5	Physiotherapy	No treatment	-0.11 (-0.59, 0.36)	No	Unclear	Low

Table 47. Exercise Plus Manual Physical Therapy Versus Non-Therapeutic Intensity Ultrasound

Study	Outcome	N	Powered for MCII	Week	Group 1	Group 2	SMD (Odds Ratio or Raw Mean Difference When Indicated)	Sig	Clinical Importance	Strength of Evidence
Deyle (2000)	WOMAC Total	69	Yes	8	Exercise plus manual physical therapy	Placebo (non-therapeutic intensity ultrasound)	-0.83 (-1.33, -0.34)	Favors exercise plus PT	Possibly clinically significant	Moderate
Deyle (2000)	6 minute walk distance (m)	70	Yes	4	Exercise plus manual physical therapy	Placebo (non-therapeutic intensity ultrasound)	0.65 (0.16, 1.13)	Favors exercise plus PT	Unclear	Moderate
Deyle (2000)	6 minute walk distance (m)	71	Yes	8	Exercise manual physical therapy	Placebo (non-therapeutic intensity ultrasound)	0.61 (0.13, 1.09)	Favors exercise plus PT	Unclear	Moderate

Table 48. Proprioceptive Training Versus Control: Pain Measures

Study	Outcome	N	Powered for MCII	Week	Group 1	Group 2	SMD (Odds Ratio or Raw Mean Difference When Indicated)	Sig	Clinical Importance	Strength of Evidence
Lin (2009)	WOMAC Pain	72	Yes	8	Proprioceptive training	No exercise	-1.02 (-1.52, -0.53)	Favors proprioceptive training	Clinically important	High

Table 49. Proprioceptive Training Versus No Exercise: Function

Study	Outcome	N	Sufficient Power	Week	Group 1	Group 2	SMD (Odds Ratio or Raw Mean Difference When Indicated)	Sig	Clinical Importance	Strength of Evidence
Lin (2009)	Walk time-level ground	72	Yes	8	Proprioceptive training	No exercise	-0.55 (-1.02, -0.08)	Favors PrT	Unclear	High
Lin (2009)	WOMAC Function	72	Yes	8	Proprioceptive training	No exercise	-0.95 (-1.44, -0.46)	Favors PrT	Clinically important	High
Lin (2009)	Spongy surface walk time	72	Yes	8	Proprioceptive training(PrT)	No exercise	-1.57 (-2.11, -1.04)	Favors PrT	Unclear	High
Lin (2009)	Stair climb walk time	72	Yes	8	Proprioceptive training(PrT)	No exercise	-1.29 (-1.80, -0.78)	Favors PrT	Unclear	High

Table 50. Agility and Perturbation Training Plus Usual Exercise Versus Exercise Only (Fitzgerald 2011)

Outcome	N	Sufficient Power	Week	Group 1	Group 2	SMD	Sig	Clinical Importance	Strength of Evidence
WOMAC Total	183	Yes	52	Agility plus perturbation	Exercise only	-0.02 (-	No	True	High

						0.31, 0.27)		negative	
WOMAC Function	183	Yes	52	Agility plus perturbation	Exercise only	-0.26 (-0.55, 0.03)	No	True negative	High
Knee pain (numerical rating scale)	183	Unclear	52	Agility plus perturbation	Exercise only	0.11 (-0.18, 0.40)	No	True negative	High
Global rating of change	183	Unclear	52	Agility plus perturbation	Exercise only	0.00 (-0.29, 0.29)	No	True negative	High
Get up and go test	183	Unclear	52	Agility plus perturbation	Exercise only	0.26 (-0.03, 0.55)	No	True negative	High

Table 51. Agility and Perturbation Training Plus Usual Exercise Versus Exercise Only: Odds of Improvement From Baseline for WOMAC Functional Tasks (Teixeira 2011)

Outcome	N	Sufficient Power	Week	Group 1	Group 2	Odds Ratio	Sig	Clinical Importance	Strength of Evidence
When down the stairs?	91	Unclear	8	Agility plus perturbation	Exercise only	1.25 (0.55 ,2.87)	No	Unclear	Low
When going up stairs?	91	Unclear	8	Agility plus perturbation	Exercise only	1.25 (0.55 ,2.87)	No	Unclear	Low
Getting up from sitting position	91	Unclear	8	Agility plus perturbation	Exercise only	0.98 (0.44 ,2.16)	No	Unclear	Low
While standing?	91	Unclear	8	Agility plus perturbation	Exercise only	1.7 (0.70 ,4.09)	No	Unclear	Low
While bending to the floor?	91	Unclear	8	Agility plus perturbation	Exercise only	2.57 (1.2 ,5.52)	Favors agility plus perturbation	Unclear	Low
When walking on a flat surface?	91	Unclear	8	Agility plus perturbation	Exercise only	1.57 (0.71 ,3.50)	No	Unclear	Low

Outcome	N	Sufficient Power	Week	Group 1	Group 2	Odds Ratio	Sig	Clinical Importance	Strength of Evidence
While getting in/out of car?	91	Unclear	8	Agility plus perturbation	Exercise only	0.89 (0.41 ,1.96)	No	Unclear	Low
While going shopping?	91	Unclear	8	Agility plus perturbation	Exercise only	1.56 (0.73 ,3.35)	No	Unclear	Low
When putting on socks/stockings?	91	Unclear	8	Agility plus perturbation	Exercise only	1.02 (0.42 ,2.46)	No	Unclear	Low
While getting out of bed?	91	Unclear	8	Agility plus perturbation	Exercise only	1.25 (0.58 ,2.68)	No	Unclear	Low
When taking off socks/stockings?	91	Unclear	8	Agility plus perturbation	Exercise only	0.81 (0.36 ,1.84)	No	Unclear	Low
While lying in bed?	91	Unclear	8	Agility plus perturbation	Exercise only	1.14 (0.48 ,2.72)	No	Unclear	Low
When getting in/out of bath?	91	Unclear	8	Agility plus perturbation	Exercise only	0.79 (0.36 ,1.70)	No	Unclear	Low
While sitting?	91	Unclear	8	Agility plus perturbation	Exercise only	1.33 (0.64 ,2.77)	No	Unclear	Low
When getting on/off toilet?	91	Unclear	8	Agility plus perturbation	Exercise only	1.37 (0.60 ,3.1)	No	Unclear	Low
While doing heavy household chores	91	Unclear	8	Agility plus perturbation	Exercise only	1.52 (0.64 ,3.6)	No	Unclear	Low
While doing light household chores?	91	Unclear	8	Agility plus perturbation	Exercise only	1.23 (0.54 ,2.82)	No	Unclear	Low

Table 52. Kinesthesia Plus Strength Training Versus Strength Training: Function

Study	Outcome	N	Sufficient Power	Week	Group 1	Group 2	SMD (Odds Ratio or Raw Mean Difference When Indicated)	Sig	Clinical Importance	Strength of Evidence
Diracoglu (2005)	SF-36 Physical	126	Yes	8	Kinesthesia (K) plus balance (B) plus strengthening (S)	Strengthening exercises	0.75 (0.22, 1.27)	Favors K plus B plus S	Clinically important	Moderate
Diracoglu (2005)	SF-36 Role Limitations	126	Unclear	8	Kinesthesia plus balance plus strengthening	Strengthening exercises	0.50 (-0.02, 1.01)	No	Unclear	Moderate
Diracoglu (2005)	SF-36 Vitality	126	Yes	8	Kinesthesia plus balance plus strengthening	Strengthening exercises	0.55 (0.03, 1.06)	Favors K plus B plus S	Unclear	Moderate
Diracoglu (2005)	10m walk	126	Yes	8	Kinesthesia plus balance plus strengthening	Strengthening exercises	-0.56 (-1.07, -0.04)	Favors K plus B plus S	Unclear	Moderate

Table 53. Weight Bearing and Non-Weight Bearing Exercise

Study	Outcome	N	Sufficient Power	Week	Group 1	Group 2	SMD (Odds Ratio or Raw Mean Difference When Indicated)	Sig	Clinical Importance	Strength of Evidence
Jan (2009)	WOMAC Function	71	Yes	8 weeks	Weight bearing exercise	Control	-1.16 (-1.66, -0.65)	Favors weight bearing exercise	Clinically significant	Moderate
Jan (2009)	Level ground walking time(s)	71	Yes	8 weeks	Weight bearing exercise	Control	-0.59 (-1.07, -0.11)	Favors weight bearing exercise	Unclear	Moderate
Jan (2009)	Stair climb time	71	Yes	8 weeks	Weight bearing exercise	Control	-1.01 (-1.5, -0.51)	Favors weight bearing exercise	Unclear	Moderate
Jan (2009)	Figure 8 walking time	71	Yes	8 weeks	Weight bearing exercise	Control	-0.97 (-1.46, -0.47)	Favors weight bearing exercise	Unclear	Moderate
Jan (2009)	Sponge walk time	71	Yes	8 weeks	Weight bearing exercise	Control	-1.76 (-2.31, -1.21)	Favors weight bearing exercise	Unclear	Moderate
Jan (2009)	WOMAC Function	70	Yes	8 weeks	Non-weight bearing exercise	Control	-1.33 (-1.85, -0.81)	Favors non-weight bearing exercise	Clinically significant	Moderate

Study	Outcome	N	Sufficient Power	Week	Group 1	Group 2	SMD (Odds Ratio or Raw Mean Difference When Indicated)	Sig	Clinical Importance	Strength of Evidence
Jan (2009)	Level ground walking time(s)	70	Yes	8 weeks	Non-weight bearing exercise	Control	-0.85 (-1.34, -0.36)	Favors non-weight bearing exercise	Unclear	Moderate
Jan (2009)	Stair climb time	70	Yes	8 weeks	Non-weight bearing exercise	Control	-1.49 (-2.03, -0.96)	Favors non-weight bearing exercise	Unclear	Moderate
Jan (2009)	Figure-8 walking time	70	Yes	8 weeks	Non-weight bearing exercise	Control	-0.48 (-0.96, -0.01)	Favors non-weight bearing exercise	Unclear	Moderate
Jan (2009)	Sponge walk time	70	Yes	8 weeks	Non-weight bearing exercise	Control	-0.61 (-1.09, -0.13)	Favors non-weight bearing exercise	Unclear	Moderate
Jan (2009)	Level ground walking time(s)	71	Unclear	8 weeks	Weight bearing exercise	Non-weight bearing exercise	0.24 (-0.23, 0.7)	NS	Unclear	Moderate

Study	Outcome	N	Sufficient Power	Week	Group 1	Group 2	SMD (Odds Ratio or Raw Mean Difference When Indicated)	Sig	Clinical Importance	Strength of Evidence
Jan (2009)	Stair climb time	71	Yes	8 weeks	Weight bearing exercise	Non-weight bearing exercise	0.58 (0.11, 1.06)	Favors non-weight bearing exercise	Unclear	Moderate
Jan (2009)	Figure 8 walking time	71	Unclear	8 weeks	Weight bearing exercise	Non-weight bearing exercise	-0.44 (-0.91, 0.04)	NS	Unclear	Moderate
Jan (2009)	Sponge walk time	71	Yes	8 weeks	Weight bearing exercise	Non-weight bearing exercise	-1.06 (-1.55, -0.56)	Favors weight bearing exercise	Unclear	Moderate

Table 54. Water Versus Land-Based Exercise: Pain

Study	Outcome	N	Power to Detect MCII	Week	Group 1	Group 2	SMD (Odds Ratio or Raw Mean Difference When Indicated)	Sig	Clinical Importance	Strength of Evidence
Silva (2008)	VAS Pain	64	Yes	18	Water exercise	Land exercise	-0.41 (-0.91, 0.08)	No	Negative	Moderate
Silva (2008)	VAS Pain after 50 foot walk	64	Yes	9	Water exercise	Land exercise	-0.19 (-0.68, 0.30)	No	Negative	Moderate

Study	Outcome	N	Power to Detect MCII	Week	Group 1	Group 2	SMD (Odds Ratio or Raw Mean Difference When Indicated)	Sig	Clinical Importance	Strength of Evidence
Silva (2008)	VAS Pain after 50 foot walk	64	Yes	18	Water exercise	Land exercise	-0.68 (-1.19, -0.18)	Favors water exercise	Not clinically important	Moderate
Silva (2008)	VAS Pain before 50 foot walk	64	Yes	9	Water exercise	Land exercise	-0.19 (-0.68, 0.30)	No	Negative	Moderate
Silva (2008)	VAS Pain before 50 foot walk	64	Yes	18	Water exercise	Land exercise	-0.53 (-1.03, -0.03)	Favors water exercise	Not clinically important	Moderate

Table 55. Water Versus Land-Based Exercise: Lequesne Index

Study	Outcome	N	Sufficient Power	Week	Group 1	Group 2	SMD (Odds Ratio or Raw Mean Difference When Indicated)	Sig	Clinical Importance	Strength of Evidence
Silva (2008)	Lequesne index	64	Unclear	18	Water exercise	Land exercise	-0.39 (-0.89, 0.10)	No	Unclear	Moderate

Table 56. Home-Based and Hospital-Based Exercise Programs

Study	Outcome	N	Sufficient Power	Week	Group 1	Group 2	SMD (Odds Ratio or Raw Mean Difference When Indicated)	Sig	Clinical Importance	Strength of Evidence
O'Reilly (1999)	Global Pain Score	180	Yes	26	Home exercise	No intervention	-0.54 (-0.84, -0.24)	Favors home exercise	Not clinically important	High
O'Reilly (1999)	VAS Walking	180	Yes	26	Home exercise	No intervention	-0.33 (-0.63, 0.03)	Favors home exercise	Not clinically important	High
O'Reilly (1999)	VAS Stairs	180	Yes	26	Home exercise	No intervention	-0.35 (-0.63, 0.05)	Favors home exercise	Not clinically important	High
O'Reilly (1999)	WOMAC Physical function	180	Yes	26	Home exercise	No intervention	-0.4 (-0.7, -.10)	Favors home exercise	Possibly clinically important	High
O'Reilly (1999)	Mental health	180	Unclear	26	Home exercise	No intervention	0.18 (-0.11, 0.48)	NS	Unclear	High
O'Reilly (1999)	Energy	180	Unclear	26	Home exercise	No intervention	0.11 (-0.19, 0.41)	NS	Unclear	High
O'Reilly (1999)	Health perception	180	Unclear	26	Home exercise	No intervention	0.19 (-0.11, 0.48)	NS	Unclear	High
O'Reilly (1999)	Role limitation physical	180	Unclear	26	Home exercise	No intervention	0.28 (-0.02, 0.58)	NS	Unclear	High
O'Reilly (1999)	Role limitation emotional	180	Unclear	26	Home exercise	No intervention	0.03 (-0.27, 0.32)	NS	Unclear	High

Study	Outcome	N	Sufficient Power	Week	Group 1	Group 2	SMD (Odds Ratio or Raw Mean Difference When Indicated)	Sig	Clinical Importance	Strength of Evidence
O'Reilly (1999)	Social functioning	180	Unclear	26	Home exercise	No intervention	0 (-0.3, 0.3)	NS	Unclear	High
McCarthy (2004)	WOMAC Pain	151	Yes	52	Home-based exercise alone	Home-based plus class based exercise	0.42 (0.09, 0.74)	Favors home-based and class based programs	Possibly clinically important	High
McCarthy (2004)	WOMAC Stiffness	151	Yes	26	Home-based exercise alone	Home-based plus class based exercise	0.40 (0.08, 0.73)	Favors home-based and class based programs	Possibly clinically important	High
McCarthy (2004)	WOMAC Stiffness	151	Yes	52	Home-based exercise alone	Home-based plus class based exercise	0.39 (0.07, 0.71)	Favors home-based and class based programs	Possibly clinically important	High
McCarthy (2004)	VAS Pain	151	Yes	26	Home-based exercise alone	Home-based plus class based exercise	0.58 (0.25, 0.91)	Favors home-based and class based programs	Not clinically important	High
McCarthy (2004)	VAS Pain	151	Yes	52	Home based exercise alone	Home-based plus class based exercise	0.78 (0.45, 1.11)	Favors home-based and class based programs	Not clinically important	High
McCarthy (2004)	WOMAC Pain	151	Yes	26	Home-based exercise alone	Home-based plus class based exercise	0.29 (-0.03, 0.61)	NS	True negative	High

Study	Outcome	N	Sufficient Power	Week	Group 1	Group 2	SMD (Odds Ratio or Raw Mean Difference When Indicated)	Sig	Clinical Importance	Strength of Evidence
Tunay (2010)	Left knee VAS Rest	60	Yes	6	Hospital-based proprioceptive and strength exercise	Home-based proprioceptive and strength exercise	0.07 (-0.44, 0.57)	NS	True negative	Moderate
Tunay (2010)	Left knee VAS Activity	60	Yes	6	Hospital-based proprioceptive and strength exercise	Home-based proprioceptive and strength exercise	-0.65 (-1.17, -0.13)	Favors hospital-based proprioceptive and strength exercise	Not clinically important	Moderate
Tunay (2010)	Left knee VAS Night	60	Yes	6	Hospital-based proprioceptive and strength exercise	Home-based proprioceptive and strength exercise	-0.3 (-0.81, 0.21)	NS	True negative	Moderate
Tunay (2010)	Right knee VAS Rest	60	Yes	6	Hospital-based proprioceptive and strength exercise	Home-based proprioceptive and strength exercise	-0.24 (-0.75, 0.27)	NS	True negative	Moderate
Tunay (2010)	Right knee VAS Activity	60	Yes	6	Hospital-based proprioceptive and strength exercise	Home-based proprioceptive and strength exercise	-0.46 (-0.98, 0.05)	NS	True negative	Moderate

Study	Outcome	N	Sufficient Power	Week	Group 1	Group 2	SMD (Odds Ratio or Raw Mean Difference When Indicated)	Sig	Clinical Importance	Strength of Evidence
Tunay (2010)	Right knee VAS Night	60	Yes	6	Hospital-based proprioceptive and strength exercise	Home-based proprioceptive and strength exercise	0.19 (-0.32, 0.69)	NS	True negative	Moderate

Table 57. Aerobic Exercise Versus Control: Function

Study	Outcome	N	Sufficient Power	Week	Group 1	Group 2	SMD (Odds Ratio or Raw Mean Difference When Indicated)	Sig	Clinical Importance	Strength of Evidence
Rejeski (2003)	SF-36 Mental Health	69	Unclear	78	Aerobic exercise	Healthy life style education control	0.08 (-0.26, 0.41)	No	Unclear	Low

Table 58. Aerobic Exercise Versus Control: Functional Task

Study	Outcome	N	Sufficient Power	Week	Group 1	Group 2	SMD (Odds Ratio or Raw Mean Difference When Indicated)	Sig	Clinical Importance	Strength of Evidence
Ettinger (1997)	Lift and carry task time(s)	265	Yes	18	Aerobic exercise	Education	-0.38 (-0.63, -0.14)	Favors aerobic exercise	Unclear	Moderate
Ettinger (1997)	Stair climb	265	Unclear	18	Aerobic exercise	Education	-0.15 (-0.39, 0.09)	No	Unclear	Moderate
Ettinger (1997)	Time to get in and out of car	265	Yes	18	Aerobic exercise	Education	-0.46 (-0.71, -0.22)	Favors aerobic exercise	Unclear	Moderate
Ettinger (1997)	Walk distance	265	Yes	18	Aerobic exercise	Education	0.30 (0.06, 0.54)	Favors aerobic exercise	Unclear	Moderate
Focht (2005)	Stair climb time	80	Unclear	78	Aerobic exercise	Health education	-0.14 (-0.45, 0.17)	No	Unclear	Low

Table 59. Supervised Walking Versus Usual Care: Pain

Study	Outcome	N	Power to Detect MCII	Week	Group 1	Group 2	SMD (Odds Ratio or Raw Mean Difference When Indicated)	Sig	Clinical Importance	Strength of Evidence
Kovar (1992)	AIMS Arthritis Pain	92	Yes	8	Supervised walking plus	Usual care	-0.51 (-0.93, -0.10)	Favors walking	Unclear	Moderate

					education					

Table 60. Supervised Walking Versus Usual Care: Function

Study	Outcome	N	Power to Detect MCII	Week	Group 1	Group 2	SMD (Odds Ratio or Raw Mean Difference When Indicated)	Sig	Clinical Importance	Strength of Evidence
Kovar (1992)	AIMS Physical Activity	92	Yes	8	Supervised walking plus education	Usual care	-0.88 (-1.30, -0.45)	Favors walking	Unclear	Moderate
Kovar (1992)	AIMS Arthritis Impact	92	Unclear	8	Supervised walking plus education	Usual care	-0.10 (-0.51, 0.30)	No	Unclear	Moderate
Kovar (1992)	6 minute Walk Distance	92	Yes	8	Supervised walking plus education	Usual care	0.91 (0.48, 1.34)	Favors supervised walking	Unclear	Moderate

Table 61. Supervised Walking Versus Control: Arthritis Impact Measurement Scale (Medications Use)

Study	Outcome	N	Power to Detect MCII	Week	Group 1	Group 2	SMD (Odds Ratio or Raw Mean Difference When Indicated)	Sig	Clinical Importance	Strength of Evidence
Kovar (1992)	AIMS Medications Use	92	Unclear	8	Supervised walking plus education	Usual care	0.37 (-0.04, 0.79)	No	Unclear	Low

Table 62. Self-Management Versus Waitlist Control

Study	Outcome	N	Power	Week	Group 1	Group 2	SMD/Mean difference	Sig	Clinical Importance	Strength of Evidence
Coleman (2012)	WOMAC Pain	139	Yes	8	Class-based self-management program	Weight list control	-1.46 (-2.18, -.73)	Favors self-management	Possibly clinically significant	High
Coleman (2012)	WOMAC Pain	136	Yes	26	Class-based self-management program	Weight list control	-.49(-1.26, .28)	No	True negative	High
Coleman (2012)	WOMAC Stiffness	139	Yes	8	Class-based self-management program	Weight list control	-.5(-.91, -.08)	Favors self-management	Possibly clinically significant	High
Coleman (2012)	WOMAC Stiffness	136	Yes	26	Class-based self-management program	Weight list control	-.29(-.73, .15)	No	Inconclusive	High
Coleman (2012)	WOMAC Function	139	Yes	8	Class-based self-management program	Weight list control	-5.55(-7.38, -3.31)	Favors self-management	Possibly clinically significant	High
Coleman (2012)	WOMAC Function	136	Yes	26	Class-based self-management program	Weight list control	-4.35(-6.2,-.91)	Favors self-management	Possibly clinically significant	High
Coleman (2012)	WOMAC Total	139	Yes	8	Class-based self-management program	Weight list control	-7.73(-9.98, -4.49)	Favors self-management	Possibly clinically significant	High

Study	Outcome	N	Power	Week	Group 1	Group 2	SMD/Mean difference	Sig	Clinical Importance	Strength of Evidence
Coleman (2012)	WOMAC Total	136	Yes	26	Class-based self-management program	Weight list control	-4.08(-7.47, -.68)	Favors self-management	Possibly clinically significant	High
Coleman (2012)	SF-36 Physical Function	136	Yes	26	Class-based self-management program	Weight list control	5.67 (0.40, 10.93)	Favors self-management	Possibly clinically significant	High
Coleman (2012)	SF-36 Role Physical	136	Unclear	26	Class-based self-management program	Weight list control	7.37 (-5.93, 20.67)	No	Unclear	High
Coleman (2012)	SF-36 Body Pain	136	Yes	26	Class-based self-management program	Weight list control	6.06 (0.04, 12.07)	Favors self-management	Possibly clinically significant	High
Coleman (2012)	SF-36 General Health	136	Unclear	26	Class-based self-management program	Weight list control	3.59 (-1.19, 8.37)	No	Unclear	High
Coleman (2012)	SF-36 Vitality	136	Unclear	26	Class-based self-management program	Weight list control	4.72 (-0.11, 9.55)	No	Unclear	High
Coleman (2012)	SF-36 Social Function	136	Unclear	26	Class-based self-management program	Weight list control	4.07(-2.08, 12.22)	No	Unclear	High

Study	Outcome	N	Power	Week	Group 1	Group 2	SMD/Mean difference	Sig	Clinical Importance	Strength of Evidence
Coleman (2012)	SF-36 Role Emotional	136	Unclear	26	Class-based self-management program	Weight list control	1.35 (-11.06, 13.76)	No	Unclear	High
Coleman (2012)	SF-36 Mental Health	136	Unclear	26	Class-based self-management program	Weight list control	3.85 (-0.21, 7.91)	No	Unclear	High
Coleman (2012)	SF-36 Physical Function	139	Yes	8	Class-based self-management program	Weight list control	5.61 (1.84, 9.37)	Favors self-management	Possibly clinically significant	High
Coleman (2012)	SF-36 Role Physical	139	Yes	8	Class-based self-management program	Weight list control	17.06 (5.90, 28.21)	Favors self-management	Unclear	High
Coleman (2012)	SF-36 Body Pain	139	Yes	8	Class-based self-management program	Weight list control	7.19 (1.93, 12.44)	Favors self-management	Possibly clinically significant	High
Coleman (2012)	SF-36 General Health	139	Unclear	8	Class-based self-management program	Weight list control	2.11 (-1.45, 5.67)	No	Unclear	High
Coleman (2012)	SF-36 Vitality	139	Yes	8	Class-based self-management program	Weight list control	6.02 (1.87, 10.16)	Favors self-management	Unclear	High

Study	Outcome	N	Power	Week	Group 1	Group 2	SMD/Mean difference	Sig	Clinical Importance	Strength of Evidence
Coleman (2012)	SF-36 Social Function	139	Yes	8	Class-based self-management program	Weight list control	10.72 (4.81, 16.62)	Favors self-management	Unclear	High
Coleman (2012)	SF-36 Role Emotional	139	Unclear	8	Class-based self-management program	Weight list control	5.18 (-5.64, 16.00)	No	Unclear	High
Allen (2010)	AIMS2 Pain	344	Yes	52	Telephone-based self-management program	Attention control	-.6 p=.007	Favors telephone-based self-management	Unclear	Modereate
Allen (2010)	AIMS2 Function	344	Unclear	52	Telephone-based self-management program	Attention control	-.2 p=.093	No	Unclear	Modereate
Allen (2010)	AIMS2 walking and bending	344	Yes	52	Telephone-based self-management program	Attention control	-.5 p=.035	Favors telephone-based self-management	Unclear	Modereate
Allen (2010)	AIMS2 Mobility	344	Unclear	52	Telephone-based self-management program	Attention control	-.2 p=.21	No	Unclear	Modereate
Allen (2010)	AIMS2 Affect	344	Unclear	52	Telephone-based self-management program	Attention control	.1 p=.78	No	Unclear	Modereate

Study	Outcome	N	Power	Week	Group 1	Group 2	SMD/Mean difference	Sig	Clinical Importance	Strength of Evidence
Allen (2010)	Arthritis Self-Efficacy Scale	344	Yes	52	Telephone-based self-management program	Attention control	.4 p=.043	Favors telephone-based self-management	Unclear	Modereate
Allen (2010)	VAS Pain	344	Yes	52	Telephone-based self-management program	Attention control	-10 p<.001	Favors telephone-based self-management	Unclear	Modereate
Allen (2010)	AIMS2 Pain	343	Unclear	52	Telephone-based self-management program	Usual care	-.4 p=.105	No	Unclear	Modereate
Allen (2010)	AIMS2 Function	343	Unclear	52	Telephone-based self-management program	Usual care	-.1 p=.43	No	Unclear	Modereate
Allen (2010)	AIMS2 walking and bending	343	Unclear	52	Telephone-based self-management program	Usual care	-.2 p=.41	No	Unclear	Modereate
Allen (2010)	AIMS2 Mobility	343	Unclear	52	Telephone-based self-management program	Usual care	-.0 p=.93	No	Unclear	Modereate
Allen (2010)	AIMS2 Affect	343	Unclear	52	Telephone-based self-management program	Usual care	.00 p=.79	No	Unclear	Modereate

Study	Outcome	N	Power	Week	Group 1	Group 2	SMD/Mean difference	Sig	Clinical Importance	Strength of Evidence
Allen (2010)	Arthritis Self-Efficacy Scale	343	Unclear	52	Telephone-based self-management program	Usual care	.4 p=.066	No	Unclear	Modereate
Allen (2010)	VAS Pain	343	Yes	52	Telephone-based self-management program	Usual care	-11 p<.001	Favors telephone-based self-management	Unclear	Modereate

Table 63. Self-Management Plus Exercise Versus Usual Care: Pain

Study	Outcome	N	Powered to Detect MCII	Week	Group 1	Group 2	SMD (Odds Ratio or Raw Mean Difference When Indicated)	Sig	Clinical Importance	Strength of Evidence
Yip (2007)	Arthritis Self-Efficacy Pain Score improvement	176	Yes	16	Self-management plus exercise plus usual care	Usual care	0.54 (0.24, 0.84)	Favors self-management plus exercise plus usual care	Unclear	Moderate
Yip (2007)	VAS Pain improvement	176	Yes	16	Self-management plus exercise plus usual care	Usual care	0.62 (0.31, 0.92)	Favors self-management plus exercise plus usual care	Not clinically important	Moderate

Table 64. Self-Management Plus Exercise Versus Usual Care: Function

Study	Outcome	N	Power to Detect MCII	Week	Group 1	Group 2	SMD (Odds Ratio or Raw Mean Difference When Indicated)	Sig	Clinical Importance	Strength of Evidence
Yip (2007)	Health Assessment Questionnaire improvement	176	Unclear	16	Self-management plus Exercise plus usual care	Usual care	0.12 (-0.17, 0.42)	No	Unclear	Moderate

Study	Outcome	N	Power to Detect MCII	Week	Group 1	Group 2	SMD (Odds Ratio or Raw Mean Difference When Indicated)	Sig	Clinical Importance	Strength of Evidence
Yip (2007)	Arthritis Self-Efficacy other symptoms improvement	176	Yes	16	Self-management plus exercise plus usual care	Usual care	0.51 (0.21, 0.81)	Favors Self-management plus exercise plus usual care	Unclear	Moderate
Yip (2007)	Hours of light exercise improvement	176	Yes	16	Self-management plus exercise plus usual care	Usual care	0.57 (0.27, 0.87)	Favors Self-management plus exercise plus usual care	Unclear	Moderate

Table 65. Structured Consultation Versus Control: Function

Study	Outcome	N	Power to Detect MCII	Week	Group 1	Group 2	SMD (Odds Ratio or Raw Mean Difference When Indicated)	Sig	Clinical Importance	Strength of Evidence
Ravaud (2009)	SF-12 Mental Function improvement	327	Unclear	16	Standardized structured physician consultation program (education)	Usual care	0.30 (0.08, 0.51)	Favors education	Unclear	Moderate

Study	Outcome	N	Power to Detect MCII	Week	Group 1	Group 2	SMD (Odds Ratio or Raw Mean Difference When Indicated)	Sig	Clinical Importance	Strength of Evidence
Ravaud (2009)	SF-12 Physical Function improvement	327	Yes	16	Standardized structured physician consultation program (education)	Usual care	0.16 (-0.06, 0.38)	No	Inconclusive	Moderate
Ravaud (2009)	WOMAC Function improvement	327	Yes	16	Standardized structured physician consultation program (education)	Usual care	0.15 (-0.06, 0.37)	No	Inconclusive	Moderate

Table 66. Integrated Exercise, Self-Management, and Coping Strategies Versus Usual Care (Hurley 2007)

Outcome	N	Sufficient Power	Week	Group 1	Group 2	SMD (Odds Ratio or Raw Mean Difference When Indicated)	Sig	Clinical Importance	Strength of Evidence
WOMAC Function	342	Yes	26	Integrated exercise, self-management and coping strategies	Usual care	-.29(-.52, -.07)	Favors Group 1	Possibly clinically important	Moderate
WOMAC Pain	342	Yes	26	Integrated exercise, self-management and coping strategies	Usual care	-0.27 (-0.5, -0.05)	Favors Group 1	Possibly clinically important	Moderate
WOMAC Total	342	Yes	26	Integrated exercise, self-management and coping strategies	Usual care	-0.28 (-0.5, -0.05)	Favors Group 1	Possibly clinically important	Moderate

Outcome	N	Sufficient Power	Week	Group 1	Group 2	SMD (Odds Ratio or Raw Mean Difference When Indicated)	Sig	Clinical Importance	Strength of Evidence
Aggregate Functional Performance time(s)	342	Unclear	26	Integrated exercise, self-management and coping strategies	Usual care	-0.17 (-0.41,0.06)	No	Unclear	Moderate
Exercise Health Beliefs Self-Efficacy Subscale	342	Yes	26	Integrated exercise, self-management and coping strategies	Usual care	0.41 (0.17,0.63)	Favors Group 1	Unclear	Moderate
Exercise Health Beliefs Total Score	342	Yes	26	Integrated exercise, self-management and coping strategies	Usual care	0.51 (0.28,0.75)	Favors Group 1	Unclear	Moderate
Hospital Anxiety and Depression Scale Depression Subscale	342	Yes	26	Integrated exercise, self-management and coping strategies	Usual care	-0.23 (-0.46,-0.01)	Favors Group 1	Unclear	Moderate

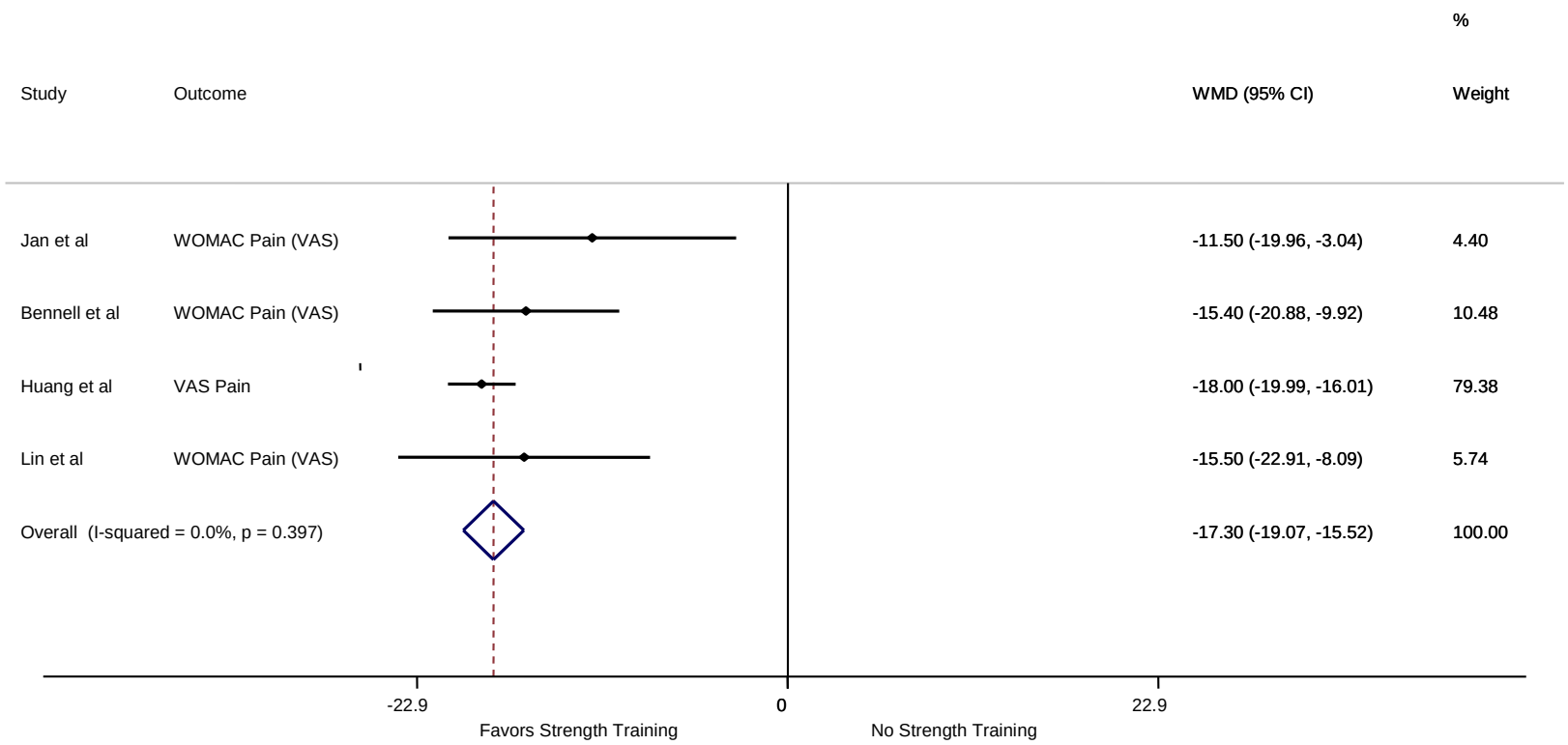
Outcome	N	Sufficient Power	Week	Group 1	Group 2	SMD (Odds Ratio or Raw Mean Difference When Indicated)	Sig	Clinical Importance	Strength of Evidence
Hospital Anxiety and Depression Scale Anxiety Subscale	342	Unclear	26	Integrated exercise, self-management and coping strategies	Usual care	-0.16 (-0.38,0.07)	No	Unclear	Moderate
MACTAR	342	Yes	26	Integrated exercise, self-management and coping strategies	Usual care	0.27 (0.04,0.5)	Favors Group 1	Unclear	Moderate
EQ-5D	342	Unclear	26	Integrated exercise, self-management and coping strategies	Usual care	-0.09 (-0.39,0.21)	No	Unclear	Moderate

Table 67. Yoga Plus Physiotherapy Versus Physiotherapy Only (Ebenezer 2011)

Study	Outcome	N	Sufficient Power	Week	Group 1	Group 2	SMD (Odds Ratio or Raw Mean Difference When Indicated)	Sig	Clinical Importance	Strength of Evidence
Ebnezar (2011)	Physical functioning	235	Yes	13	Yoga plus physiotherapy	Physiotherapy only	1.35 (1.06, 1.63)	Favors yoga plus physiotherapy	Clinically significant	Low
Ebnezar (2011)	Role limitations	235	Yes	13	Yoga plus physiotherapy	Physiotherapy only	0.84 (0.57, 1.1)	Favors yoga plus physiotherapy	Unclear	Low
Ebnezar (2011)	Emotional problems	235	Yes	13	Yoga plus physiotherapy	Physiotherapy only	0.91 (0.64, 1.18)	Favors yoga plus physiotherapy	Unclear	Low
Ebnezar (2011)	Energy/fatigue	235	Yes	13	Yoga plus physiotherapy	Physiotherapy only	-2.59 (-2.94, -2.24)	Favors yoga plus physiotherapy	Unclear	Low
Ebnezar (2011)	Emotional well-being	235	Yes	13	Yoga plus physiotherapy	Physiotherapy only	-3.14 (-3.53, -2.76)	Favors yoga plus physiotherapy	Unclear	Low
Ebnezar (2011)	Social function	235	Yes	13	Yoga plus physiotherapy	Physiotherapy only	0.71 (0.44, 0.97)	Favors yoga plus physiotherapy	Unclear	Low
Ebnezar (2011)	Pain	235	Yes	13	Yoga plus physiotherapy	Physiotherapy only	2.24 (1.91, 2.56)	Favors yoga plus physiotherapy	Clinically significant	Low

Ebnezar (2011)	General health	235	Yes	13	Yoga plus physiotherapy	Physiotherapy only	1 (0.73, 1.27)	Favors yoga plus physiotherapy	Unclear	Low
Ebnezar (2012)	Resting pain	235	Yes	13	Yoga plus physiotherapy	Physiotherapy only	-1.678 (-1.976, -1.38)	Favors yoga plus physiotherapy	Unclear	Low
Ebnezar (2012)	Early morning stiffness	235	Yes	13	Yoga plus physiotherapy	Physiotherapy only	-1.285 (-1.567, -1.004)	Favors yoga plus physiotherapy	Unclear	Low
Ebnezar (2012)	Walking pain	235	Yes	13	Yoga plus physiotherapy	Physiotherapy only	-1.577 (-1.871, -1.284)	Favors yoga plus physiotherapy	Unclear	Low
Ebnezar (2012)	WOMAC Function	235	Yes	13	Yoga plus physiotherapy	Physiotherapy only	-1.746 (-2.047, -1.444)	Favors yoga plus physiotherapy	Clinically significant	High
Ebnezar (2012)	Walking time	235	Yes	13	Yoga plus physiotherapy	Physiotherapy only	-1.553 (-1.846, -1.261)	Favors yoga plus physiotherapy	Unclear	High

Figure 12. Strength Training Versus Control: Pain



RECOMMENDATION 2

We suggest weight loss for patients with symptomatic osteoarthritis of the knee and a BMI ≥ 25.

Strength of Recommendation: Moderate

Description: Evidence from two or more "Moderate" strength studies with consistent findings, or evidence from a single "High" quality study for recommending for or against the intervention. A **Moderate** recommendation means that the benefits exceed the potential harm (or that the potential harm clearly exceeds the benefits in the case of a negative recommendation), but the quality/applicability of the supporting evidence is not as strong.

Implications: Practitioners should generally follow a **Moderate** recommendation but remain alert to new information and be sensitive to patient preferences.

RATIONALE

There was one moderate- and two low- strength studies included in this recommendation. Physical Function on the SF-36 showed minimum clinically important improvement in outcomes for this patient population. WOMAC function also showed statistical improvement which was possibly clinically significant. Diet and exercise combined revealed improved results. The workgroup considers that the public and patient health benefits of weight loss warranted an upgrade of the recommendation strength to moderate. [53-55]

SUPPORTING EVIDENCE

QUALITY

Relevant Tables: Table 68-Table 70, Table 71-Table 74

Two low quality studies[46;47] compared exercise-based weight loss to health education. Neither had treatment integrity, group comparability or measurement flaws. However, they were flawed in their hypotheses were retrospective. Additionally, they were flawed in the group assignment, blinding, and investigator bias domains. Focht et al.[46] was the only aerobic exercise study that was sufficiently blinded.

There were three included studies that compared weight loss programs (diet and/or exercise) to health education controls. Two studies were of low quality[46;47], and the other was of moderate quality[56] The treatment integrity, group comparability and measurement domains were not flawed. The group assignment and investigator bias domains were. Rejeski et al.[47]and Focht et al.[46] were retrospective and therefore flawed in the hypothesis domain. Miller et al.[56]was the only study that was sufficiently blinded.

Three studies compared very low energy diets to conventional low energy diets. Bliddal et al.[57] and Riecke et al.[58] were low quality, and Christensen et al.[59] was of moderate quality. The studies were not flawed in terms of treatment integrity and measurement, but flawed in the group assignment, group comparability and investigator bias domains. Additionally, Reicke et al. and Bliddal et al. did not contain prospective hypotheses and were flawed in the blinding domain.

Two included studies compared diet to exercise. Jenkinson et al.[60] was a high quality study that was appropriate in every quality domain except for investigator bias. The other study[46] was not flawed in the treatment integrity and measurement domains. However, it was flawed in the hypothesis, group assignment, blinding, group comparability, and investigator bias domains and was given a low quality rating.

APPLICABILITY

Relevant Tables: Table 68-Table 70, Table 71-Table 74

The participants and the administration of the interventions may not have been representative of clinical practice in the included exercise-based weight loss studies[46;47] Compliance and adherence were similar in both studies. Intent to treat analysis was used in both studies.

The three studies that compared weight loss to education likewise contained uncertainty as to whether the participants and the treatment interventions reflected typical clinical practice[46;47;56] Compliance and adherence were not representative in the Miller et al. study. The studies included all enrolled patients in their final analysis.

Compliance and adherence were representative of clinical practice in the studies that compared low energy diets to conventional diets. However, it was unclear if the treatment intervention was representative. Christensen et al.[59] enrolled participants that might not have been representative of clinical practice, and did not include all enrolled patients in the final analysis.

The diet versus exercise studies had a non-representative application of the treatment intervention, and Focht et al.[46] included patients that might not have been similar to those seen in clinical practice. Compliance and adherence were representative of clinical practice in one of the studies, and both included all enrolled patients in their final analyses.

FINAL STRENGTH OF EVIDENCE

All studies in this recommendation were rated as having moderate applicability. Therefore, low quality studies were rated as low strength of evidence, and moderate quality studies were rated as moderate strength.

Table 68. Quality and Applicability Summary: Weight Loss Versus Education

Study	Outcome	Duration (Weeks)	Quality	Applicability	Strength of Evidence
Miller et al. (2006)	WOMAC Function improvement	26	Moderate	Moderate	Moderate
Focht (2005)	6 minute walk distance(ft)	78	Low	Moderate	Low
Focht (2005)	6 minute walk distance(ft)	78	Low	Moderate	Low

Study	Outcome	Duration (Weeks)	Quality	Applicability	Strength of Evidence
Focht (2005)	Stair climb time(s)	78	Low	Moderate	Low
Focht (2005)	Stair climb time(s)	78	Low	Moderate	Low
Miller et al. (2006)	WOMAC Pain improvement	26	Moderate	Moderate	Moderate
Miller et al. (2006)	WOMAC Total improvement	26	Moderate	Moderate	Moderate
Rejeski et al. (2002)	SF-36 Mental Function	26 and 78 week average	Low	Moderate	Low
Rejeski et al. (2002)	SF-36 Mental Function	26 and 78 week average	Low	Moderate	Low
Rejeski et al. (2002)	SF-36-Physical Function	26 and 78 week average	Low	Moderate	Low
Rejeski et al. (2002)	SF-36-Physical Function	26 and 78 week average	Low	Moderate	Low

Table 69. Quality and Applicability Summary: Low Energy Diet Versus Conventional Diet

Study	Outcome	Duration (Weeks)	Quality	Applicability	Strength of Evidence
Christensen (2005)	WOMAC Function improvement	8	Moderate	Moderate	Moderate
Bliddal (2011)	Health Assessment Questionnaire	52	Low	Moderate	Low
Riecke (2010)	KOOS Function in Daily Life improvement	16	Low	Moderate	Low
Riecke (2010)	KOOS Sports and Recreation improvement	16	Low	Moderate	Low
Riecke (2010)	SF-36 MCS improvement	16	Low	Moderate	Low
Riecke (2010)	SF-36 PCS improvement	16	Low	Moderate	Low
Riecke (2010)	VAS Disability improvement	16	Low	Moderate	Low
Riecke (2010)	VAS Global improvement	16	Low	Moderate	Low
Riecke (2010)	KOOS Pain improvement	16	Low	Moderate	Low
Riecke (2010)	VAS Pain improvement	16	Low	Moderate	Low

Study	Outcome	Duration (Weeks)	Quality	Applicability	Strength of Evidence
Riecke (2010)	KOOS Quality of Life improvement	16	Low	Moderate	Low
Christensen (2005)	WOMAC Total improvement	8	Moderate	Moderate	Moderate
Christensen (2005)	Lequesne index improvement	8	Moderate	Moderate	Moderate
Riecke (2010)	KOOS Symptoms improvement	16	Low	Moderate	Low
Riecke (2010)	OARSI Responders	16	Low	Moderate	Low

Table 70. Quality and Applicability Summary: Diet Versus Exercise

Study	Outcome	Duration (Weeks)	Quality	Applicability	Strength of Evidence
Focht (2005)	6 minute walk distance(ft)	78	Low	Moderate	Low
Focht (2005)	6 minute walk distance(ft)	78	Low	Moderate	Low
Focht (2005)	6 minute walk distance(ft)	78	Low	Moderate	Low
Focht (2005)	Stair climb time(s)	78	Low	Moderate	Low
Focht (2005)	Stair climb time(s)	78	Low	Moderate	Low
Focht (2005)	Stair climb time(s)	78	Low	Moderate	Low
Jenkinson et al. (2009)	WOMAC Pain 30% reduction	104	High	Moderate	High

RESULTS

Relevant Tables: Figure 13-Figure 15, Table 75-Table 79

Focht et al[46] and Rejeski et al.[47] used data from the arthritis, diet, and activity promotion trial (ADAPT) to evaluate exercise-based weight loss programs. When SF-36 Mental Health and timed stair climb scores were compared to a healthy lifestyle education control group, there were no statistically significant differences.

Figure 13 contains a summary of results for studies comparing weight loss programs to health education controls. The weight loss programs consisted of dietary interventions alone, or a combination of exercise and diet. Six out of 11 outcomes were statistically significant in favor of the weight loss intervention. Pain and function were the critical outcomes for this recommendation. Three of five self-reported functional outcomes were statistically significant in favor of weight loss; two of which were clinically important,

and one possibly clinically significant. The pain outcome was clinically significant in favor of the weight loss intervention.

Three out of 15 outcomes were statistically significant in favor of low energy versus conventional diets. WOMAC total was significantly improved in the low energy diet group, and two out of seven functional outcomes were higher. There were no significant differences in the pain or quality of life outcomes (Figure 14).

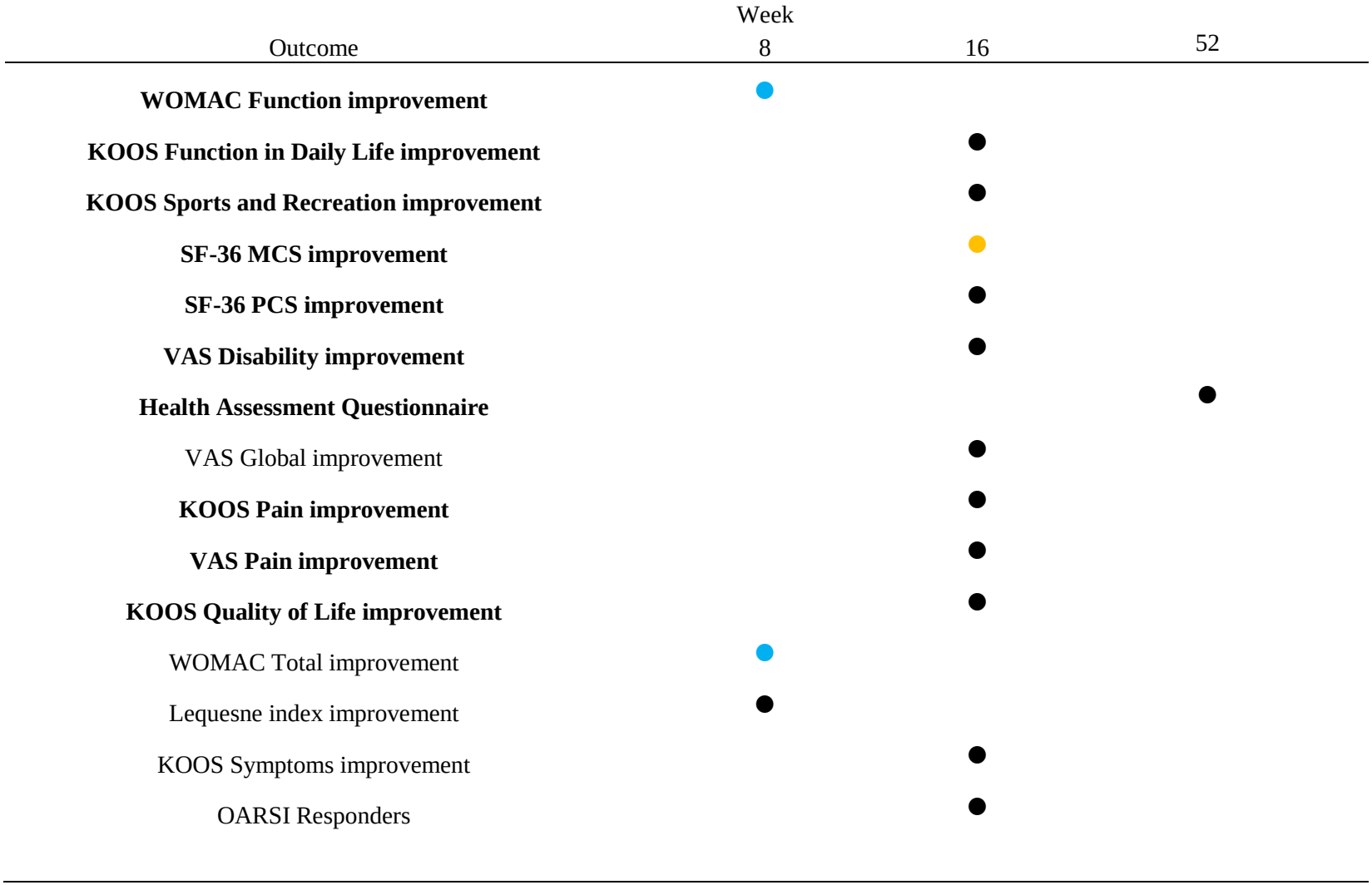
There were two studies that compared diet to exercise. Focht et al[46] found that 6-minute walk distances were significantly longer in the exercise group than in the diet group. Furthermore, participants who received exercise and diet walked significantly lengthier distances than those treated with a diet intervention alone, but there was no significant difference compared to patients in the exercise-only group. Jenkinson et al.[60] found that the proportion of patients who achieved a 30% reduction in WOMAC pain did not differ significantly in the exercise group compared to the group receiving diet treatments.

Figure 13. Summary of Results: Diet, Exercise, and Weight Loss

	Outcome	Week 26	Week Average of 26 and 78	Week 78
Targeted Weight Loss Versus Education	WOMAC Total improvement	🔵		
	WOMAC Function improvement	🔵		
	WOMAC Pain improvement	🔵		
Diet Versus Health Education	SF-36 Mental Function		⚫	
	SF-36-Physical Function		🔴	
	6 minute walk distance(ft)			⚫
	Stair climb time(s)			⚫
Diet Plus Exercise Versus Health Education	SF-36 Mental Function		⚫	
	SF-36-Physical Function		🔴	
	6 minute walk distance(ft)			🟡
	Stair climb time(s)			⚫

Key: ⚫=Not Significant; 🟡=Statistically Significant; 🔵=Possibly Clinically Important; 🔴 =Clinically Significant

Figure 14. Results Summary: Low Energy Diet Versus Conventional Diet



Key: ●=Not Significant; ●=Statistically Significant; ●=Possibly Clinically Important

Figure 15. Results Summary: Diet Versus Exercise

		Week 78	Week 104
Exercise Versus Diet	6 minute walk distance(ft)	●	
	Stair climb time(s)	●	
Diet Plus Exercise Versus Diet Only	6 minute walk distance(ft)	●	
	Stair climb time(s)	●	
Diet Plus Exercise Versus Exercise Only	6 minute walk distance(ft)	●	
	Stair climb time(s)	●	
	30% WOMAC Pain improvement		●

Key: ●=Not Significant; ●= Statistically Significant in Favor of Exercise; ●= Statistically Significant in Favor of Diet Plus Exercise

EVIDENCE TABLES AND FIGURES

QUALITY AND APPLICABILITY

Table 71. Quality and Applicability: Exercise-Based Weight Loss Program Versus Health Education

●: Domain free of flaws

○: Domain flaws present

◐: Moderate power

Study	*Outcome*	*Duration (Weeks)*	Prospective	Power	Group Assignment	Blinding	Group Comparability	Treatment Integrity	Measurement	Investigator Bias	*Quality*	Participants	Intervention and Expertise	Compliance and Adherence	Analysis	*Applicability Study*
Rejeski (2002)	SF-36 Mental Health	78	○	◐	○	○	●	●	●	○	**Low**	○	○	●	●	**Moderate**
Focht (2005)	Stair climb time	78	○	◐	○	○	●	●	●	○	**Low**	○	○	●	●	**Moderate**

Table 72. Quality and Applicability: Weight Loss Versus Education Programs

●: Domain free of flaws

○: Domain flaws present

◐: Moderate power

Study	*Outcome*	*Duration (Weeks)*	Prospective	Power	Group Assignment	Blinding	Group Comparability	Treatment Integrity	Measurement	Investigator Bias	*Quality*	Participants	Intervention and Expertise	Compliance and Adherence	Analysis	*Applicability Study*
Miller et al. (2006)	WOMAC Function improvement	26	●	●	○	●	●	●	●	○	**Moderate**	○	○	○	●	**Moderate**
Focht (2005)	6 minute walk distance(ft)	78	○	◐	○	○	●	●	●	○	**Low**	○	○	●	●	**Moderate**
Focht (2005)	6 minute walk distance(ft)	78	○	●	○	○	●	●	●	○	**Low**	○	○	●	●	**Moderate**
Focht (2005)	Stair climb time(s)	72	○	◐	○	○	●	●	●	○	**Low**	○	○	●	●	**Moderate**
Focht (2005)	Stair climb time(s)	72	○	◐	○	○	●	●	●	○	**Low**	○	○	●	●	**Moderate**
Miller et al. (2006)	WOMAC Pain improvement	26	●	●	○	●	●	●	●	○	**Moderate**	○	○	○	●	**Moderate**
Miller et al. (2006)	WOMAC Total improvement	26	●	●	○	●	●	●	●	○	**Moderate**	○	○	○	●	**Moderate**
Rejeski et al. (2002)	SF-36 Mental function	26 and 78 week average	○	◐	○	○	●	●	●	○	**Low**	○	○	●	●	**Moderate**

●: Domain free of flaws

○: Domain flaws present

◐: Moderate power

Study	*Outcome*	*Duration (Weeks)*	**Prospective**	**Power**	**Group Assignment**	**Blinding**	**Group Comparability**	**Treatment Integrity**	**Measurement**	**Investigator Bias**	*Quality*	**Participants**	**Intervention and Expertise**	**Compliance and Adherence**	**Analysis**	*Applicability Study*
Rejeski et al. (2002)	SF-36 Mental Function	26 and 78 week average	○	◐	○	○	●	●	●	○	**Low**	○	○	●	●	**Moderate**
Rejeski et al. (2002)	SF-36 Physical Function	26 and 78 week average	○	●	○	○	●	●	●	○	**Low**	○	○	●	●	**Moderate**

Table 73. Quality and Applicability: Low Energy Diet Versus Control Diet

●: Domain free of flaws

○: Domain flaws present

◐: Moderate power

Study	*Outcome*	*Duration (Weeks)*	Prospective	Power	Group Assignment	Blinding	Group Comparability	Treatment Integrity	Measurement	Investigator Bias	*Quality*	Participants	Intervention and Expertise	Compliance and Adherence	Analysis	*Applicability Study*
Christensen (2005)	WOMAC Function improvement	8	●	●	○	●	○	●	●	○	**Moderate**	○	○	●	○	**Moderate**
Riecke (2010)	KOOS Function in Daily Life improvement	16	○	◐	○	○	○	●	●	○	**Low**	●	○	●	●	**Moderate**
Riecke (2010)	KOOS Sports and Recreation improvement	16	○	◐	○	○	○	●	●	○	**Low**	●	○	●	●	**Moderate**
Riecke (2010)	SF-36 MCS improvement	16	○	●	○	○	○	●	●	○	**Low**	●	○	●	●	**Moderate**
Riecke (2010)	SF-36 PCS improvement	16	○	●	○	○	○	●	●	○	**Low**	●	○	●	●	**Moderate**
Riecke (2010)	VAS Disability improvement	16	○	◐	○	○	○	●	●	○	**Low**	●	○	●	●	**Moderate**
Riecke (2010)	VAS Global improvement	16	○	●	○	○	○	●	●	○	**Low**	●	○	●	●	**Moderate**
Riecke (2010)	KOOS Pain improvement	16	○	◐	○	○	○	●	●	○	**Low**	●	○	●	●	**Moderate**

●: Domain free of flaws

○: Domain flaws present

◐: Moderate power

Study	*Outcome*	*Duration (Weeks)*	**Prospective**	**Power**	**Group Assignment**	**Blinding**	**Group Comparability**	**Treatment Integrity**	**Measurement**	**Investigator Bias**	*Quality*	**Participants**	**Intervention and Expertise**	**Compliance and Adherence**	**Analysis**	*Applicability Study*
Riecke (2010)	VAS Pain improvement	16	○	●	○	○	○	●	●	○	**Low**	●	○	●	●	**Moderate**
Riecke (2010)	KOOS Quality of Life improvement	16	○	◐	○	○	○	●	●	○	**Low**	●	○	●	●	**Moderate**
Christensen (2005)	WOMAC Total improvement	8	●	●	○	●	○	●	●	○	**Moderate**	○	○	●	○	**Moderate**
Christensen (2005)	Lequesne index improvement	8	●	◐	○	●	○	●	●	○	**Moderate**	○	○	●	○	**Moderate**
Bliddal(2011	Health Assessment Questionnaire		○	◐	○	○	○	●	●	○	**Low**	○	○	●	●	**Moderate**
Riecke (2010)	KOOS Symptoms improvement	16	○	◐	○	○	○	●	●	○	**Low**	●	○	●	●	**Moderate**
Riecke (2010)	OARSI Responders	16	○	◐	○	○	○	●	●	○	**Low**	●	○	●	●	**Moderate**

Table 74. Quality and Applicability: Diet Versus Exercise

●: Domain free of flaws

○: Domain flaws present

◐: Moderate power

Study	*Outcome*	*Duration (Weeks)*	Prospective	Power	Group Assignment	Blinding	Group Comparability	Treatment Integrity	Measurement	Investigator Bias	*Quality*	Participants	Intervention and Expertise	Compliance and Adherence	Analysis	*Applicability Study*
Focht (2005)	6 minute walk distance(ft)	78	○	◐	○	○	○	●	●	○	**Low**	○	○	●	●	**Moderate**
Focht (2005)	6 minute walk distance(ft)	78	○	●	○	○	○	●	●	○	**Low**	○	○	●	●	**Moderate**
Focht (2005)	6 minute walk distance(ft)	78	○	●	○	○	○	●	●	○	**Low**	○	○	●	●	**Moderate**
Focht (2005)	Stair climb time(s)	78	○	◐	○	○	○	●	●	○	**Low**	○	○	●	●	**Moderate**
Focht (2005)	Stair climb time(s)	78	○	◐	○	○	○	●	●	○	**Low**	○	○	●	●	**Moderate**
Focht (2005)	Stair climb time(s)	78	○	◐	○	○	○	●	●	○	**Low**	○	○	●	●	**Moderate**
Jenkinson et al. (2009)	WOMAC Pain 30% reduction	104	●	◐	●	●	●	●	●	○	**High**	●	○	○	●	**Moderate**
Focht (2005)	6 minute walk distance(ft)	78	○	◐	○	○	○	●	●	○	**Low**	○	○	●	●	**Moderate**

FINDINGS

Table 75. Weight Loss-Exercise Only Versus Control: Function

Study	Outcome	N	Sufficient Power	Week	BMI	Group 1	Group 2	SMD (Odds Ratio or Raw Mean Difference When Indicated)	Sig	Clinical Importance	Strength of Evidence
Rejeski et al. (2003)	SF-36 Mental Health	69	Unclear	72	28+	Aerobic exercise	Healthy life style education control	0.08 (-0.26, 0.41)	No	N/A	Low

Table 76. Weight Loss-Exercise Only Versus Control: Functional Task

Study	Outcome	N	Sufficient Power	Week	BMI	Group 1	Group 2	SMD (Odds Ratio or Raw Mean Difference When Indicated)	Sig	Clinical Importance	Strength of Evidence
Focht (2005)	Stair climb time	80	Unclear	72	28+	Aerobic exercise	Health education	-0.14 (-0.45, 0.17)	No	N/A	Low

Table 77. Dietary Weight Loss (With and Without Exercise) Versus Education Control

Outcome Type	Study	Outcome	N	Powered	Week	BMI	Group 1	Group 2	SMD (Odds Ratio or Raw Mean Difference When Indicated)	Sig	Clinical Importance	Strength of Evidence
Function	Miller et al. (2006)	WOMAC Function	74	Yes	26	30+	Weight loss program	Weight stable education	-0.65 (-1.11, -0.18)	Favors diet plus weight loss	Possibly clinically significant	Moderate
	Rejeski et al. (2002)	SF-36 Mental Function	141	Unclear	26 and 78 averaged	28+	Diet	Monthly health education session	0.07 (-0.26, 0.40)	No	N/A	Low
	Rejeski et al. (2002)	SF-36 Mental Function	136	Unclear	26 and 78 averaged	28+	Diet plus exercise	Monthly health education session	0.11 (-0.23, 0.45)	No	N/A	Low
	Rejeski et al. (2002)	SF-36-Physical Function	141	Yes	26 and 78 averaged	28+	Diet	Monthly health education session	0.51 (0.18, 0.85)	Favors diet	Clinically significant	Low
	Rejeski et al. (2002)	SF-36 Physical Function	136	Yes	26 and 78 averaged	28+	Diet plus exercise	Monthly health education session	0.62 (0.27, 0.96)	Favors diet plus exercise	Clinically significant	Low
Functional Tasks	Focht (2005)	6 minute walk distance(ft)	160	Unclear	78	28+	Diet	Health education control	0.08 (-0.23, 0.39)	No	N/A	Low

	Focht (2005)	6 minute walk distance(ft)	240	Yes	78	28+	Diet plus exercise	Health education control	0.38 (0.10, 0.65)	Favors diet plus exercise	N/A	Low
	Focht (2005)	Stair climb time(s)	160	Unclear	72	28+	Diet	Health education control	0.00 (-0.31, 0.31)	No	N/A	Low
	Focht (2005)	Stair climb time(s)	240	Unclear	72	28+	Diet plus exercise	Health education control	-0.19 (-0.46, 0.08)	No	N/a	Low
Pain	Miller et al. (2006)	WOMAC Pain	74	Yes	26	30+	Weight loss program	Weight stable education	-0.78 (-1.25, -0.31)	Favors diet plus weight loss	Possibly clinically significant	Moderate
WOMAC Total	Miller et al. (2006)	WOMAC Total	74	Yes	26	30+	Weight loss program	Weight stable education	-0.67 (-1.14, -0.20)	Favors diet plus weight loss	Possibly clinically significant	Moderate

Table 78. Low Energy Diet Versus Control Diet

Outcome Type	Study	Outcome	N	Powered	Week	BMI	Group 1	Group 2	SMD (Odds Ratio or Raw Mean Difference When Indicated)	Sig	Clinical Importance	Strength of Evidence
Function	Christensen (2005)	WOMAC Function	80	Yes	8	28+	Low energy diet (3.4mj/day)	Control diet (5mj/day)	-0.51 (-0.96, -0.07)	Favors low energy diet	Possibly clinically significant	Moderate
	Riecke (2010)	KOOS Function in Daily Life	192	Unclear	16	30+	Very low energy diet	Low energy diet control	-0.01 (-0.29, 0.27)	No	N/A	Low
	Riecke (2010)	KOOS Sports and Recreation	192	Unclear	16	30+	Very low energy diet	Low energy diet control	0.02 (-0.27, 0.30)	No	N/A	Low
	Riecke (2010)	SF-36 Mental	192	Yes	16	30+	Very low energy diet	Low energy diet control	0.37 (0.08, 0.65)	Favors very low energy diet	N/A	Low
	Riecke (2010)	SF-36 Physical	192	Yes	16	30+	Very low energy diet	Low energy diet control	-0.06 (-0.34, 0.22)	No	True negative	Low
	Riecke (2010)	VAS Disability	192	Unclear	16	30+	Very low energy diet	Low energy diet control	-0.08 (-0.36, 0.20)	No	N/A	Low

Outcome Type	Study	Outcome	N	Powered	Week	BMI	Group 1	Group 2	SMD (Odds Ratio or Raw Mean Difference When Indicated)	Sig	Clinical Importance	Strength of Evidence
	Bliddal	HAQ	89	Yes	52	28+	Low energy diet	Conventional diet	-0.28 (-0.70, 0.14)	No	N/A	Low
Global Assessment	Riecke (2010)	VAS Global	192	Yes	16 weeks	30+	Very low energy diet	Low energy diet control	0.09 (-0.19, 0.37)	No	True negative	Low
Pain	Riecke (2010)	KOOS Pain	192	Unclear	16	30+	Very low energy diet (415 kcal/day)	Low energy diet control (810 kcal/day)	-0.12 (-0.40, 0.16)	No	N/A	Low
	Riecke (2010)	VAS Pain	192	Yes	16	30+	Very low energy diet (415 kcal/day)	Low energy diet control (810 kcal/day)	-0.06 (-0.34, 0.22)	No	True negative	Low
Quality of Life	Riecke (2010)	KOOS Quality of Life	192	Unclear	16	30+	Very low energy diet (415 kcal/day)	Low energy diet control (810 kcal/day)	-0.03 (-0.32, 0.25)	No	N/A	Low
WOMAC Total	Christensen (2005)	WOMAC Total	80	Yes	8	28+	Low energy diet (3.4mj/day)	Control diet (5mj/day) diet	-0.49 (-0.93, -0.04)	Favors low energy diet	Possibly clinically significant	Moderate
Lequesne index	Christensen (2005)	Lequesne index	80	Unclear	8	28+	Low energy diet(3.4mj/day)	Control diet (5mj/day) diet	-0.08 (-0.52, 0.36)	No	N/A	Moderate

Outcome Type	Study	Outcome	N	Powered	Week	BMI	Group 1	Group 2	SMD (Odds Ratio or Raw Mean Difference When Indicated)	Sig	Clinical Importance	Strength of Evidence
Symptoms	Riecke (2010)	KOOS Symptoms	192	Unclear	16	30+	Very low energy diet (415 kcal/day)	Low energy diet control (810 kcal/day)	0.03 (-0.25, 0.32)	No	N/A	Low
OARSI Responders	Riecke (2010)	OARSI Responders	192	Unclear	16	30+	Very low energy diet (415 kcal/day)	Low energy diet control (810 kcal/day)	0.84 (0.46, 1.50)	No	N/A	Low

Table 79. Diet Versus Exercise

Study	Outcome	N	Sufficient Power	Week	BMI	Group 1	Group 2	SMD (Odds Ratio or Raw Mean Difference When Indicated)	Sig	Clinical Importance	Strength of Evidence
Focht (2005)	6 minute walk distance(ft)	242	Unclear	78	28+	Exercise plus diet	Exercise	-0.09 (-0.35, 0.18)	No	N/A	Low
Focht (2005)	6 minute walk distance(ft)	162	Yes	78	28+	Diet	Exercise	-0.42 (-0.73, -0.11)	Favors exercise	N/A	Low
Focht (2005)	6 minute walk distance(ft)	244	Yes	78	28+	Diet	Exercise plus diet	-0.30 (-0.57, -0.04)	Favors exercise plus diet	N/A	Low

Study	Outcome	N	Sufficient Power	Week	BMI	Group 1	Group 2	SMD (Odds Ratio or Raw Mean Difference When Indicated)	Sig	Clinical Importance	Strength of Evidence
Focht (2005)	Stair climb time(s)	162	Unclear	78	28+	Diet	Exercise	0.10 (-0.21, 0.41)	No	N/A	Low
Focht (2005)	Stair climb time(s)	244	Unclear	78	28+	Diet	Exercise plus diet	0.15 (-0.12, 0.42)	No	N/A	Low
Focht (2005)	Stair climb time(s)	242	Unclear	78	28+	Exercise plus diet	Exercise	-0.06 (-0.33, 0.21)	No	N/A	Low
Jenkinson et al. (2009)	WOMAC Pain 30% reduction	0	Yes	104	28+	Diet or diet plus exercise	Exercise or leaflet	OR=0.98 (0.65, 1.48)	No	N/A	High

RECOMMENDATION 3A

We cannot recommend using acupuncture in patients with symptomatic osteoarthritis of the knee.

Strength of Recommendation: Strong

Description: Evidence is based on two or more "High" strength studies with consistent findings for recommending for or against the intervention. A **Strong** recommendation means that the quality of the supporting evidence is high. A harms analysis on this recommendation was not performed

Implications: Practitioners should follow a **Strong** recommendation unless a clear and compelling rationale for an alternative approach is present.

RECOMMENDATION 3B

We are unable to recommend for or against the use of physical agents (including electrotherapeutic modalities) in patients with symptomatic osteoarthritis of the knee.

Strength of Recommendation: Inconclusive

Description: Evidence from a single low quality study or conflicting findings that do not allow a recommendation for or against the intervention. An **Inconclusive** recommendation means that there is a lack of compelling evidence that has resulted in an unclear balance between benefits and potential harm.

Implications: Practitioners should feel little constraint in following a recommendation labeled as **Inconclusive,** exercise clinical judgment, and be alert for emerging evidence that clarifies or helps to determine the balance between benefits and potential harm. Patient preference should have a substantial influencing role.

RECOMMENDATION 3C

We are unable to recommend for or against manual therapy in patients with symptomatic osteoarthritis of the knee.

Strength of Recommendation: Inconclusive

Description: Evidence from a single low quality study or conflicting findings that do not allow a recommendation for or against the intervention. An **Inconclusive** recommendation means that there is a lack of compelling evidence that has resulted in an unclear balance between benefits and potential harm.

Implications: Practitioners should feel little constraint in following a recommendation labeled as **Inconclusive,** exercise clinical judgment, and be alert for emerging evidence that clarifies or helps to determine the balance between benefits and potential harm. Patient preference should have a substantial influencing role.

RATIONALE

Variable strengths of evidence were reported in studies of patients with osteoarthritis of the knee.

3A

There were five high- and five moderate- strength studies that compared acupuncture to comparison groups receiving non-intervention sham, usual care, or education. The five moderate-strength studies were included because they reported outcomes that were different than the high-strength evidence. High-strength studies included: Berman et al, [61]

Suarez-Almazor et al.,[62] Weiner et al.,[63] Williamson et al.[64] and Taechaarpornkul et al.[65] Moderate-strength studies included: Sandgee et al.,[66] Vas et al.,[67] Witt et al.[68] and Berman et al.[69] The majority of studies were not statistically significant and an even larger proportion of the evidence was not clinically significant. Some outcomes were associated with clinical- but not statistical- significance. The strength of this recommendation was based on lack of efficacy, not on potential harm.

3B

The evidence was mixed regarding the efficacy of physical agents and electrotherapeutic modalities because of contradiction in findings, design flaws, or a low count of like studies. A single low-strength[70] and a single-moderate strength study[71]comparing pulsed electrical stimulation to placebo produced contradictory results. See the results of the Fary et al.[70] and Zizic et al.[71] articles in table 96. Trock et al.[72] conducted a moderate-strength study evaluating pulsed electromagnetic stimulation and found that it did not generate a statistically significant effect on pain during passive motion, but that tenderness and physician's overall assessment scores were superior in the experimental group. Atamaz et al.[73] conducted a moderate-strength study that compared transcutaneous electrical nerve stimulation (TENS), shortwave diathermy, and interferential current to a sham procedure. None of the treatments were associated with statistically significant effects on pain, physical mobility, or ambulation time at four, 12, or 26 weeks. Battisti et al.,[74] also in a moderate-strength study, found that therapeutic application of modulated electromagnetic field therapy (TAMMEF) did not produce statistically significant improvements in pain or Lequesne Index scores, compared to extremely low-frequency electromagnetic field therapy.

However, there was evidence that ultrasound was effective in patients with knee osteoarthritis. Huang et al.[75] and Yang et al.[76] conducted moderate-strength studies that compared ultrasound to a control group. Huang et al. found that patients who received isotonic exercise with ultrasound had significantly superior ambulation speed, Lequesne Index scores, and VAS pain scores. Yang et al. found VAS pain and Lequesne Index scores were significantly superior at 4 weeks in patients who received ultrasound over those who received a sham treatment.

Due to the overall inconsistent findings for various physical agents and electrotherapeutic modalities, we were unable to make a recommendation for or against their use in patients with symptomatic osteoarthritis of the knee.

3C

We were unable to recommend for or against manual therapy due to the lack of studies examining most manual therapy techniques. No studies evaluating joint mobilization, joint manipulation, chiropractic therapy, patellar mobilization, or myofascial release were found that met our inclusion criteria. Perlman et al.[77] examined Swedish massage therapy using a low-strength study design. The findings showed statistically significant results at 8 weeks, but not at 16 weeks. A conclusive recommendation regarding Swedish massage therapy could not be made based on this single low strength of evidence study.

SUPPORTING EVIDENCE

QUALITY

Relevant Tables: Table 80-Table 85, Table 86-Table 91

There were five high quality studies, and four moderate quality studies that compared acupuncture to a control group (sham, usual care, or education). None of the studies were flawed in the hypothesis, treatment integrity, and measurement domains. Five of nine studies were flawed in the group assignment domain. Seven and six of nine articles were appropriate in the blinding and group comparability domains. Vas et al.,[67] Witt et al.,[68] and Taechaarpornkul et al.[65] had investigator bias.

One high quality study, Wiener et al.,[63] compared periosteal stimulation therapy to regular acupuncture and was unflawed in every quality domain except for group assignment.

Pulsed electrical stimulation was compared to placebo by Fary et al.[70] This study was of low quality with flaws in the hypothesis, blinding, group assignment and group comparability domains.

Pulsed electromagnetic therapy was compared to placebo in studies by Trock et al.[72] and Zizic et al.[71] The former was of moderate quality with flaws in the group assignment, comparability and investigator bias domains. Quality of the latter was affected by uncertain group comparability as well as investigator bias.

Battisti et al.[74] compared Therapeutic Application of Modulated Electro Magnetic Field (TAMMEF) treatments to extremely low frequency electromagnetic field therapy. Since there was uncertainty concerning group assignment and group comparability, this study was given a rating of moderate quality.

Atamaz et al.[73] compared transcutaneous electrical nerve stimulation (TENS), interferential currents, and short wave diathermy to a sham control group. Since group comparability at baseline was uncertain and the treatment integrity domain was flawed, the study was of moderate quality.

One study[77] compared Swedish massage therapy to usual care. This low quality study was flawed in the group assignment, blinding, group comparability and treatment integrity domains. Where it was not flawed was in the hypothesis, measurement and investigator bias domains.

Huang et al.,[75] a moderate quality study, compared ultrasonic wave therapy in combination with exercise to an exercise intervention alone. The study was flawed in the binding and investigator bias domains and not flawed in the hypothesis, group assignment, group comparability, treatment integrity and measurement domains.

Yang et al.[76] compared ultrasound therapy to placebo. This moderate quality study was only flawed in the group assignment and group comparability domains.

APPLICABILITY

Relevant Tables: Table 80-Table 85, Table 86-Table 91

In all nine included acupuncture studies, the treatments might not have been administered in a manner representative of clinical practice. Similarly, it was not clear if the study participants were similar to the typical patient population in all but one of the studies. Compliance was similar in all included acupuncture studies. Nine out of 10 studies based their final analyses on all enrolled patients. The studies were of moderate applicability.

Participants, treatment administration, and compliance in the Swedish massage therapy study might not have been similar to that typically found in clinical practice. However, the study included all enrolled patients in the final analysis. It was rated as having moderate applicability.

It was not certain if participants and the treatment administration were representative of typical clinical practice for the ultrasound,[75;76] pulsed electrical stimulation and pulsed electromagnetic therapy studies.[70-72] The study by Battisti et al.[74] of TAMMEF was flawed in the representativeness of treatment administration. Compliance followed a similar pattern to clinical practice for these studies. Also, with the exception of the Zizic et al.[71] study, all enrolled patients were included in the final analyses. The applicability ratings were determined to be moderate.

The Atamaz et al.[73] study examining treatment efficacy of TENS, interferential currents, and short wave diathermy included a sufficient percentage of enrolled patients in the final analysis. However, the treatment administration, patients who received the interventions, and the monitoring of compliance and adherence in the study were not representative of regular clinical practice.

FINAL STRENGTH OF EVIDENCE

All strength of evidence ratings were the same as the quality ratings since all studies were rated as having moderate applicability.

Table 80. Quality and Applicability Summary: Acupuncture Versus Control

Study	Outcome	Weeks	Quality	Applicability	Strength of Evidence
Berman (1999)	WOMAC Pain	4	Moderate	Moderate	Moderate
Berman (1999)	WOMAC Pain	4	Moderate	Moderate	Moderate
Berman (1999)	Lequesne index	4	Moderate	Moderate	Moderate
Berman (1999)	Lequesne index	8	Moderate	Moderate	Moderate
Berman (1999)	Lequesne index	12	Moderate	Moderate	Moderate
Berman (1999)	WOMAC Pain	8	Moderate	Moderate	Moderate

Berman (1999)	WOMAC Pain	12	Moderate	Moderate	Moderate
Berman (1999)	WOMAC Function	4	Moderate	Moderate	Moderate
Berman (1999)	WOMAC Function	8	Moderate	Moderate	Moderate
Berman (1999)	WOMAC Function	12	Moderate	Moderate	Moderate
Berman (2004)	6 minute walk distance	8	High	Moderate	High
Berman (2004)	6 minute walk distance	26	High	Moderate	High
Berman (2004)	6 minute walk distance	8	High	Moderate	High
Berman (2004)	6 minute walk distance	26	High	Moderate	High
Berman (2004)	WOMAC Pain	8	High	Moderate	High
Berman (2004)	WOMAC Pain	14	High	Moderate	High
Berman (2004)	WOMAC Pain	26	High	Moderate	High
Berman (2004)	WOMAC Function	4	High	Moderate	High
Berman (2004)	WOMAC Function	8	High	Moderate	High
Berman (2004)	WOMAC Function	14	High	Moderate	High
Berman (2004)	WOMAC Function	26	High	Moderate	High
Sandgee (2002)	50 foot walk time	4	Moderate	Moderate	Moderate
Sandgee (2002)	Lequesne index	4	Moderate	Moderate	Moderate
Suarez-Almazor (2010)	SF-12 Physical Health	4	High	Moderate	High
Suarez-Almazor (2010)	SF-12 Physical Health	6	High	Moderate	High

Suarez-Almazor (2010)	SF-12 Physical Health	13	High	Moderate	High
Suarez-Almazor (2010)	SF-12 Mental Health	4	High	Moderate	High
Suarez-Almazor (2010)	SF-12 Mental Health	6	High	Moderate	High
Suarez-Almazor (2010)	SF-12 Mental Health	13	High	Moderate	High
Suarez-Almazor (2010)	WOMAC Pain	4	High	Moderate	High
Suarez-Almazor (2010)	WOMAC Pain	6	High	Moderate	High
Suarez-Almazor (2010)	WOMAC Pain	13	High	Moderate	High
Suarez-Almazor (2010)	WOMAC Function	4	High	Moderate	High
Suarez-Almazor (2010)	WOMAC Function	6	High	Moderate	High
Suarez-Almazor (2010)	WOMAC Function	13	High	Moderate	High
Taechaarpornkul (2009)	WOMAC Pain	13	High	Moderate	High
Taechaarpornkul (2009)	Cox-2 consumption	5	High	Moderate	High
Taechaarpornkul (2009)	Cox-2 consumption	13	High	Moderate	High
Taechaarpornkul (2009)	WOMAC Pain	5	High	Moderate	High
Taechaarpornkul (2009)	WOMAC Function	5	High	Moderate	High
Taechaarpornkul (2009)	WOMAC Function	13	High	Moderate	High
VAS (2004)	PLQC-Negative Mood	13	Moderate	Moderate	Moderate

VAS (2004)	PLQC-Physical Capability	13	Moderate	Moderate	Moderate
VAS (2004)	PLQC-Psychological Functioning	13	Moderate	Moderate	Moderate
VAS (2004)	PLQC- Social Functioning	13	Moderate	Moderate	Moderate
VAS (2004)	PLQC-Social Well-Being	13	Moderate	Moderate	Moderate
VAS (2004)	NSAID Consumption	13	Moderate	Moderate	Moderate
VAS (2004)	VAS Pain	13	Moderate	Moderate	Moderate
Weiner (2004)	WOMAC Pain	6	High	Moderate	High
Witt (2005)	SF-36-Physical Health	8	Moderate	Moderate	Moderate
Williamson (2007)	OKS	7	High	Moderate	High
Williamson (2007)	OKS	12	High	Moderate	High
Williamson (2007)	OKS	12 post-op	High	Moderate	High
Williamson (2007)	50m walk	7	High	Moderate	High
Williamson (2007)	50m walk	12	High	Moderate	High
Williamson (2007)	50m walk	12 post-op	High	Moderate	High
Williamson (2007)	Post-op stay (days)	12 post-op	High	Moderate	High
Williamson (2007)	VAS (cm)	7	High	Moderate	High
Williamson (2007)	VAS (cm)	12	High	Moderate	High

Williamson (2007)	VAS (cm)	12 post-op	High	Moderate	High
Williamson (2007)	HAD Anxiety	7	High	Moderate	High
Williamson (2007)	HAD Anxiety	12	High	Moderate	High
Williamson (2007)	HAD Anxiety	12 post-op	High	Moderate	High
Williamson (2007)	HAD Score Depression	7	High	Moderate	High
Williamson (2007)	HAD Score Depression	12	High	Moderate	High
Williamson (2007)	HAD Score Depression	12 post-op	High	Moderate	High

Table 81. Quality and Applicability Summary: Periosteal Stimulation Therapy

Study	Outcome	Weeks	Quality	Applicability	Strength of Evidence
Weiner (2004)	WOMAC Pain	6	High	Moderate	High
Weiner (2004)	Geriatric Depression Scale	6	High	Moderate	High
Weiner (2004)	Geriatric Depression Scale	12	High	Moderate	High
Weiner (2004)	Pittsburgh Sleep Quality index	6	High	Moderate	High
Weiner (2004)	Pittsburgh Sleep Quality index	12	High	Moderate	High
Weiner (2004)	Stair climb time	6	High	Moderate	High
Weiner (2004)	Stair climb time	12	High	Moderate	High

Table 82. Quality and Applicability Summary: Pulsed Electrical Stimulation

Study	Outcome	Weeks	Quality	Applicability	Strength of Evidence

Fary (2011)	Patient Global Assessment of Disease Activity	26	Low	Moderate	Low
Fary (2011)	SF-36 Mental	26	Low	Moderate	Low
Fary (2011)	Human activity profile maximum activity	26	Low	Moderate	Low
Fary (2011)	Human activity profile adjusted activity	26	Low	Moderate	Low
Fary (2011)	Daily accelerometer count	26	Low	Moderate	Low
Fary (2011)	Daily resting time, minutes	26	Low	Moderate	Low
Zizic (1995)	VAS Pain % change	8	Moderate	Moderate	Moderate
Zizic (1995)	VAS Function % change	8	Moderate	Moderate	Moderate
Zizic (1995)	Percent change adjusted mean physician evaluation (VAS)	8	Moderate	Moderate	Moderate
Zizic (1995)	At least 15 minute improvement in morning stiffness	8	Moderate	Moderate	Moderate
Battisti (2004)	Complete reduction of pain	6.4	Moderate	Moderate	Moderate
Battisti (2004)	Lequesne index: Total recovery of articular function	6.4	Moderate	Moderate	Moderate
Fary (2011)	Daily light	26	Low	Moderate	Low

	activity, minutes				
Fary (2011)	Daily moderate activity, minutes	26	Low	Moderate	Low
Fary (2011)	Daily hard activity, minutes	26	Low	Moderate	Low

Table 83. Quality and Applicability Summary: Pulsed Electromagnetic Therapy

Study	Outcome	Weeks	Quality	Applicability	Strength of Evidence
Trock (1994)	Pain on passive motion	4	Moderate	Moderate	Moderate
Trock (1994)	Tenderness	4	Moderate	Moderate	Moderate
Trock (1994)	Physician Overall Assessment	4	Moderate	Moderate	Moderate

Table 84. Quality and Applicability Summary: Swedish Massage Therapy

Study	Outcome	Weeks	Quality	Applicability	Strength of Evidence
Perlman (2006)	50 foot walk time	8	Low	Moderate	Low
Perlman (2006)	50 foot walk time	16	Low	Moderate	Low
Perlman (2006)	VAS Pain	8	Low	Moderate	Low
Perlman (2006)	VAS Pain	16	Low	Moderate	Low
Perlman (2006)	WOMAC Function	8	Low	Moderate	Low
Perlman (2006)	WOMAC Function	16	Low	Moderate	Low
Perlman (2006)	WOMAC Total	8	Low	Moderate	Low

Perlman (2006)	WOMAC Total	16	Low	Moderate	Low
Perlman (2006)	WOMAC Pain	8	Low	Moderate	Low
Perlman (2006)	WOMAC Pain	16	Low	Moderate	Low
Perlman (2006)	WOMAC Stiffness	8	Low	Moderate	Low
Perlman (2006)	WOMAC Stiffness	16	Low	Moderate	Low

Table 85. Quality and Applicability Summary: Ultrasound

Study	Outcome	Weeks	Quality	Applicability	Strength of Evidence
Huang (2005)	Walk speed (m/min)	8	Moderate	Moderate	Moderate
Huang (2005)	Lequesne index	8	Moderate	Moderate	Moderate
Huang (2005)	VAS Pain	8	Moderate	Moderate	Moderate
Huang (2005)	Walk speed (m/min)	52	Moderate	Moderate	Moderate
Huang (2005)	Lequesne index	52	Moderate	Moderate	Moderate
Huang (2005)	VAS Pain	52	Moderate	Moderate	Moderate
Huang (2005)	Walk speed (m/min)	8	Moderate	Moderate	Moderate
Huang (2005)	Walk speed (m/min)	8	Moderate	Moderate	Moderate
Huang (2005)	Lequesne index	8	Moderate	Moderate	Moderate
Yang (2011)	VAS curative effect of	4	Moderate	Moderate	Moderate

	treatment				
Yang (2011)	Lequesne index curative effect of treatment	4	Moderate	Moderate	Moderate

RESULTS

Relevant Tables: Figure 16-Figure 20, Figure 21-Figure24, Table 92-Table 101

There were 57 total outcomes comparing acupuncture to a control group. Twelve were statistically significant in favor of acupuncture (see Figure 16 for a summary of the results). The critical outcomes reported by the acupuncture studies were pain, function and quality of life. Meta-analyses were run for WOMAC pain and function at four to five weeks, six to eight weeks, and 12 to 14 weeks and are described in Figures19 and 20. For each outcome, subgroups of studies were combined when their follow-up durations were similar.

There were 13 included pain outcomes, three of which were statistically significant over placebo. The meta-analysis results showed that acupuncture had a statistically non-significant (and not clinically important) effect on pain at four to five weeks and at six to eight weeks (Figure 16). The acupuncture effect was not statistically significant at 12 to 14 weeks, but the confidence interval did include the MCII (making the 12 to 14 week effect inconclusive).

Three out of 31 functional outcomes were statistically significant in favor of acupuncture over sham/placebo. The meta-analysis results (Figure 24) indicated that the WOMAC Function scores were significantly superior to sham at six to eight weeks and at 12 to 14 weeks. However, none of the statistically significant outcomes were clinically important.

Vas et al.[67] addressed the effect of acupuncture on quality of life with the five subsections of the Profile of Quality of Life in the Chronically Ill (PQLC). These subsections included negative mood, physical capability, psychological function, social function and social well being. No outcome achieved statistical significance.

One study compared periosteal stimulation therapy (PST) to regular acupuncture.[59] There were a total of seven outcomes studied. Only WOMAC pain at six weeks (the only critical outcome) was statistically significant in favor of PST (Table 97).

Fary et al.,[70] Trock et al.[72] and Zizic et al.[71] compared the effectiveness of pulsed electrical stimulation to placebo. Five out of 16 outcomes were statistically significant in favor of the treatment (Figure 19). The critical outcomes addressed were activities of daily life (ADL), self-reported function, and pain. All of the ADL outcomes were not statistically significant when compared to placebo. One out of two functional outcomes, and one out of two pain outcomes were statistically significant in favor of pulsed electrical stimulation over placebo.

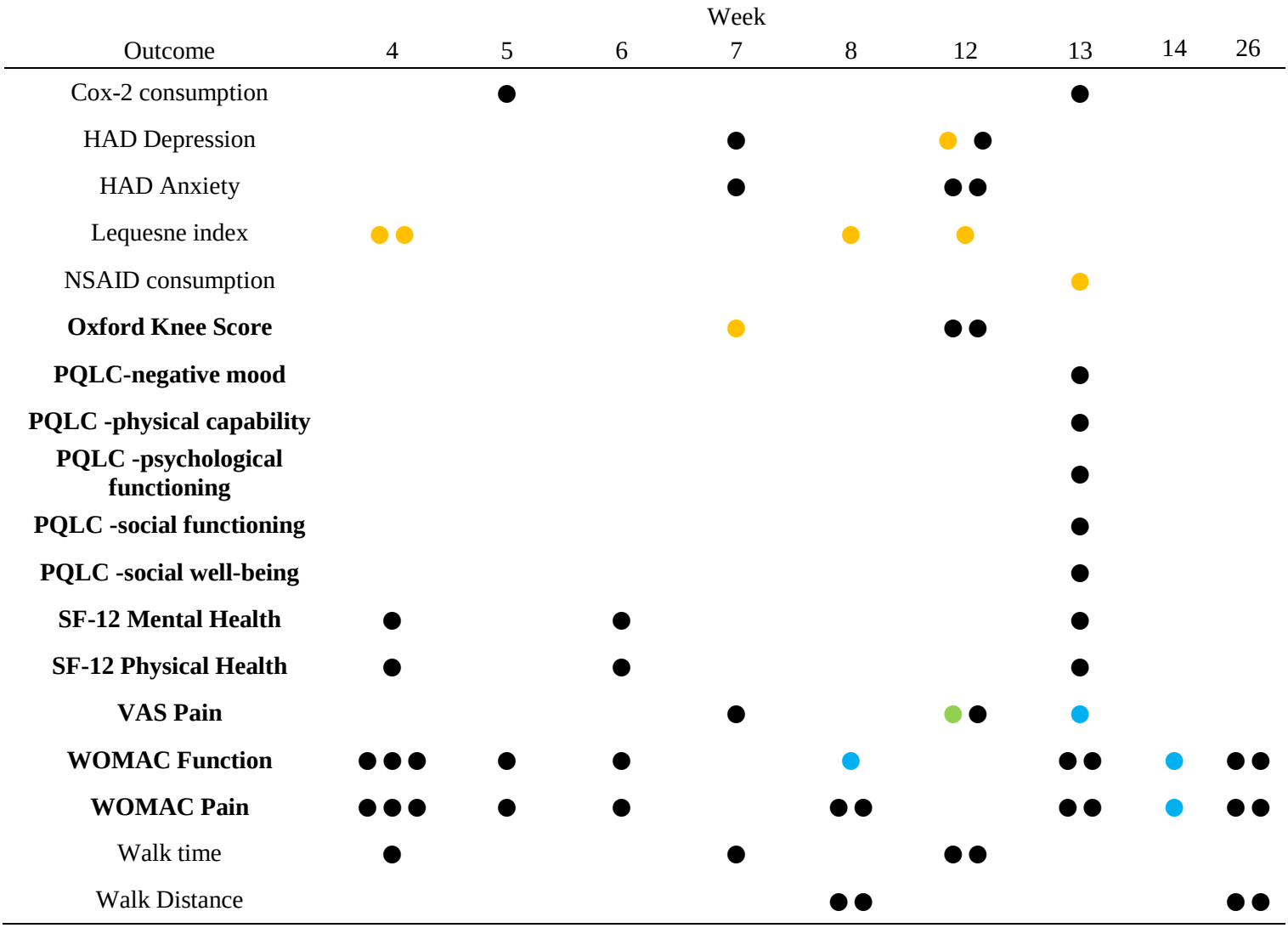
Trock et al.[72] compared the effect of pulsed electromagnetic fields to placebo. Pain on passive motion was not statistically different between groups. However, tenderness and Physician's Global Assessment were significantly improved in the treatment group. One additional study compared therapeutic application of modulated electro-magnetic field (TAMMEF) therapy to extremely low frequency electromagnetic field therapy.[74] There were no significant differences in pain and Lequesne index scores between the two treatments.

Pearlman et al.[77] compared Swedish massage therapy to a waitlist control at eight and 16 weeks based on twelve outcomes (table 99). The treatment group had significantly better scores on all outcomes at eight weeks. At 16 weeks, every outcome was not significantly different when comparing the treatment arms. However, five outcomes were not sufficiently powered. VAS pain, WOMAC pain and WOMAC function were the critical outcomes included in this study. Massage therapy had a possibly clinically important effect on VAS pain and WOMAC function scores at eight weeks. Swedish Massage Therapy had a clinically significant effect on WOMAC pain scores at eight weeks.

Huang et al.[75] and Yang et al.[76] compared ultrasound therapy to a control group. One study compared ultrasound to placebo, and the other compared isotonic exercise plus ultrasound to a control group who only received exercise therapy. Seven out of eight outcomes were statistically significant in favor of ultrasound (see Figure 18). VAS pain was the only critical outcome included in these studies. Two of three pain outcomes were statistically significant in favor of the ultrasound group (Figure 18).

Atamaz et al.[73] compared TENS, interferential current therapy (IFC), and short wave diathermy (SWD) to sham treatments (sham TENS, sham IFC, sham SWD). There were no statistically significant differences between any active treatments and their sham counterparts.

Figure 16. Results Summary: Acupuncture Versus Control



Key: ●=Not Significant; ●= Statistically Significant; ●=Possibly Clinically Important; ●=Significant But Not Clinically Important. Bold text indicates a critical outcome.

Figure 17. Results Summary: Electro-acupuncture Versus Control

Outcome	6	12
Geriatric Depression Scale	●	●
Pittsburgh Sleep Quality index	●	●
Stair climb time	●	●
WOMAC Pain	●	

Key: ●=Not Significant; ●=Possibly Clinically Important.

Bold text indicates a critical outcome.

Figure 18. Results Summary: Swedish Massage Therapy and Ultrasound Versus Control

	Outcome	Week 4	8	12	16	26	36	52
Swedish Massage Therapy	50 foot walk time		🟡		⚫			
	VAS Pain		🔵		⚫			
	WOMAC Function		🔵		⚫			
	WOMAC Total		🔵		⚫			
	WOMAC Pain		🔴		⚫			
	WOMAC Stiffness		🔵		⚫			
Ultrasound	Walk speed (m/min)		🟡					🟡
	Lequesne index	🟡	🟡					🟡
	VAS Pain	🟡	⚫					🔵

Key: ⚫=Not Significant; 🟡=Statistically Significant; 🔴=Clinically Significant; 🔵=Possibly Clinically Important; 🟢=Significant But Not Clinically Important.
Bold text indicates a critical outcome.

Figure 19. Results Summary: Pulsed Electrical Stimulation

Outcome	Week 4	8	26
Patient Global Assessment of Disease Activity			●
Physician overall assessment		●	
SF-36 Mental			●
Human activity profile maximum activity			●
Human activity profile adjusted activity			●
Daily accelerometer count			●
Daily resting time, minutes			●
Daily light activity, minutes			●
Daily moderate activity, minutes			●
Daily hard activity, minutes			●
Pain on passive motion	●		
VAS Pain		●	
VAS Function		●	
Morning stiffness		●	
Tenderness	●		
Physician's overall assessment	●		

Key: ● =Not Significant; ● =Statistically Significant. Bold text indicates a critical outcome.

Figure 20. Results Summary: Electromagnetic Fields

	Outcome	Week 4	Week 6.4
Pulsed Electromagnetic Field	**Pain on passive motion**	●	
	Tenderness	🟡	
	Physician's overall assessment	🟡	
Therapeutic Application of Modulated Electro Magnetic Field (TAMMEF) Versus Extremely Low Frequency Electromagnetic Field Therapy	**Complete reduction of pain**		●
	Lequesne index: Total recovery of articular function		●

Key: ● =Not Significant; 🟡 =Statistically Significant.

Bold text indicates a critical outcome.

EVIDENCE TABLES AND FIGURES

QUALITY AND APPLICABILITY

Table 86. Quality and Applicability: Acupuncture Versus Control

●: Domain free of flaws

○: Domain flaws present

◐: Moderate power

Study	*Outcome*	*Duration (Weeks)*	**Prospective**	**Power**	**Group Assignment**	**Blinding**	**Group Comparability**	**Treatment Integrity**	**Measurement**	**Investigator Bias**	*Quality*	**Participants**	**Intervention and Expertise**	**Compliance and Adherence**	**Analysis**	*Applicability Study*
Berman (1999)	WOMAC Pain	4	●	●	○	○	●	●	●	●	**Moderate**	○	○	●	●	**Moderate**
Berman (1999)	WOMAC Pain	4	●	●	○	○	●	●	●	●	**Moderate**	○	○	●	●	**Moderate**
Berman (1999)	Lequesne index	4	●	●	○	○	●	●	●	●	**Moderate**	○	○	●	●	**Moderate**
Berman (1999)	Lequesne index	8	●	●	○	○	●	●	●	●	**Moderate**	○	○	●	●	**Moderate**
Berman (1999)	Lequesne index	12	●	◐	○	○	●	●	●	●	**Moderate**	○	○	●	●	**Moderate**

●: Domain free of flaws

○: Domain flaws present

◐: Moderate power

Study	*Outcome*	*Duration (Weeks)*	**Prospective**	**Power**	**Group Assignment**	**Blinding**	**Group Comparability**	**Treatment Integrity**	**Measurement**	**Investigator Bias**	*Quality*	**Participants**	**Intervention and Expertise**	**Compliance and Adherence**	**Analysis**	*Applicability Study*
Berman (1999)	WOMAC Pain	8	●	●	○	○	●	●	●	●	**Moderate**	○	○	●	●	**Moderate**
Berman (1999)	WOMAC Pain	12	●	●	○	○	●	●	●	●	**Moderate**	○	○	●	●	**Moderate**
Berman (1999)	WOMAC Function	4	●	●	○	○	●	●	●	●	**Moderate**	○	○	●	●	**Moderate**
Berman (1999)	WOMAC Function	8	●	●	○	○	●	●	●	●	**Moderate**	○	○	●	●	**Moderate**
Berman (1999)	WOMAC Function	12	●	●	○	○	●	●	●	●	**Moderate**	○	○	●	●	**Moderate**
Berman (2004)	6 minute walk distance	8	●	◐	●	●	●	●	●	●	**High**	○	○	●	○	**Moderate**
Berman	6 minute walk	26	●	◐	●	●	●	●	●	●	**High**	○	○	●	○	**Moderate**

●: Domain free of flaws

○: Domain flaws present

◐: Moderate power

Study	*Outcome*	*Duration (Weeks)*	**Prospective**	**Power**	**Group Assignment**	**Blinding**	**Group Comparability**	**Treatment Integrity**	**Measurement**	**Investigator Bias**	*Quality*	**Participants**	**Intervention and Expertise**	**Compliance and Adherence**	**Analysis**	*Applicability Study*
(2004)	distance															
Berman (2004)	6 minute walk distance	8	●	◐	●	●	●	●	●	●	**High**	○	○	●	○	**Moderate**
Berman (2004)	6 minute walk distance	26	●	◐	●	●	●	●	●	●	**High**	○	○	●	○	**Moderate**
Berman (2004)	WOMAC Pain	8	●	●	●	●	●	●	●	●	**High**	○	○	●	○	**Moderate**
Berman (2004)	WOMAC Pain	14	●	●	●	●	●	●	●	●	**High**	○	○	●	○	**Moderate**
Berman (2004)	WOMAC Pain	26	●	●	●	●	●	●	●	●	**High**	○	○	●	○	**Moderate**
Berman (2004)	WOMAC Function	4	●	●	●	●	●	●	●	●	**High**	○	○	●	○	**Moderate**

●: Domain free of flaws

○: Domain flaws present

◐: Moderate power

Study	*Outcome*	*Duration (Weeks)*	**Prospective**	**Power**	**Group Assignment**	**Blinding**	**Group Comparability**	**Treatment Integrity**	**Measurement**	**Investigator Bias**	*Quality*	**Participants**	**Intervention and Expertise**	**Compliance and Adherence**	**Analysis**	*Applicability Study*
Berman (2004)	WOMAC Function	8	●	●	●	●	●	●	●	●	**High**	○	○	●	○	**Moderate**
Berman (2004)	WOMAC Function	14	●	●	●	●	●	●	●	●	**High**	○	○	●	○	**Moderate**
Berman (2004)	WOMAC Function	26	●	●	●	●	●	●	●	●	**High**	○	○	●	○	**Moderate**
Sandgee (2002)	50 foot walk time	4	●	◐	○	●	○	●	●	●	**Moderate**	○	○	●	●	**Moderate**
Sandgee (2002)	Lequesne index	4	●	●	○	●	○	●	●	●	**Moderate**	○	○	●	●	**Moderate**
Suarez-Almazor (2010)	SF-12 Physical Health	4	●	◐	●	●	●	●	●	●	**High**	●	○	●	●	**Moderate**

●: Domain free of flaws

○: Domain flaws present

◐: Moderate power

Study	*Outcome*	*Duration (Weeks)*	**Prospective**	**Power**	**Group Assignment**	**Blinding**	**Group Comparability**	**Treatment Integrity**	**Measurement**	**Investigator Bias**	*Quality*	**Participants**	**Intervention and Expertise**	**Compliance and Adherence**	**Analysis**	*Applicability Study*
Suarez-Almazor (2010)	SF-12 Physical Health	6	●	◐	●	●	●	●	●	●	**High**	●	○	●	●	**Moderate**
Suarez-Almazor (2010)	SF-12 Physical Health	13	●	◐	●	●	●	●	●	●	**High**	●	○	●	●	**Moderate**
Suarez-Almazor (2010)	SF-12 Mental Health	4	●	◐	●	●	●	●	●	●	**High**	●	○	●	●	**Moderate**
Suarez-Almazor (2010)	SF-12 Mental Health	6	●	◐	●	●	●	●	●	●	**High**	●	○	●	●	**Moderate**
Suarez-Almazor (2010)	SF-12 Mental Health	13	●	◐	●	●	●	●	●	●	**High**	●	○	●	●	**Moderate**

●: Domain free of flaws

○: Domain flaws present

◐: Moderate power

Study	*Outcome*	*Duration (Weeks)*	**Prospective**	**Power**	**Group Assignment**	**Blinding**	**Group Comparability**	**Treatment Integrity**	**Measurement**	**Investigator Bias**	*Quality*	**Participants**	**Intervention and Expertise**	**Compliance and Adherence**	**Analysis**	*Applicability Study*
Suarez-Almazor (2010)*	WOMAC Pain	4	●	●	●	●	●	●	●	●	**High**	●	○	●	●	**Moderate**
Suarez-Almazor (2010)*	WOMAC Pain	6	●	●	●	●	●	●	●	●	**High**	●	○	●	●	**Moderate**
Suarez-Almazor (2010)*	WOMAC Pain	13	●	●	●	●	●	●	●	●	**High**	●	○	●	●	**Moderate**
Suarez-Almazor (2010)*	WOMAC Function	4	●	●	●	●	●	●	●	●	**High**	●	○	●	●	**Moderate**
Suarez-Almazor (2010)*	WOMAC Function	6	●	●	●	●	●	●	●	●	**High**	●	○	●	●	**Moderate**

●: Domain free of flaws

○: Domain flaws present

◐: Moderate power

Study	*Outcome*	*Duration (Weeks)*	**Prospective**	**Power**	**Group Assignment**	**Blinding**	**Group Comparability**	**Treatment Integrity**	**Measurement**	**Investigator Bias**	*Quality*	**Participants**	**Intervention and Expertise**	**Compliance and Adherence**	**Analysis**	*Applicability Study*
Suarez-Almazor (2010)*	WOMAC Function	13	●	●	●	●	●	●	●	●	**High**	●	○	●	●	**Moderate**
Taechaarpornkul (2009)	WOMAC Pain	13	●	◐	●	●	●	●	●	○	**High**	○	○	●	●	**Moderate**
Taechaarpornkul (2009)	Cox-2 consumption	5	●	◐	●	●	●	●	●	○	**High**	○	○	●	●	**Moderate**
Taechaarpornkul (2009)	Cox-2 consumption	13	●	◐	●	●	●	●	●	○	**High**	○	○	●	●	**Moderate**
Taechaarpornkul (2009)*	WOMAC Pain	5	●	◐	●	●	●	●	●	○	**High**	○	○	●	●	**Moderate**
Taechaarpornkul (2009)*	WOMAC Function	5	●	◐	●	●	●	●	●	○	**High**	○	○	●	●	**Moderate**

●: Domain free of flaws

○: Domain flaws present

◐: Moderate power

Study	*Outcome*	*Duration (Weeks)*	**Prospective**	**Power**	**Group Assignment**	**Blinding**	**Group Comparability**	**Treatment Integrity**	**Measurement**	**Investigator Bias**	*Quality*	**Participants**	**Intervention and Expertise**	**Compliance and Adherence**	**Analysis**	*Applicability Study*
Taechaarpornkul (2009)*	WOMAC Function	13	●	◐	●	●	●	●	●	○	**High**	○	○	●	●	**Moderate**
VAS (2004)	PLQC- Negative Mood	13	●	◐	○	●	○	●	●	○	**Moderate**	○	○	●	●	**Moderate**
VAS (2004)	PLQC- Physical capability	13	●	◐	○	●	○	●	●	○	**Moderate**	○	○	●	●	**Moderate**
VAS (2004)	PLQC- Psychological Functioning	13	●	◐	○	●	○	●	●	○	**Moderate**	○	○	●	●	**Moderate**
VAS (2004)	PLQC- Social Functioning	13	●	◐	○	●	○	●	●	○	**Moderate**	○	○	●	●	**Moderate**
VAS (2004)	PLQC- Social Well-Being	13	●	◐	○	●	○	●	●	○	**Moderate**	○	○	●	●	**Moderate**
VAS (2004)	NSAID consumption	13	●	●	○	●	○	●	●	○	**Moderate**	○	○	●	●	**Moderate**

●: Domain free of flaws

○: Domain flaws present

◐: Moderate power

Study	*Outcome*	*Duration (Weeks)*	**Prospective**	**Power**	**Group Assignment**	**Blinding**	**Group Comparability**	**Treatment Integrity**	**Measurement**	**Investigator Bias**	*Quality*	**Participants**	**Intervention and Expertise**	**Compliance and Adherence**	**Analysis**	*Applicability Study*
VAS (2004)	VAS Pain	13	●	●	○	●	○	●	●	○	**Moderate**	○	○	●	●	**Moderate**
Weiner (2004)	WOMAC Pain	6	●	●	○	●	●	●	●	●	**High**	○	○	●	●	**Moderate**
Witt (2005)	SF-36 Physical Health	8	●	●	○	●	○	●	●	○	**Moderate**	○	○	●	●	**Moderate**
Williamson (2007)	OKS	Williamson (2007)	●	◐	●	○	●	●	●	●	**High**	○	○	●	●	**Moderate**
Williamson (2007)	OKS	Williamson (2007)	●	◐	●	○	●	●	●	●	**High**	○	○	●	●	**Moderate**
Williamson (2007)	OKS	Williamson (2007)	●	◐	●	○	●	●	●	●	**High**	○	○	●	●	**Moderate**
Williamson (2007)	50m walk(s)	Williamson (2007)	●	◐	●	○	●	●	●	●	**High**	○	○	●	●	**Moderate**

●: Domain free of flaws

○: Domain flaws present

◐: Moderate power

Study	*Outcome*	*Duration (Weeks)*	**Prospective**	**Power**	**Group Assignment**	**Blinding**	**Group Comparability**	**Treatment Integrity**	**Measurement**	**Investigator Bias**	*Quality*	**Participants**	**Intervention and Expertise**	**Compliance and Adherence**	**Analysis**	*Applicability Study*
Williamson (2007)	50m walk(s)	Williamson (2007)	●	◐	●	○	●	●	●	●	**High**	○	○	●	●	**Moderate**
Williamson (2007)	50m walk(s)	Williamson (2007)	●	◐	●	○	●	●	●	●	**High**	○	○	●	●	**Moderate**
Williamson (2007)	Post-op stay (days)	Williamson (2007)	●	◐	●	○	●	●	●	●	**High**	○	○	●	●	**Moderate**
Williamson (2007)	VAS (cm)	Williamson (2007)	●	●	●	○	●	●	●	●	**High**	○	○	●	●	**Moderate**
Williamson (2007)	VAS (cm)	Williamson (2007)	●	●	●	○	●	●	●	●	**High**	○	○	●	●	**Moderate**
Williamson (2007)	VAS (cm)	Williamson (2007)	●	●	●	○	●	●	●	●	**High**	○	○	●	●	**Moderate**
Williamson	HAD Anxiety	Williamson (2007)	●	◐	●	○	●	●	●	●	**High**	○	○	●	●	**Moderate**

●: Domain free of flaws

○: Domain flaws present

◐: Moderate power

Study	*Outcome*	*Duration (Weeks)*	**Prospective**	**Power**	**Group Assignment**	**Blinding**	**Group Comparability**	**Treatment Integrity**	**Measurement**	**Investigator Bias**	*Quality*	**Participants**	**Intervention and Expertise**	**Compliance and Adherence**	**Analysis**	*Applicability Study*
(2007)																
Williamson (2007)	HAD Anxiety	Williamson (2007)	●	◐	●	○	●	●	●	●	**High**	○	○	●	●	**Moderate**
Williamson (2007)	HAD Anxiety	Williamson (2007)	●	◐	●	○	●	●	●	●	**High**	○	○	●	●	**Moderate**
Williamson (2007)	HAD Depression	Williamson (2007)	●	◐	●	○	●	●	●	●	**High**	○	○	●	●	**Moderate**
Williamson (2007)	HAD Depression	Williamson (2007)	●	◐	●	○	●	●	●	●	**High**	○	○	●	●	**Moderate**
Williamson (2007)	HAD Depression	Williamson (2007)	●	◐	●	○	●	●	●	●	**High**	○	○	●	●	**Moderate**

Table 87. Quality and Applicability: Periosteal Stimulation Therapy

●: Domain free of flaws

○: Domain flaws present

◐: Moderate power

Study	*Outcome*	*Duration (Weeks)*	**Prospective**	**Power**	**Group Assignment**	**Blinding**	**Group Comparability**	**Treatment Integrity**	**Measurement**	**Investigator Bias**	*Quality*	**Participants**	**Intervention and Expertise**	**Compliance and Adherence**	**Analysis**	*Applicability Study*
Weiner (2004)	WOMAC Pain	6	●	●	○	●	●	●	●	●	**High**	○	○	●	●	**Moderate**
Weiner (2004)	Geriatric Depression Scale	6	●	◐	○	●	●	●	●	●	**High**	○	○	●	●	**Moderate**
Weiner (2004)	Geriatric Depression Scale	12	●	◐	○	●	●	●	●	●	**High**	○	○	●	●	**Moderate**
Weiner (2004)	Pittsburgh Sleep Quality index	6	●	◐	○	●	●	●	●	●	**High**	○	○	●	●	**Moderate**
Weiner (2004)	Pittsburgh Sleep Quality index	12	●	◐	○	●	●	●	●	●	**High**	○	○	●	●	**Moderate**
Weiner (2004)	Stair climb time	6	●	◐	○	●	●	●	●	●	**High**	○	○	●	●	**Moderate**
Weiner (2004)	Stair climb time	12	●	◐	○	●	●	●	●	●	**High**	○	○	●	●	**Moderate**

Table 88. Quality and Applicability: Pulsed Electrical and Electromagnetic Therapy

●: Domain free of flaws

○: Domain flaws present

◐: Moderate power

Study	*Outcome*	*Duration (Weeks)*	**Prospective**	**Power**	**Group Assignment**	**Blinding**	**Group Comparability**	**Treatment Integrity**	**Measurement**	**Investigator Bias**	*Quality*	**Participants**	**Intervention and Expertise**	**Compliance and Adherence**	**Analysis**	*Applicability Study*
Fary (2011)	Patient Global Assessment of Disease Activity	26	○	◐	○	○	○	●	●	○	**Low**	○	○	●	●	**Moderate**
Fary (2011)	SF-36 Mental	26	○	◐	○	○	○	●	●	○	**Low**	○	○	●	●	**Moderate**
Fary (2011)	Human activity profile maximum activity	26	○	◐	○	○	○	●	●	○	**Low**	○	○	●	●	**Moderate**
Fary (2011)	Human activity profile adjusted activity	26	○	◐	○	○	○	●	●	○	**Low**	○	○	●	●	**Moderate**
Fary (2011)	Daily accelerometer count	26	○	◐	○	○	○	●	●	○	**Low**	○	○	●	●	**Moderate**
Fary (2011)	Daily resting time, minutes	26	○	◐	○	○	○	●	●	○	**Low**	○	○	●	●	**Moderate**

●: Domain free of flaws

○: Domain flaws present

◐: Moderate power

Study	*Outcome*	*Duration (Weeks)*	**Prospective**	**Power**	**Group Assignment**	**Blinding**	**Group Comparability**	**Treatment Integrity**	**Measurement**	**Investigator Bias**	*Quality*	**Participants**	**Intervention and Expertise**	**Compliance and Adherence**	**Analysis**	*Applicability Study*
Fary (2011)	Daily light activity, minutes	26	○	◐	○	○	○	●	●	○	**Low**	○	○	●	●	**Moderate**
Fary (2011)	Daily moderate activity, minutes	26	○	◐	○	○	○	●	●	○	**Low**	○	○	●	●	**Moderate**
Fary (2011)	Daily hard activity, minutes	26	○	◐	○	○	○	●	●	○	**Low**	○	○	●	●	**Moderate**
Trock (1994)	Pain on passive motion	4 weeks after treatment completion	●	◐	○	●	○	●	●	○	**Moderate**	○	○	●	●	**Moderate**
Trock (1994)	Tenderness	4 weeks after treatment completion	●	◐	○	●	○	●	●	○	**Moderate**	○	○	●	●	**Moderate**
Trock (1994)	Physician overall assessment	4 weeks after treatment	●	◐	○	●	○	●	●	○	**Moderate**	○	○	●	●	**Moderate**

●: Domain free of flaws

○: Domain flaws present

◐: Moderate power

Study	*Outcome*	*Duration (Weeks)*	**Prospective**	**Power**	**Group Assignment**	**Blinding**	**Group Comparability**	**Treatment Integrity**	**Measurement**	**Investigator Bias**	*Quality*	**Participants**	**Intervention and Expertise**	**Compliance and Adherence**	**Analysis**	*Applicability Study*
		completion														
Zizic (1995)	VAS Pain % change	8	●	◐	○	●	●	●	●	○	**Moderate**	○	○	●	○	**Moderate**
Zizic (1995)	VAS Function % change	8	●	◐	○	●	●	●	●	○	**Moderate**	○	○	●	○	**Moderate**
Zizic (1995)	Percent change adjusted mean physician evaluation (VAS)	8	●	◐	○	●	●	●	●	○	**Moderate**	○	○	●	○	**Moderate**
Zizic (1995)	At least 15 minute improvement in morning stiffness	8	●	◐	○	●	●	●	●	○	**Moderate**	○	○	●	○	**Moderate**
Battisti (2004)	Complete reduction of pain	6.4	●	◐	○	●	○	●	●	●	**Moderate**	●	○	●	●	**Moderate**
Battisti (2004)	Lequesne index: Total recovery of articular function	6.4	●	◐	○	●	○	●	●	●	**Moderate**	●	○	●	●	**Moderate**

Table 89. Quality and Applicability: TENS, Interferential Current, and Short Wave Diathermy

●: Domain free of flaws

○: Domain flaws present

◐: Moderate power

Study	*Outcome*	*Duration (Weeks)*	**Prospective**	**Power**	**Group Assignment**	**Blinding**	**Group Comparability**	**Treatment Integrity**	**Measurement**	**Investigator Bias**	*Quality*	**Participants**	**Intervention and Expertise**	**Compliance and Adherence**	**Analysis**	*Applicability Study*
4	VAS Pain TENS		●	◐	○	●	●	○	●	●	**Moderate**	○	○	○	●	**Moderate**
4	VAS Pain IFC		●	◐	○	●	●	○	●	●	**Moderate**	○	○	○	●	**Moderate**
4	VAS Pain SWD		●	◐	○	●	●	○	●	●	**Moderate**	○	○	○	●	**Moderate**
13	VAS Pain TENS		●	◐	○	●	●	○	●	●	**Moderate**	○	○	○	●	**Moderate**
13	VAS Pain IFC		●	◐	○	●	●	○	●	●	**Moderate**	○	○	○	●	**Moderate**
13	VAS Pain SWD		●	◐	○	●	●	○	●	●	**Moderate**	○	○	○	●	**Moderate**
26	VAS Pain TENS		●	◐	○	●	●	○	●	●	**Moderate**	○	○	○	●	**Moderate**
26	VAS Pain IFC		●	◐	○	●	●	○	●	●	**Moderate**	○	○	○	●	**Moderate**

●: Domain free of flaws

○: Domain flaws present

◐: Moderate power

Study	*Outcome*	*Duration (Weeks)*	**Prospective**	**Power**	**Group Assignment**	**Blinding**	**Group Comparability**	**Treatment Integrity**	**Measurement**	**Investigator Bias**	*Quality*	**Participants**	**Intervention and Expertise**	**Compliance and Adherence**	**Analysis**	*Applicability Study*
26	VAS Pain SWD		●	◐	○	●	●	○	●	●	**Moderate**	○	○	○	●	**Moderate**
4	Nottingham Health Profile-Pain TENS		●	◐	○	●	●	○	●	●	**Moderate**	○	○	○	●	**Moderate**
4	Nottingham Health Profile-Pain IFC		●	◐	○	●	●	○	●	●	**Moderate**	○	○	○	●	**Moderate**
4	Nottingham Health Profile-Pain SWD		●	◐	○	●	●	○	●	●	**Moderate**	○	○	○	●	**Moderate**
13	Nottingham Health Profile-Pain TENS		●	◐	○	●	●	○	●	●	**Moderate**	○	○	○	●	**Moderate**
13	Nottingham Health Profile-Pain IFC		●	◐	○	●	●	○	●	●	**Moderate**	○	○	○	●	**Moderate**
13	Nottingham Health Profile-Pain SWD		●	◐	○	●	●	○	●	●	**Moderate**	○	○	○	●	**Moderate**
26	Nottingham Health Profile-Pain TENS		●	◐	○	●	●	○	●	●	**Moderate**	○	○	○	●	**Moderate**
26	Nottingham Health Profile-Pain IFC		●	◐	○	●	●	○	●	●	**Moderate**	○	○	○	●	**Moderate**

●: Domain free of flaws

○: Domain flaws present

◐: Moderate power

Study	*Outcome*	*Duration (Weeks)*	**Prospective**	**Power**	**Group Assignment**	**Blinding**	**Group Comparability**	**Treatment Integrity**	**Measurement**	**Investigator Bias**	*Quality*	**Participants**	**Intervention and Expertise**	**Compliance and Adherence**	**Analysis**	*Applicability Study*
26	Nottingham Health Profile-Pain SWD		●	◐	○	●	●	○	●	●	**Moderate**	○	○	○	●	**Moderate**
4	Timed walk TENS		●	◐	○	●	●	○	●	●	**Moderate**	○	○	○	●	**Moderate**
4	Timed walk IFC		●	◐	○	●	●	○	●	●	**Moderate**	○	○	○	●	**Moderate**
4	Timed walk SWD		●	◐	○	●	●	○	●	●	**Moderate**	○	○	○	●	**Moderate**
13	Timed walk TENS		●	◐	○	●	●	○	●	●	**Moderate**	○	○	○	●	**Moderate**
13	Timed walk IFC		●	◐	○	●	●	○	●	●	**Moderate**	○	○	○	●	**Moderate**
13	Timed walk SWD		●	◐	○	●	●	○	●	●	**Moderate**	○	○	○	●	**Moderate**
26	Timed walk TENS		●	◐	○	●	●	○	●	●	**Moderate**	○	○	○	●	**Moderate**
26	Timed walk IFC		●	◐	○	●	●	○	●	●	**Moderate**	○	○	○	●	**Moderate**

●: Domain free of flaws

○: Domain flaws present

◐: Moderate power

Study	*Outcome*	*Duration (Weeks)*	**Prospective**	**Power**	**Group Assignment**	**Blinding**	**Group Comparability**	**Treatment Integrity**	**Measurement**	**Investigator Bias**	*Quality*	**Participants**	**Intervention and Expertise**	**Compliance and Adherence**	**Analysis**	*Applicability Study*
26	Timed walk SWD		●	◐	○	●	●	○	●	●	**Moderate**	○	○	○	●	**Moderate**
4	Nottingham Health Profile: Physical TENS		●	◐	○	●	●	○	●	●	**Moderate**	○	○	○	●	**Moderate**
4	Nottingham Health Profile: Physical IFC		●	◐	○	●	●	○	●	●	**Moderate**	○	○	○	●	**Moderate**
4	Nottingham Health Profile: Physical SWD		●	◐	○	●	●	○	●	●	**Moderate**	○	○	○	●	**Moderate**
13	Nottingham Health Profile: Physical TENS		●	◐	○	●	●	○	●	●	**Moderate**	○	○	○	●	**Moderate**
13	Nottingham Health Profile: Physical IFC		●	◐	○	●	●	○	●	●	**Moderate**	○	○	○	●	**Moderate**
13	Nottingham Health Profile: Physical SWD		●	◐	○	●	●	○	●	●	**Moderate**	○	○	○	●	**Moderate**
26	Nottingham Health Profile: Physical TENS		●	◐	○	●	●	○	●	●	**Moderate**	○	○	○	●	**Moderate**

●: Domain free of flaws

○: Domain flaws present

◐: Moderate power

Study	*Outcome*	*Duration (Weeks)*	**Prospective**	**Power**	**Group Assignment**	**Blinding**	**Group Comparability**	**Treatment Integrity**	**Measurement**	**Investigator Bias**	*Quality*	**Participants**	**Intervention and Expertise**	**Compliance and Adherence**	**Analysis**	*Applicability Study*
26	Nottingham Health Profile: Physical IFC		●	◐	○	●	●	○	●	●	**Moderate**	○	○	○	●	**Moderate**
26	Nottingham Health Profile: Physical SWD		●	◐	○	●	●	○	●	●	**Moderate**	○	○	○	●	**Moderate**

Note 1 TENS= Transcutaneous electrical nerve stimulation; IFC=Interferential current; SWD=Short Wave Diathermy

Table 90. Swedish Massage Therapy Versus Usual Care

●: Domain free of flaws

○: Domain flaws present

◐: Moderate power

Study	*Outcome*	*Duration (Weeks)*	**Prospective**	**Power**	**Group Assignment**	**Blinding**	**Group Comparability**	**Treatment Integrity**	**Measurement**	**Investigator Bias**	*Quality*	**Participants**	**Intervention and Expertise**	**Compliance and Adherence**	**Analysis**	*Applicability Study*
Perlman (2006)	50 foot walk time	8	●	●	○	○	○	○	●	●	**Low**	○	○	●	●	**Moderate**
Perlman (2006)	50 foot walk time	16	●	◐	○	○	○	○	●	●	**Low**	○	○	●	●	**Moderate**
Perlman (2006)	VAS Pain	8	●	●	○	○	○	○	●	●	**Low**	○	○	●	●	**Moderate**
Perlman (2006)	VAS Pain	16	●	○	○	○	○	○	●	●	**Low**	○	○	●	●	**Moderate**
Perlman (2006)	WOMAC Function	8	●	●	○	○	○	○	●	●	**Low**	○	○	●	●	**Moderate**
Perlman (2006)	WOMAC Function	16	●	○	○	○	○	○	●	●	**Low**	○	○	●	●	**Moderate**
Perlman (2006)	WOMAC Total	8	●	●	○	○	○	○	●	●	**Low**	○	○	●	●	**Moderate**
Perlman (2006)	WOMAC Total	16	●	○	○	○	○	○	●	●	**Low**	○	○	●	●	**Moderate**

●: Domain free of flaws

○: Domain flaws present

◐: Moderate power

Study	*Outcome*	*Duration (Weeks)*	**Prospective**	**Power**	**Group Assignment**	**Blinding**	**Group Comparability**	**Treatment Integrity**	**Measurement**	**Investigator Bias**	*Quality*	**Participants**	**Intervention and Expertise**	**Compliance and Adherence**	**Analysis**	*Applicability Study*
Perlman (2006)	WOMAC Pain	8	●	●	○	○	○	○	●	●	**Low**	○	○	●	●	**Moderate**
Perlman (2006)	WOMAC Pain	16	●	○	○	○	○	○	●	●	**Low**	○	○	●	●	**Moderate**
Perlman (2006)	WOMAC Stiffness	8	●	●	○	○	○	○	●	●	**Low**	○	○	●	●	**Moderate**
Perlman (2006)	WOMAC Stiffness	16	●	○	○	○	○	○	●	●	**Low**	○	○	●	●	**Moderate**

Table 91. Ultrasonic Wave Plus Exercise Versus Exercise Alone

●: Domain free of flaws

○: Domain flaws present

◐: Moderate power

Study	*Outcome*	*Duration (Weeks)*	**Prospective**	**Power**	**Group Assignment**	**Blinding**	**Group Comparability**	**Treatment Integrity**	**Measurement**	**Investigator Bias**	*Quality*	**Participants**	**Intervention and Expertise**	**Compliance and Adherence**	**Analysis**	*Applicability Study*
Huang (2005)	Walk speed (m/min)	8	●	●	●	○	●	●	●	○	**Moderate**	○	○	●	●	**Moderate**
Huang (2005)	Lequesne index	8	●	●	●	○	●	●	●	○	**Moderate**	○	○	●	●	**Moderate**
Huang (2005)	VAS Pain	8	●	●	●	○	●	●	●	○	**Moderate**	○	○	●	●	**Moderate**
Huang (2005)	Walk speed (m/min)	52	●	●	●	○	●	●	●	○	**Moderate**	○	○	●	●	**Moderate**
Huang (2005)	Lequesne index	52	●	●	●	○	●	●	●	○	**Moderate**	○	○	●	●	**Moderate**
Huang (2005)	VAS Pain	52	●	●	●	○	●	●	●	○	**Moderate**	○	○	●	●	**Moderate**
Huang (2005)	Walk speed (m/min)	8	●	●	●	○	●	●	●	○	**Moderate**	○	○	●	●	**Moderate**
Yang (2011)	VAS Pain	4	●	●	○	●	○	●	●	●	**Moderate**	○	○	●	●	**Moderate**

●: Domain free of flaws

○: Domain flaws present

◐: Moderate power

Study	*Outcome*	*Duration (Weeks)*	**Prospective**	**Power**	**Group Assignment**	**Blinding**	**Group Comparability**	**Treatment Integrity**	**Measurement**	**Investigator Bias**	*Quality*	**Participants**	**Intervention and Expertise**	**Compliance and Adherence**	**Analysis**	*Applicability Study*
Yang (2011)	Lequesne index	4	●	●	○	●	○	●	●	●	**Moderate**	○	○	●	●	**Moderate**

FINDINGS

Table 92. Acupuncture Versus Control: Pain

Study	Outcome	N	Power to Detect MCII	Week	Group 1	Group 2	SMD (Odds Ratio or Raw Mean Difference When Indicated)	Sig	Clinical Importance	Strength of Evidence
Berman (2004)	WOMAC Pain	336	Yes	4	Acupuncture	Sham acupuncture	-0.08 (-0.29, 0.14)	No	True negative	High
Suarez-Almazor (2010)	WOMAC Pain	301	Yes	4	Traditional Chinese acupuncture	Sham	-0.05 (-0.27, 0.18)	No	True negative	High
Taechaarpornkul (2009)	WOMAC Pain	66	Unclear	5	Six point Chinese acupuncture	Two point Chinese acupuncture	-0.08 (-0.57, 0.40)	No	Inconclusive	High
Suarez-Almazor (2010)	WOMAC Pain	301	Yes	6	Traditional Chinese acupuncture	Sham	-0.18 (-0.40, 0.05)	No	Inconclusive	High
Berman (2004)	WOMAC Pain	330	Yes	8	Acupuncture	Sham acupuncture	-0.14 (-0.35, 0.08)	No	True negative	High
Berman (2004)	WOMAC Pain	315	Yes	14	Acupuncture	Sham acupuncture	-0.24 (-0.46, -0.01)	Favors electro-acupuncture	Possibly clinically significant	High
Taechaarpornkul (2009)	WOMAC Pain	66	Unclear	13	Six point Chinese acupuncture	Two point Chinese acupuncture	-0.29 (-0.77, 0.20)	No	Inconclusive	High
Suarez-Almazor (2010)	WOMAC Pain	301	Yes	13	Traditional Chinese acupuncture	Sham	-0.05 (-0.28, 0.18)	No	True negative	High

Study	Outcome	N	Power to Detect MCII	Week	Group 1	Group 2	SMD (Odds Ratio or Raw Mean Difference When Indicated)	Sig	Clinical Importance	Strength of Evidence
VAS (2004)	VAS Pain	97	Yes	13	Acupuncture	Placebo	-1.31 (-1.75, -0.87)	Favors acupuncture	Possibly clinically significant	Moderate
Berman (2004)	WOMAC Pain	283	Yes	26	Acupuncture	Sham acupuncture	-0.23 (-0.47, 0.00)	No	Inconclusive	High
Williamson (2007)	VAS Pain	121	Yes	7	Acupuncture	Usual care	-.232 (-.59 , .125)	No	Not clinically important	High
Williamson (2007)	VAS Pain	121	Yes	12	Acupuncture	Usual care	-.301 (-.66 ,.058)	No	Not clinically important	High
Williamson (2007)	VAS Pain	121	Yes	12 post TKA surgery	Acupuncture	Usual care	-.382 (-.741, -.022)	Favors acupuncture	Not clinically important	High

Table 93. Acupuncture Versus Control: Function

Study	Outcome	N	Power	Week	Group 1	Group 2	SMD (Odds Ratio or Raw Mean Difference When Indicated)	Sig	Clinical Importance	Strength of Evidence
Sandgee (2002)	50 foot walk time	91	Unclear	4	Electro-acupuncture	Sham	0.41 (-0.01, 0.82)	No	N/A	Moderate

Study	Outcome	N	Power	Week	Group 1	Group 2	SMD (Odds Ratio or Raw Mean Difference When Indicated)	Sig	Clinical Importance	Strength of Evidence
Williamson (2007)	50m walk time(s)	121	Unclear	7	Acupuncture	Usual care	-0.16 (-0.52 ,0.2)	No	Unclear	High
Williamson (2007)	50m walk time(s)	121	Unclear	12	Acupuncture	Usual care	-0.15 (-0.51 ,0.20)	No	Unclear	High
Williamson (2007)	50m walk time(s)	121	Unclear	12 post TKA surgery	Acupuncture	Usual care	0.35 (-0.01 ,0.71)	No	Unclear	High
Berman (2004)	6 minute walk distance	319	Unclear	8	Acupuncture	Sham	-0.02 (-0.24, 0.20)	No	N/A	High
Berman (2004)	6 minute walk distance	265	Unclear	26	Acupuncture	Sham	-0.13 (-0.37, 0.11)	No	N/A	High
Berman (2004)	6 minute walk distance	252	Unclear	8	Acupuncture	Education	0.26 (-0.00, 0.52)	No	N/A	High
Berman (2004)	6 minute walk distance	211	Unclear	26	Acupuncture	Education	0.27 (-0.01, 0.56)	No	N/A	High
Williamson (2007)	Oxford Knee Score	121	Unclear	7	Acupuncture	Usual care	-0.442 (-0.803 ,-0.081)	Favors acupuncture	Unclear	High
Williamson (2007)	Oxford Knee Score	121	Unclear	12	Acupuncture	Usual care	-0.356 (-0.72 ,0.004)	No	Unclear	High
Williamson (2007)	Oxford Knee Score	121	Unclear	12 post TKA surgery	Acupuncture	Usual care	-0.13 (-0.49 ,0.22)	No	Unclear	High

Study	Outcome	N	Power	Week	Group 1	Group 2	SMD (Odds Ratio or Raw Mean Difference When Indicated)	Sig	Clinical Importance	Strength of Evidence
Suarez-Almazor (2010)	SF-12 Mental Health	301	Unclear	4	Traditional Chinese acupuncture	Sham	0.08 (-0.14, 0.31)	No	N/A	High
Suarez-Almazor (2010)	SF-12 Mental Health	301	Unclear	6	Traditional Chinese acupuncture	Sham	0.15 (-0.08, 0.38)	No	N/A	High
Suarez-Almazor (2010)	SF-12 Mental Health	301	Unclear	13	Traditional Chinese acupuncture	Sham	0.08 (-0.15, 0.31)	No	N/A	High
Suarez-Almazor (2010)	SF-12 Physical Health	301	Unclear	4	Traditional Chinese acupuncture	Sham	-0.03 (-0.26, 0.19)	No	N/A	High
Suarez-Almazor (2010)	SF-12 Physical Health	301	Unclear	6	Traditional Chinese acupuncture	Sham	-0.07 (-0.30, 0.15)	No	N/A	High
Suarez-Almazor (2010)	SF-12 Physical Health	301	Unclear	13	Traditional Chinese acupuncture	Sham	0.11 (-0.12, 0.33)	No	N/A	High
Berman (2004)	WOMAC Function	336	Yes	4	Acupuncture	Sham acupuncture	-0.18 (-0.39, 0.04)	No	Inconclusive	High
Berman (2004)	WOMAC Function	330	Yes	8	Acupuncture	Sham	-0.27 (-0.49, -0.06)	Favors electro-acupuncture	Possibly clinically significant	High

Study	Outcome	N	Power	Week	Group 1	Group 2	SMD (Odds Ratio or Raw Mean Difference When Indicated)	Sig	Clinical Importance	Strength of Evidence
Berman (2004)	WOMAC Function	315	Yes	14	Acupuncture	Sham acupuncture	-0.23 (-0.45, -0.01)	Favors electro-acupuncture	Possibly clinically significant	High
Berman (2004)	WOMAC Function	283	Yes	26	Acupuncture	Sham acupuncture	-0.21 (-0.44, 0.03)	No	Inconclusive	High
Suarez-Almazor (2010)	WOMAC Function	301	Yes	4	Traditional Chinese acupuncture	Sham	-0.10 (-0.33, 0.12)	No	True negative	High
Suarez-Almazor (2010)	WOMAC Function	301	Yes	6	Traditional Chinese acupuncture	Sham	-0.10 (-0.33, 0.12)	No	True negative	High
Suarez-Almazor (2010)	WOMAC Function	301	Yes	13	Traditional Chinese acupuncture	Sham	-0.05 (-0.28, 0.18)	No	True negative	High
Taechaarpornkul (2009)	WOMAC Function	66	Unclear	5	Six point Chinese acupuncture	Two point Chinese acupuncture	-0.05 (-0.53, 0.43)	No	Inconclusive	High
Taechaarpornkul (2009)	WOMAC Function	66	Unclear	13	Six point Chinese acupuncture	Two point Chinese acupuncture	-0.39 (-0.88, 0.09)	No	Inconclusive	High

Study	Outcome	N	Power	Week	Group 1	Group 2	SMD (Odds Ratio or Raw Mean Difference When Indicated)	Sig	Clinical Importance	Strength of Evidence
Vas (2004)	Profile of quality of life in the chronically ill (PQLC): Negative Mood	97	Unclear	13	Acupuncture	Sham	0.14 (-0.26, 0.54)	No	N/A	Moderate
Vas(2004)	PQLC: Physical Capability	97	Unclear	13	Acupuncture	Sham	0.40 (-0.01, 0.80)	No	No	Moderate
Vas (2004)	PLQC-Psychological Functioning	97	Unclear	13	Acupuncture	Sham	0.39 (-0.01, 0.79)	No	N/A	Moderate
Vas (2004)	PLQC- Social Functioning	97	Unclear	13	Acupuncture	Sham	0.16 (-0.24, 0.56)	No	N/A	Moderate
Vas (2004)	PLQC: Social Well-Being	97	Unclear	13	Acupuncture	Sham	0.00 (-0.40, 0.40)	No	N/A	Moderate

Table 94. Acupuncture Versus Usual Care: Hospital Anxiety and Depression Score

Study	Outcome	N	Power	Week	Group 1	Group 2	SMD (Odds Ratio or Raw Mean Difference When Indicated)	Sig	Clinical Importance	Strength of Evidence
Williamson (2007)	HAD Anxiety	121	Unclear	7	Acupuncture	Usual care	-0.026 (-0.382 ,0.33)	No	Unclear	High
Williamson (2007)	HAD Anxiety	121	Unclear	12	Acupuncture	Usual care	0.084 (-0.27 ,0.44)	No	Unclear	High
Williamson (2007)	HAD Anxiety	121	Unclear	12 post TKA surgery	Acupuncture	Usual care	0.082 (-0.27 ,0.439)	No	Unclear	High
Williamson (2007)	HAD Depression	121	Unclear	7	Acupuncture	Usual care	-0.079 (-0.436 ,0.28)	No	Unclear	High
Williamson (2007)	HAD Depression	121	Unclear	12	Acupuncture	Usual care	-0.121 (-0.48 ,0.236)	No	Unclear	High
Williamson (2007)	HAD Depression	121	Unclear	12 post TKA surgery	Acupuncture	Usual care	-0.409 (-0.77 ,0.05)	Favors acupuncture	Unclear	High

Table 95. Acupuncture Versus Control: Lequesne Index

Study	N	Power	Week	Group 1	Group 2	SMD (Odds Ratio or Raw Mean Difference When Indicated)	Sig	Clinical Importance	Strength of Evidence
Berman (1999)	336	Yes	4	Acupuncture	Usual care	-0.68 (-1.16, -0.21)	Favors acupuncture	N/A	Moderate
Sandgee (2002)	73	Yes	4	Electro-acupuncture	Sham	-0.70 (-1.12, -0.27)	Favors electro-acupuncture	N/A	Moderate
Berman (1999)	301	Yes	8	Acupuncture	Usual care	-0.98 (-1.47, -0.49)	Favors acupuncture	N/A	Moderate
Berman (1999)	66	Unclear	12	Acupuncture	Usual care	-0.80 (-1.28, -0.32)	Favors acupuncture	N/A	Moderate

Table 96. Acupuncture Versus Control: Consumption of Concomitant Medication

Study	N	Outcome	Power	Weeks	Group 1	Group 2	SMD (Odds Ratio or Raw Mean Difference When Indicated)	Sig	Clinical Importance	Strength of Evidence
Taechaarpornkul (2009)	66	Cox-2 consumption	Unclear	5	6 point acupuncture	2 point acupuncture	0.10 (-0.38, 0.58)	No	N/A	High
Taechaarpornkul (2009)	66	Cox-2 consumption	Unclear	13	6 point acupuncture	2 point acupuncture	-0.16 (-0.64, 0.33)	No	N/A	High
VAS (2004)	97	NSAID consumption	Yes	13	Acupuncture	Sham	-0.74 (-1.15, -0.33)	Favors acupuncture	N/A	Moderate

Table 97. Periosteal Stimulation Therapy Versus Regular Acupuncture (Weiner 2007)

Outcome	N	Power	Weeks	Group 1	Group 2	SMD (Odds Ratio or Raw Mean Difference When Indicated)	Sig	Clinical Importance	Strength of Evidence
WOMAC Pain	88	Yes	6	Periosteal stimulation therapy	Regular acupuncture	-0.53 (-0.96, -0.11)	Favors PST	Possibly clinically important	High

Outcome	N	Power	Weeks	Group 1	Group 2	SMD (Odds Ratio or Raw Mean Difference When Indicated)	Sig	Clinical Importance	Strength of Evidence
Geriatric Depression Scale	88	Unclear	6	Periosteal stimulation therapy	Regular acupuncture	0.01 (-0.40, 0.43)	No	N/A	High
Geriatric Depression Scale	88	Unclear	12	Periosteal stimulation therapy	Regular acupuncture	0.10 (-0.32, 0.52)	No	N/A	High
Pittsburgh Sleep Quality index	88	Unclear	6	Periosteal stimulation therapy	Regular acupuncture	-0.10 (-0.52, 0.31)	No	N/A	High
Pittsburgh Sleep Quality index	88	Unclear	12	Periosteal stimulation therapy	Regular acupuncture	0.09 (-0.32, 0.51)	No	N/A	High
Stair climb time	88	Unclear	6	Periosteal stimulation therapy	Regular acupuncture	-0.03 (-0.45, 0.39)	No	N/A	High
Stair climb time	88	Unclear	12	Periosteal stimulation therapy	Regular acupuncture	0.22 (-0.20, 0.64)	No	N/A	High

Table 98. TENS, Interferential Current, and Short Wave Diathermy Versus Sham (Atamaz et al., 2012)

Treatment	Outcome	N	Sufficient Power	Weeks	Group 1	Group 2	SMD (Odds Ratio or Raw Mean Difference When Indicated)	Sig	Clinical Importance	Strength of Evidence
TENS	VAS Pain	74	Yes	4	TENS	Sham	0.191 (-0.266, 0.648)	No	True negative	Moderate
	VAS Pain	74	Yes	12	TENS	Sham	0.175 (-0.281, 0.632)	No	True negative	Moderate
	VAS Pain	74	Yes	26	TENS	Sham	0.009 (-0.447, 0.464)	No	True negative	Moderate
	Nottingham Health Profile: Pain	74	Unclear	4	TENS	Sham	-0.136 (-0.593, 0.32)	No	Unclear	Moderate
	Nottingham Health Profile: Pain	74	Unclear	12	TENS	Sham	0.015 (-0.44, 0.471)	No	Unclear	Moderate
	Nottingham Health Profile: Pain	74	Unclear	26	TENS	Sham	0.027 (-0.429, 0.483)	No	Unclear	Moderate
	Timed walk	74	Unclear	4	TENS	Sham	-0.153 (-0.609, 0.304)	No	Unclear	Moderate
	Timed walk	74	Unclear	12	TENS	Sham	-0.025 (-0.48, 0.431)	No	Unclear	Moderate
	Timed walk	74	Unclear	26	TENS	Sham	-0.121 (-0.578, 0.335)	No	Unclear	Moderate

Treatment	Outcome	N	Sufficient Power	Weeks	Group 1	Group 2	SMD (Odds Ratio or Raw Mean Difference When Indicated)	Sig	Clinical Importance	Strength of Evidence
	Nottingham Health Profile: Physical	74	Unclear	4	TENS	Sham	-0.086 (-0.542, 0.37)	No	Unclear	Moderate
	Nottingham Health Profile: Physical	74	Unclear	12	TENS	Sham	0.015 (-0.441, 0.47)	No	Unclear	Moderate
	Nottingham Health Profile: Physical	74	Unclear	26	TENS	Sham	-0.051 (-0.507, 0.405)	No	Unclear	Moderate
Interferential Current	VAS Pain	66	Yes	4	Interferential current	Sham	-0.398 (-0.886, 0.09)	No	True negative	Moderate
	VAS Pain	66	Yes	12	Interferential current	Sham	-0.459 (-0.949, 0.031)	No	True negative	Moderate
	VAS Pain	66	Yes	26	Interferential current	Sham	-0.514 (-1.005, -0.022)	No	True negative	Moderate
	Nottingham Health Profile: Pain	66	Unclear	4	Interferential current	Sham	-0.311 (-0.798, 0.175)	No	Unclear	Moderate

Treatment	Outcome	N	Sufficient Power	Weeks	Group 1	Group 2	SMD (Odds Ratio or Raw Mean Difference When Indicated)	Sig	Clinical Importance	Strength of Evidence
	Nottingham Health Profile: Pain	66	Unclear	12	Interferential current	Sham	-0.207 (-0.691, 0.278)	No	Unclear	Moderate
	Nottingham Health Profile: Pain	66	Unclear	26	Interferential current	Sham	-0.288 (-0.774, 0.198)	No	Unclear	Moderate
	Timed walk	66	Unclear	4	Interferential current	Sham	-0.143 (-0.627, 0.341)	No	Unclear	Moderate
	Timed walk	66	Unclear	12	Interferential current	Sham	0.064 (-0.419, 0.548)	No	Unclear	Moderate
	Timed walk	66	Unclear	26	Interferential current	Sham	-0.143 (-0.627, 0.341)	No	Unclear	Moderate
	Nottingham Health Profile: Physical	66	Unclear	4	Interferential current	Sham	-0.193 (-0.677, 0.292)	No	Unclear	Moderate
	Nottingham Health Profile: Physical	66	Unclear	12	Interferential current	Sham	-0.179 (-0.664, 0.305)	No	Unclear	Moderate

Treatment	Outcome	N	Sufficient Power	Weeks	Group 1	Group 2	SMD (Odds Ratio or Raw Mean Difference When Indicated)	Sig	Clinical Importance	Strength of Evidence
	Nottingham Health Profile: Physical	66	Unclear	26	Interferential current	Sham	-0.047 (-0.531, 0.436)	No	Unclear	Moderate
Short Wave Diathermy	VAS Pain	63	Yes	4	Short wave diathermy	Sham	-0.168 (-0.663, 0.327)	No	True negative	Moderate
	VAS Pain	63	Yes	12	Short wave diathermy	Sham	-0.078 (-0.572, 0.416)	No	True negative	Moderate
	VAS Pain	63	Yes	26	Short wave diathermy	Sham	0.085 (-0.409, 0.579)	No	True negative	Moderate
	Nottingham Health Profile: Pain	63	Unclear	4	Short wave diathermy	Sham	-0.321 (-0.818, 0.176)	No	Unclear	Moderate
	Nottingham Health Profile: Pain	63	Unclear	12	Short wave diathermy	Sham	-0.245 (-0.741, 0.251)	No	Unclear	Moderate
	Nottingham Health Profile: Pain	63	Unclear	26	Short wave diathermy	Sham	-0.353 (-0.851, 0.145)	No	Unclear	Moderate
	Timed walk	63	Unclear	4	Short wave diathermy	Sham	-0.048 (-0.542, 0.446)	No	Unclear	Moderate

Treatment	Outcome	N	Sufficient Power	Weeks	Group 1	Group 2	SMD (Odds Ratio or Raw Mean Difference When Indicated)	Sig	Clinical Importance	Strength of Evidence
	Timed walk	63	Unclear	12	Short wave diathermy	Sham	-0.172 (-0.667, 0.323)	No	Unclear	Moderate
	Timed walk	63	Unclear	26	Short wave diathermy	Sham	-0.311 (-0.808, 0.186)	No	Unclear	Moderate
	Nottingham Health Profile: Physical	63	Unclear	4	Short wave diathermy	Sham	-0.173 (-0.668, 0.322)	No	Unclear	Moderate
	Nottingham Health Profile: Physical	63	Unclear	12	Short wave diathermy	Sham	0.044 (-0.45, 0.538)	No	Unclear	Moderate
	Nottingham Health Profile: Physical	63	Unclear	26	Short wave diathermy	Sham	-.055 (-.439, .549)	No	Unclear	Moderate

Table 99. Swedish Massage Therapy Versus Usual Care (Perlman 2006)

Outcome	N	Power	Week	Group 1	Group 2	SMD (Odds Ratio or Raw Mean Difference When Indicated)	Sig	Clinical Importance	Strength of Evidence
50 foot walk time	68	Yes	8	Swedish massage therapy	Waitlist control	-0.51 (-0.99, -0.02)	Favors massage therapy	N/A	Low
50 foot walk time	68	Unclear	16	Swedish massage therapy	Waitlist control	-0.40 (-0.88, 0.08)	No	N/A	Low
VAS Pain	68	Yes	8	Swedish massage therapy	Waitlist control	-0.86 (-1.36, -0.36)	Favors massage therapy	Possibly clinically important	Low
VAS Pain	68	No	16	Swedish massage therapy	Waitlist control	-0.04 (-0.51, 0.44)	No	Inconclusive	Low
WOMAC Function	68	Yes	8	Swedish massage therapy	Waitlist control	-0.78 (-1.27, -0.28)	Favors massage therapy	Possibly clinically important	Low
WOMAC Function	68	No	16	Swedish massage therapy	Waitlist control	-0.13 (-0.60, 0.35)	No	Inconclusive	Low
WOMAC Total	68	Yes	8	Swedish massage therapy	Waitlist control	-0.84 (-1.34, -0.35)	Favors massage therapy	Possibly clinically important	Low
WOMAC Total	68	No	16	Swedish massage therapy	Waitlist control	-0.84 (-1.34, -0.35)	No	Inconclusive	Low

Outcome	N	Power	Week	Group 1	Group 2	SMD (Odds Ratio or Raw Mean Difference When Indicated)	Sig	Clinical Importance	Strength of Evidence
WOMAC Pain	68	Yes	8	Swedish massage therapy	Waitlist control	-0.94 (-1.44, -0.44)	Favors massage therapy	Clinically Significant	Low
WOMAC Pain	68	No	16	Swedish massage therapy	Waitlist control	-0.22 (-0.70, 0.25)	No	Inconclusive	Low
WOMAC Stiffness	68	Yes	8	Swedish massage therapy	Waitlist control	-0.67 (-1.16, -0.18)	Favors massage therapy	Possibly clinically important	Low
WOMAC Stiffness	68	No	16	Swedish massage therapy	Waitlist control	-0.14 (-0.62, 0.33)	No	Inconclusive	Low

Table 100. Ultrasound Versus Control

Study	N	Outcome	Power	Weeks	Group 1	Group 2	SMD (Odds Ratio or Raw Mean Difference When Indicated)	Sig	Clinical Importance	Strength of Evidence
Huang (2005)	70	Walk speed (m/min)	Yes	8	Isotonic exercise plus ultrasonic wave therapy	Isotonic exercise only	1.66 (1.12, 2.21)	Favors isotonic exercise plus ultrasonic wave therapy	N/A	Moderate
Huang (2005)	70	Lequesne index	Yes	8	Isotonic exercise plus ultrasonic wave therapy	Isotonic exercise only	-1.67 (-2.22, -1.12)	Favors isotonic exercise plus ultrasonic wave therapy	N/A	Moderate
Huang (2005)	70	VAS Pain	Yes	8	Isotonic exercise plus ultrasonic wave therapy	Isotonic exercise only	-0.16 (-0.63, 0.31	No	True negative	Moderate

Study	N	Outcome	Power	Weeks	Group 1	Group 2	SMD (Odds Ratio or Raw Mean Difference When Indicated)	Sig	Clinical Importance	Strength of Evidence
Huang (2005)	70	Walk speed (m/min)	Yes	52	Isotonic exercise plus ultrasonic wave therapy	Isotonic exercise only	1.34 (0.82, 1.86)	Favors isotonic exercise plus ultrasonic wave therapy	N/A	Moderate
Huang (2005)	70	Lequesne index	Yes	52	Isotonic exercise plus ultrasonic wave therapy	Isotonic exercise only	-1.49 (-2.03, -0.96)	Favors isotonic exercise plus ultrasonic wave therapy	N/A	Moderate
Huang (2005)	70	VAS Pain	Yes	52	Isotonic exercise plus ultrasonic wave therapy	Isotonic exercise only	-0.89 (-1.38, -0.39)	Favors isotonic exercise plus ultrasonic wave therapy	Possibly clinically important	Moderate
Yang (2011)	100	VAS Pain	Yes	4	Ultrasound	Placebo	1.081 (0.66 ,1.50)	Ultrasound	Unclear	Moderate

Study	N	Outcome	Power	Weeks	Group 1	Group 2	SMD (Odds Ratio or Raw Mean Difference When Indicated)	Sig	Clinical Importance	Strength of Evidence
Yang (2011)	100	Lequesne index curative effect	Yes	4	Ultrasound	Placebo	0.877 (0.47 ,1.29)	Ultrasound	Unclear	Moderate

Table 101. Pulsed Electrical and Electromagnetic Therapy

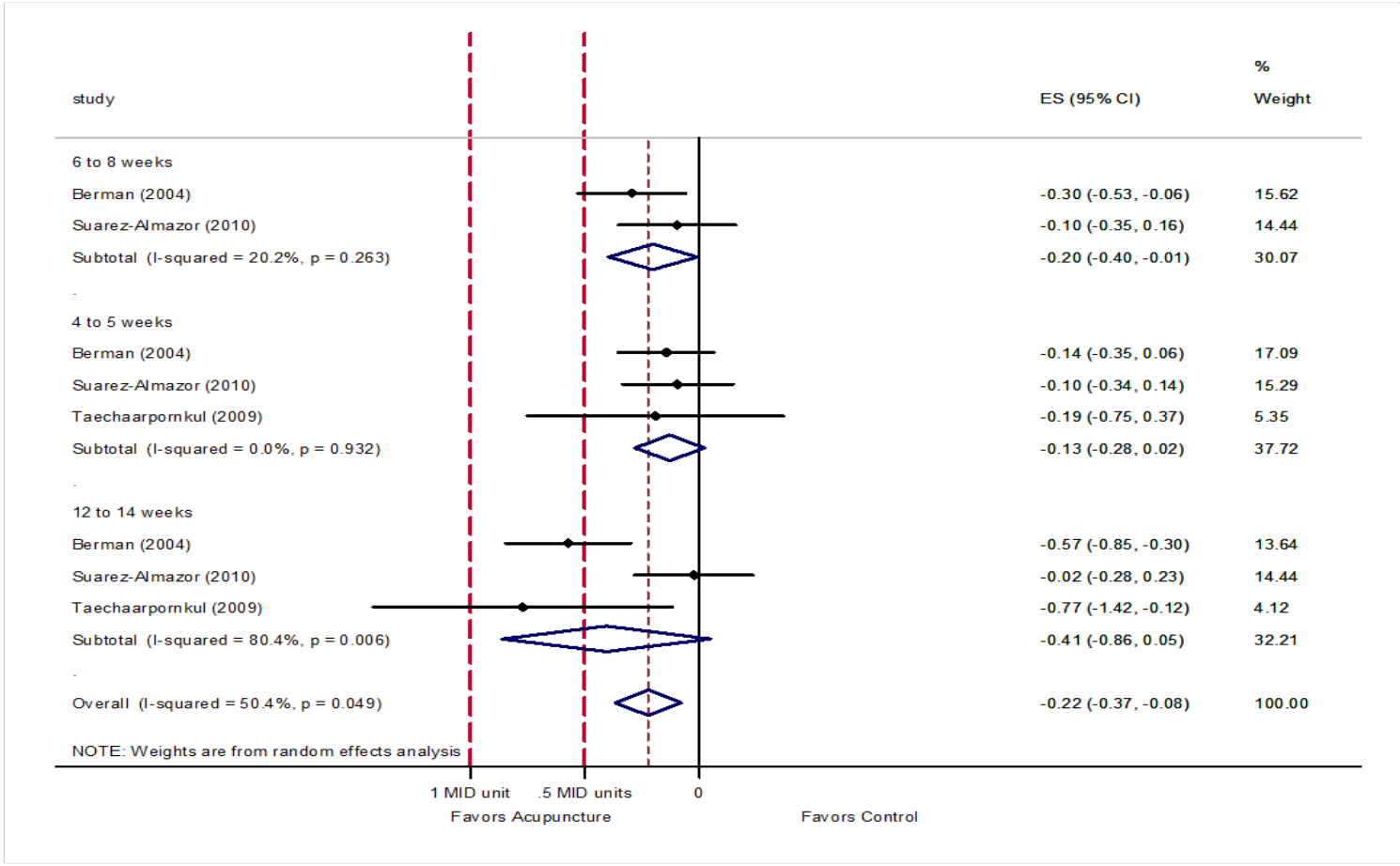
Study	N	Outcome	Power	Weeks	Group 1	Group 2	SMD (Odds Ratio or Raw Mean Difference When Indicated)	Sig	Clinical Importance	Strength of Evidence
Fary (2011)	70	Global Assessment of Disease Activity	Unclear	26	Pulsed electrical stimulation	Placebo	-0.125 (-0.595 ,0.344)	No	Unclear	Low
Fary (2011)	70	SF-36 Mental	Unclear	26	Pulsed electrical stimulation	Placebo	0.136 (-0.333 ,0.606)	No	Inconclusive	Low
Fary (2011)	70	Human activity profile maximum activity	Unclear	26	Pulsed electrical stimulation	Placebo	-0.268 (-0.739 ,0.203)	No	Unclear	Low

Study	N	Outcome	Power	Weeks	Group 1	Group 2	SMD (Odds Ratio or Raw Mean Difference When Indicated)	Sig	Clinical Importance	Strength of Evidence
Fary (2011)	70	Human activity profile adjusted activity	Unclear	26	Pulsed electrical stimulation	Placebo	-0.039 (-0.508 ,0.43)	No	Unclear	Low
Fary (2011)	70	Daily accelerometer count	Unclear	26	Pulsed electrical stimulation	Placebo	0.34 (-0.133 ,0.812)	No	Unclear	Low
Fary (2011)	70	Daily resting time, minutes	Unclear	26	Pulsed electrical stimulation	Placebo	-0.182 (-0.651 ,0.288)	No	Unclear	Low
Fary (2011)	70	Daily light activity, minutes	Unclear	26	Pulsed electrical stimulation	Placebo	-0.03 (-0.499 ,0.439)	No	Unclear	Low
Fary (2011)	70	Daily moderate activity, minutes	Unclear	26	Pulsed electrical stimulation	Placebo	0.291 (-0.18 ,0.762)	No	Unclear	Low
Fary (2011)	70	Daily hard activity, minutes	Unclear	26	Pulsed electrical stimulation	Placebo	0.11 (-0.36, 0.58)	No	Unclear	Low
Trock (1994)	72	Pain on passive motion	Unclear	4 weeks after treatment	Pulsed electromagnetic fields	Placebo	0.469 (0 ,0.939)	No	Unclear	High
Trock (1994)	72	Tenderness	Unclear	4 weeks after treatment	Pulsed electromagnetic fields	Placebo	0.518 (0.047 ,0.989)	Favors pulsed electromagnetic fields	Unclear	High

Study	N	Outcome	Power	Weeks	Group 1	Group 2	SMD (Odds Ratio or Raw Mean Difference When Indicated)	Sig	Clinical Importance	Strength of Evidence
Trock (1994)	73	Physician overall assessment	Unclear	4 weeks after treatment	Pulsed electromagnetic fields	Placebo	0.526 (0.058 ,0.995)	Favors pulsed electromagnetic fields	Unclear	High
Battisti (2004)	60	Complete reduction of pain	Unclear	6.4	Therapeutic Application of Modulated Electro Magnetic Field (TAMMEF)	Extremely low frequency electromagnetic field	OR=2.74 (0.63, 11.82)	No	Unclear	Moderate
Battisti (2004)	60	Lequesne index: Total recovery of articular function	Unclear	6.4	Therapeutic Application of Modulated Electro Magnetic Field (TAMMEF)	Extremely low frequency electromagnetic field	OR=1.35 (0.46, 3.97)	No	Unclear	Moderate
Zizic (1995)	71	At least 15 minute improvement in morning stiffness	Unclear	8	Pulsed electrical stimulation	Sham	OR=2.70 (0.97, 7.51)	No	Unclear	Moderate
Zizic (1995)	71	VAS Pain % change	Unclear	8	Pulsed electrical stimulation	Sham	Mean difference=12.29 (p=.04)	Favors pulsed electrical stimulation	Unclear	Moderate
Zizic (1995)	71	VAS Function % change	Unclear	8	Pulsed electrical stimulation	Sham	Mean difference=10.83 (p=.045)	Favors pulsed electrical stimulation	Unclear	Moderate

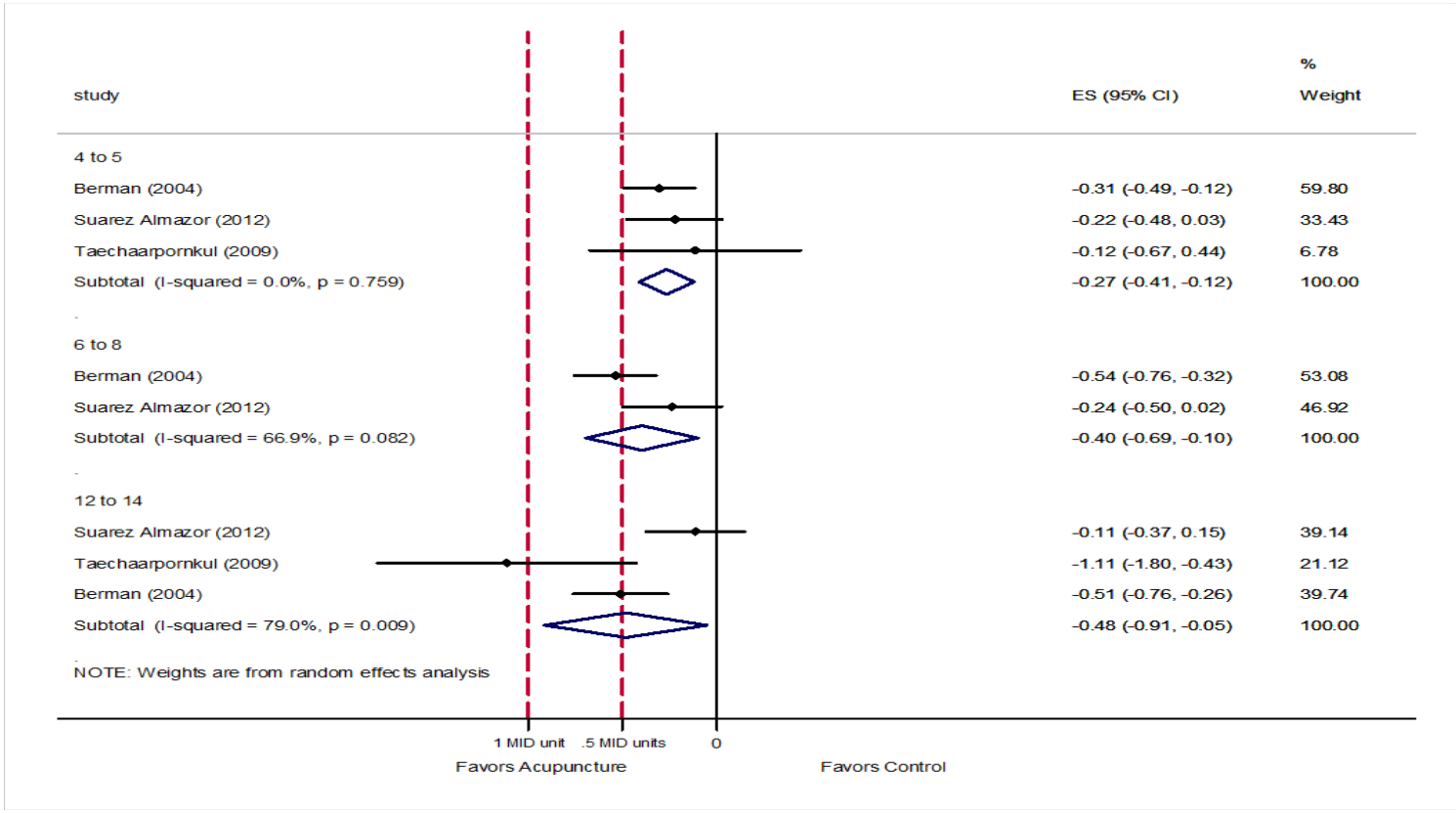
Study	N	Outcome	Power	Weeks	Group 1	Group 2	SMD (Odds Ratio or Raw Mean Difference When Indicated)	Sig	Clinical Importance	Strength of Evidence
Zizic (1995)	71	Percent change adjusted mean physician evaluation (VAS)	Unclear	8	Pulsed electrical stimulation	Sham	Mean difference=14.64 (p=.023	Favors pulsed electrical stimulation	Unclear	Moderate

Figure 21. Acupuncture: WOMAC pain in MID Units*



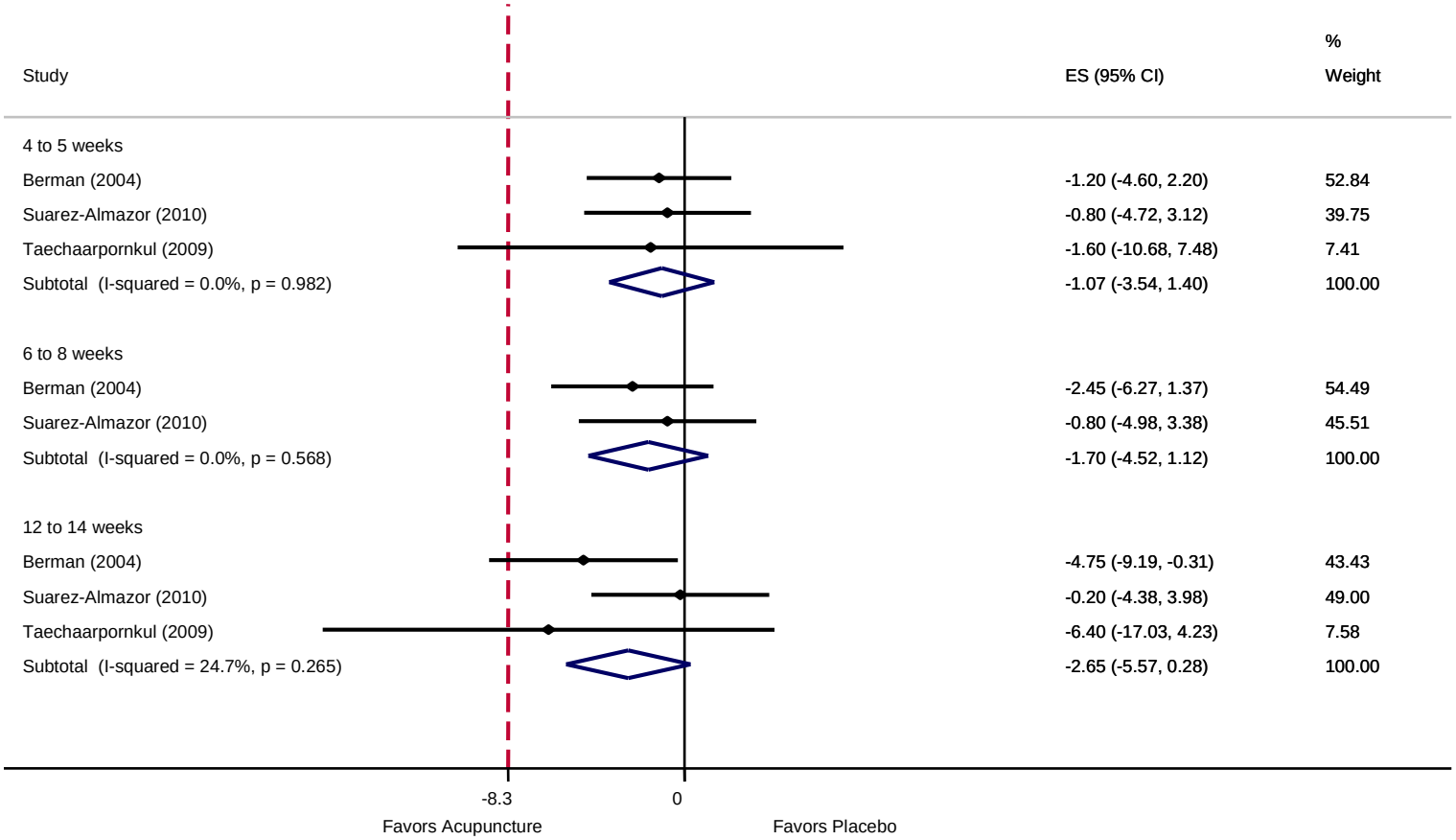
*All WOMAC scores are presented in 100mm VAS units

Figure 22. Acupuncture: WOMAC Function in MID Units*



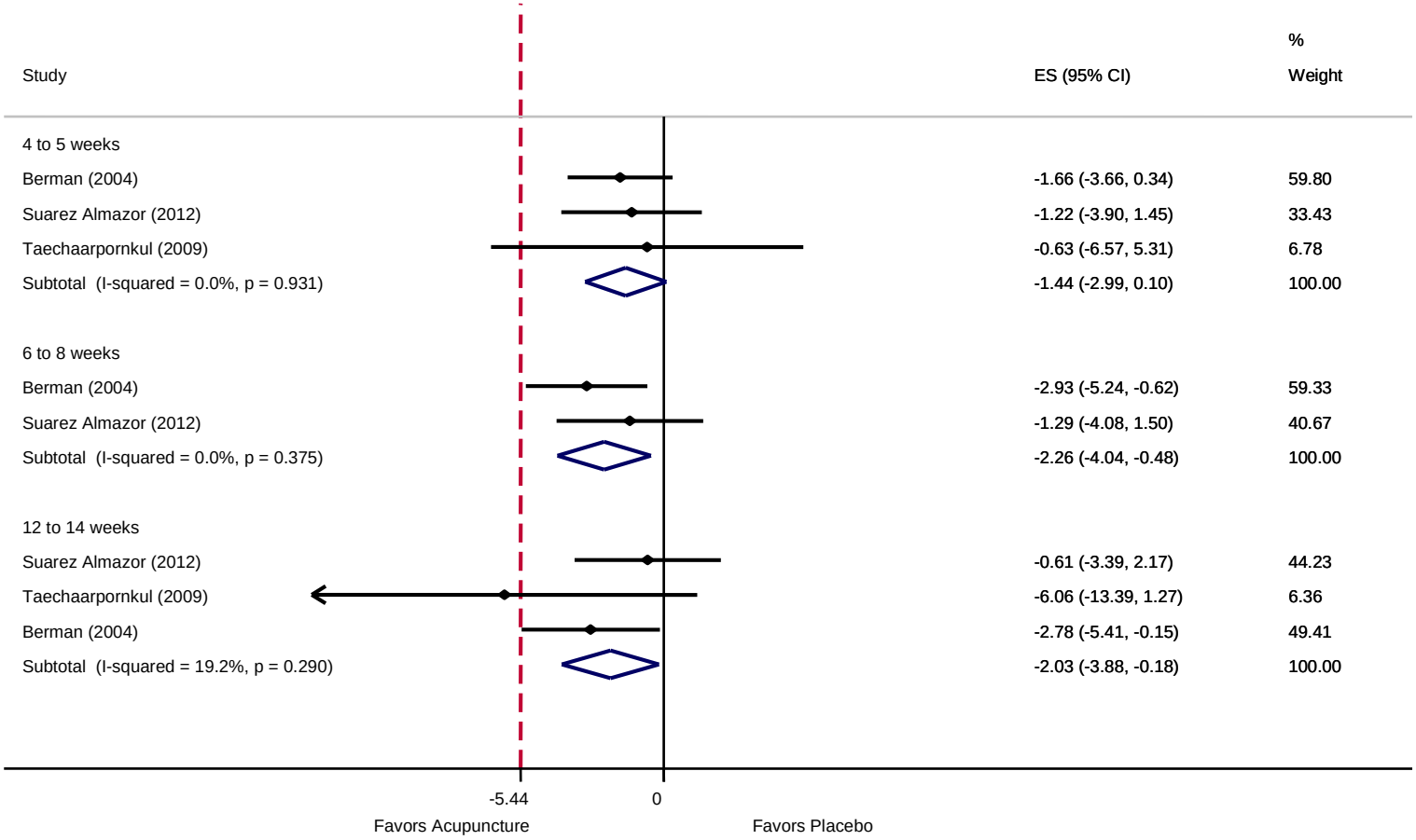
*All WOMAC scores are presented in 100mm VAS units

Figure 23. Acupuncture Versus Placebo: WOMAC Pain (1999)



The red line indicates the MCII

Figure 24. Acupuncture Versus Control: WOMAC Function



The red line indicates the MCII

RECOMMENDATION 4

We are unable to recommend for or against the use of a valgus directing force brace (medial compartment unloader) for patients with symptomatic osteoarthritis of the knee.
Strength of Recommendation: Inconclusive

Description: Evidence from a single low quality study or conflicting findings that do not allow a recommendation for or against the intervention. An **Inconclusive** recommendation means that there is a lack of compelling evidence that has resulted in an unclear balance between benefits and potential harm.

Implications: Practitioners should feel little constraint in following a recommendation labeled as **Inconclusive,** exercise clinical judgment, and be alert for emerging evidence that clarifies or helps to determine the balance between benefits and potential harm. Patient preference should have a substantial influencing role.

RATIONALE

This recommendation is based on three separate studies; one high-strength study[78] compared a valgus producing brace plus usual care to a neoprene sleeve brace plus usual care and to usual care alone. A second high-strength study compared a valgus directing force brace to a lateral wedge foot orthotic.[79] The third study of moderate-strength compared a valgus directing force brace plus usual care to usual care alone.[80] Therapies were compared with respect to how much they improved pain, stiffness, self-reported functional capacity, and physical performance measures (observed walking distance and number of stairs climbed in 30 seconds). Improvement using the varus producing brace was not consistently significant across the four studies. For all statistically significant comparisons, the clinical significance of the improvements in pain and physical function were unclear.

Based on a lack of appropriate studies, the use of a varus directing force brace was not evaluated.

SUPPORTING EVIDENCE

QUALITY

Relevant Tables: Table 102-Table 104**,** Table 105-Table 107

There were two high-[78;79] and one moderate-[80]quality randomized controlled trials that comprised the evidence for this recommendation. Two studies compared braces plus usual care to usual care alone.[78;80] One RCT compared bracing to insoles. [79] One of the three studies had a potential for investigator bias. No other quality domains were flawed in any of the included studies.

APPLICABILITY

Relevant Tables: Table 102-Table 104**,** Table 105-Table 107

In all three included studies, there was uncertainty whether the treatment administration and the study participants were representative of clinical practice. The Kirkley et al.[78] study was the only study that did not use all enrolled patients in their final analysis. Also,

the Van Raaij et al.[79] study was the only one with compliance and adherence measures that were not similar to regular practice.

FINAL STRENGTH OF EVIDENCE

All studies had high quality and moderate applicability that resulted in in high strength of evidence ratings.

Table 102. Quality and Applicability Summary: Brace Versus Usual Care

Study	Outcome	Duration	Quality	Applicability	Strength of Evidence
Kirkley (1999)	WOMAC Pain	6 months	High	Moderate	High
Kirkley (1999)	WOMAC Function	6 months	High	Moderate	High
Kirkley (1999)	WOMAC Stiffness	6 months	High	Moderate	High
Kirkley (1999)	WOMAC Total	6 months	High	Moderate	High
Kirkley (1999)	VAS Pain on 6 minute walk	6 months	High	Moderate	High
Kirkley (1999)	VAS Pain on stair climb	6 months	High	Moderate	High
Kirkley (1999)	6 minute walk distance	6 months	High	Moderate	High
Kirkley (1999)	Number of stairs climbed in 30 seconds	6 months	High	Moderate	High
Kirkley (1999)	MACTAR	6 months	High	Moderate	High
Kirkley (1999)	Clinical success rate	6 months	High	Moderate	High
Brouwer (2006)	VAS Pain	3 months	Moderate	Moderate	Moderate
Brouwer (2006)	VAS Pain	6 months	Moderate	Moderate	Moderate
Brouwer (2006)	VAS Pain	1 year	Moderate	Moderate	Moderate
Brouwer (2006)	Hospital for Special Surgery: Function	3 months	Moderate	Moderate	Moderate
Brouwer (2006)	Hospital for Special Surgery: Function	6 months	Moderate	Moderate	Moderate
Brouwer (2006)	Hospital for Special Surgery: Function	1 year	Moderate	Moderate	Moderate

Study	Outcome	Duration	Quality	Applicability	Strength of Evidence
Brouwer (2006)	Walk distance (km)	3 months	Moderate	Moderate	Moderate
Brouwer (2006)	Walk distance (km)	6 months	Moderate	Moderate	Moderate
Brouwer (2006)	Walk distance (km)	1 year	Moderate	Moderate	Moderate
Brouwer (2006)	EQ-5D	3 months	Moderate	Moderate	Moderate
Brouwer (2006)	EQ-5D	6 months	Moderate	Moderate	Moderate
Brouwer (2006)	EQ-5D	1 year	Moderate	Moderate	Moderate

Table 103. Quality and Applicability Summary: Brace Versus Sleeve

Study	Outcome	Duration	Quality	Applicability	Strength of Evidence
Kirkley (1999)	WOMAC Pain	6 months	High	Moderate	High
Kirkley (1999)	WOMAC Function	6 months	High	Moderate	High
Kirkley (1999)	WOMAC Stiffness	6 months	High	Moderate	High
Kirkley (1999)	WOMAC Total	6 months	High	Moderate	High
Kirkley (1999)	VAS Pain on 6 minute walk	6 months	High	Moderate	High
Kirkley (1999)	VAS Pain on stair climb	6 months	High	Moderate	High
Kirkley (1999)	6 minute walk distance	6 months	High	Moderate	High
Kirkley (1999)	Number of stairs climbed in 30 seconds	6 months	High	Moderate	High
Kirkley (1999)	MACTAR	6 months	High	Moderate	High
Kirkley (1999)	Clinical success rate	6 months	High	Moderate	High

Table 104. Quality and Applicability Summary: Brace Versus Insoles

Study	Outcome	Duration	Quality	Applicability	Strength of Evidence
Van Raaij	VAS Pain	6 months	High	Moderate	High

RESULTS

Relevant Tables: Figure 25-Figure 26, Table 108-Table 113

Two out of the three studies compared braces combined with usual care to usual care alone. Brouwer et al.[80] included a patient population with Ahlback grades of 1-2. Kirkley et al.[78] included patients with Kellgren and Lawrence grades of 1-4. In the Brouwer et al. study usual care consisted of education, analgesics (as needed) and physical therapy (as needed). In the Kirkley et al. study, usual care consisted of an educational pamphlet and as needed acetaminophen. Participants who were already taking NSAIDs before the study were allowed to continue using them.

There was inconclusive evidence regarding the efficacy of knee bracing. Kirkley et al.[78] found that patients in the brace group reported significantly better scores on the WOMAC subscales (pain, function, stiffness, total), VAS pain on waking, VAS pain on climbing stairs, and the MACTAR tests than the group who received only acetaminophen and an educational pamphlet. Kirkley et al. found nonsignificant differences for distance walked in 6 minutes, and number of stairs climbed in 30 seconds. Brouwer et al.[80] found statistically nonsignificant differences between the brace group and the usual care group (education, analgesic as needed, and physical therapy as needed) at three, six and 12 months, in VAS pain, knee function and quality of life. Although, walking distance was found to be significantly greater in the treatment group than the control group at each follow up period.

Kirkley et al.[78] also compared the unloader brace to the neoprene sleeve. For all pain outcomes, the brace was significantly more effective than the sleeve. However, there was no statistically significant difference between the two treatments for self reported functioning, functional tasks, WOMAC Stiffness or WOMAC Total (Figure 26).

Van Raaij et al.[79] compared the effectiveness of bracing to foot insoles. The authors found that VAS pain was significantly lessened in the brace group than the insole group.

Figure 25. Results Summary: Brace Versus Usual Care

	Week 13	Week 26	Week 52
VAS Pain	●	●	●
Walking distance	●	●	●
HSS Function	●	●	●
EQ-5D	●	●	●
1cm improvement on VAS Pain after 6 minute walk			●
VAS Pain on 30 second stair climb improvement			●
VAS Pain on 6 minute walk- improvement			●
WOMAC Pain improvement			●
30 second stair climb improvement			●
6 minute walk distance- improvement			●

MACTAR improvement	●
WOMAC Function improvement	●
WOMAC Stiffness improvement	●
WOMAC Total improvement	●

Key: ● =Not Significant; ● =Statistically Significant

Figure 26. Results Summary: Brace vs. Sleeve and Insoles

Treatment	Control	Outcome	Week 26
Brace	Sleeve	WOMAC Pain improvement	🟡
		VAS Pain on 6 minute walk improvement	🟡
		VAS Pain on 30 second stair climb improvement	🟡
		1cm improvement on VAS Pain after 6 minute walk	🟡
		WOMAC Function improvement	⚫
		MACTAR improvement	⚫
		6 minute walk distance improvement	⚫
		30 second stair climb improvement	⚫
		WOMAC Stiffness improvement	⚫
		WOMAC Total improvement	⚫
Brace	Insole	VAS Pain	🟡

Key: ⚫=Not Significant; 🟡=Statistically Significant in Favor of Treatment

EVIDENCE TABLES AND FIGURES

QUALITY AND APPLICABILITY

Table 105. Quality and Applicability: Brace Versus Usual Care

●: Domain free of flaws

○: Domain flaws present

◐: Moderate power

Study	*Outcome*	Prospective	Power	Group Assignment	Blinding	Group Comparability	Treatment Integrity	Measurement	Investigator Bias	*Quality*	Participants	Intervention and Expertise	Compliance and Adherence	Analysis	*Applicability Study*
Kirkley (1999)	WOMAC Pain	●	●	●	●	●	●	●	○	**High**	○	○	●	○	**Moderate**
Kirkley (1999)	WOMAC Function	●	●	●	●	●	●	●	○	**High**	○	○	●	○	**Moderate**
Kirkley (1999)	WOMAC Stiffness	●	●	●	●	●	●	●	○	**High**	○	○	●	○	**Moderate**
Kirkley (1999)	WOMAC Total	●	●	●	●	●	●	●	○	**High**	○	○	●	○	**Moderate**
Kirkley (1999)	VAS Pain on 6 minute walk	●	●	●	●	●	●	●	○	**High**	○	○	●	○	**Moderate**
Kirkley (1999)	VAS Pain on stair climb	●	●	●	●	●	●	●	○	**High**	○	○	●	○	**Moderate**

●: Domain free of flaws

○: Domain flaws present

◐: Moderate power

Study	*Outcome*	**Prospective**	**Power**	**Group Assignment**	**Blinding**	**Group Comparability**	**Treatment Integrity**	**Measurement**	**Investigator Bias**	*Quality*	**Participants**	**Intervention and Expertise**	**Compliance and Adherence**	**Analysis**	*Applicability Study*
Kirkley (1999)	6 minute walk distance	●	◐	●	●	●	●	●	○	**High**	○	○	●	○	**Moderate**
Kirkley (1999)	Number of stairs climbed in 30 seconds	●	◐	●	●	●	●	●	○	**High**	○	○	●	○	**Moderate**
Kirkley (1999)	MACTAR	●	●	●	●	●	●	●	○	**High**	○	○	●	○	**Moderate**
Kirkley (1999)	Clinical success rate	●	●	●	●	●	●	●	○	**High**	○	○	●	○	**Moderate**
Brouwer (2006)	VAS Pain 13 weeks	●	◐	●	●	●	●	●	●	**High**	○	○	●	●	**Moderate**
Brouwer (2006)	VAS Pain 26 weeks	●	◐	●	●	●	●	●	●	**High**	○	○	●	●	**Moderate**
Brouwer (2006)	VAS Pain 52 weeks	●	◐	●	●	●	●	●	●	**High**	○	○	●	●	**Moderate**
Brouwer (2006)	Hospital for Special Surgery: Function 13 weeks	●	●	●	●	●	●	●	●	**High**	○	○	●	●	**Moderate**

●: Domain free of flaws

○: Domain flaws present

◐: Moderate power

Study	*Outcome*	**Prospective**	**Power**	**Group Assignment**	**Blinding**	**Group Comparability**	**Treatment Integrity**	**Measurement**	**Investigator Bias**	*Quality*	**Participants**	**Intervention and Expertise**	**Compliance and Adherence**	**Analysis**	*Applicability Study*
Brouwer (2006)	Hospital for Special Surgery: Function 26 weeks	●	●	●	●	●	●	●	●	**High**	○	○	●	●	**Moderate**
Brouwer (2006)	Hospital for Special Surgery: Function 52 weeks	●	●	●	●	●	●	●	●	**High**	○	○	●	●	**Moderate**
Brouwer (2006)	Walk distance (km) 13 weeks	●	●	●	●	●	●	●	●	**High**	○	○	●	●	**Moderate**
Brouwer (2006)	Walk distance (km) 26 weeks	●	◐	●	●	●	●	●	●	**High**	○	○	●	●	**Moderate**
Brouwer (2006)	Walk distance (km) 52 weeks	●	●	●	●	●	●	●	●	**High**	○	○	●	●	**Moderate**
Brouwer (2006)	EQ-5D 13 weeks	●	◐	●	●	●	●	●	●	**High**	○	○	●	●	**Moderate**
Brouwer (2006)	EQ-5D 26 weeks	●	◐	●	●	●	●	●	●	**High**	○	○	●	●	**Moderate**
Brouwer (2006)	EQ-5D 52 weeks	●	◐	●	●	●	●	●	●	**High**	○	○	●	●	**Moderate**

Table 106. Quality and Applicability: Unloader Brace Versus Neoprene Sleeve

●: Domain free of flaws

○: Domain flaws present

◐: Moderate power

Study	*Outcome*	Prospective	Power	Group Assignment	Blinding	Group Comparability	Treatment Integrity	Measurement	Investigator Bias	*Quality*	Participants	Intervention and Expertise	Compliance and Adherence	Analysis	*Applicability Study*
Kirkley (1999)	WOMAC Pain	●	●	●	●	●	●	●	○	**High**	○	○	●	○	**Moderate**
Kirkley (1999)	WOMAC Function	●	◐	●	●	●	●	●	○	**High**	○	○	●	○	**Moderate**
Kirkley (1999)	WOMAC Stiffness	●	◐	●	●	●	●	●	○	**High**	○	○	●	○	**Moderate**
Kirkley (1999)	WOMAC Total	●	●	●	●	●	●	●	○	**High**	○	○	●	○	**Moderate**
Kirkley (1999)	VAS Pain on 6 minute walk	●	●	●	●	●	●	●	○	**High**	○	○	●	○	**Moderate**
Kirkley (1999)	VAS Pain on stair climb	●	●	●	●	●	●	●	○	**High**	○	○	●	○	**Moderate**
Kirkley (1999)	6 minute walk distance	●	◐	●	●	●	●	●	○	**High**	○	○	●	○	**Moderate**
Kirkley (1999)	Number of stairs climbed in 30 seconds	●	◐	●	●	●	●	●	○	**High**	○	○	●	○	**Moderate**

●: Domain free of flaws

○: Domain flaws present

◐: Moderate power

Study	*Outcome*	**Prospective**	**Power**	**Group Assignment**	**Blinding**	**Group Comparability**	**Treatment Integrity**	**Measurement**	**Investigator Bias**	*Quality*	**Participants**	**Intervention and Expertise**	**Compliance and Adherence**	**Analysis**	*Applicability Study*
Kirkley (1999)	MACTAR	●	◐	●	●	●	●	●	○	**High**	○	○	●	○	**Moderate**
Kirkley (1999)	Clinical success rate	●	●	●	●	●	●	●	○	**High**	○	○	●	○	**Moderate**

Table 107. Quality and Applicability: Braces Versus Insoles

●: Domain free of flaws

○: Domain flaws present

◐: Moderate power

Study	*Outcome*	Prospective	Power	Group Assignment	Blinding	Group Comparability	Treatment Integrity	Measurement	Investigator Bias	*Quality*	Participants	Intervention and Expertise	Compliance and Adherence	Analysis	*Applicability Study*
Van-Raaij (2010)	VAS Pain	●	●	●	●	●	●	●	●	**High**	○	○	●	●	**Moderate**
Van-Raaij (2010)	WOMAC Function	●	●	●	●	●	●	●	●	**High**	○	○	●	●	**Moderate**

FINDINGS

Table 108. Brace Plus Usual Care Versus Usual Care: Pain

Study	Outcome	N	Power	Week	Severity	Avg. BMI	Group 1	Group 2	SMD (Odds Ratio or Raw Mean Difference When Indicated)	Sig	Clinical Importance	Strength of Evidence
Kirkley (1999)	1cm improvement on VAS Pain after 6 minute walk	74	Yes	26	Kellgren and Lawrence Grade 1-4	NR	Unloader brace	Usual care	OR=8.59 (2.94, 25.12)	Favors brace	N/A	High
Brouwer (2006)	VAS Pain	117	Unclear	13	Ahlback 1-2	28.5	Brace	Usual care	MD= -0.73(-1.62, .16)	No	True negative	High
Brouwer (2006)	VAS Pain	117	Unclear	26	Ahlback 1-2	28.5	Brace	Usual care	MD=-0.58(-1.48, .32)	No	True negative	High
Brouwer (2006)	VAS Pain	117	Unclear	52	Ahlback 1-2	28.5	Brace	Usual care	MD=-0.81(-1.76, .14)	No	True negative	High
Kirkley (1999)	VAS Pain on 30 second stair climb improvement	74	Yes	26	Kellgren and Lawrence Grade 1-4	NR	Unloader brace	Usual care	MD=21.5 (p<.001)	Favors brace	Unclear	High

Study	Outcome	N	Power	Week	Severity	Avg. BMI	Group 1	Group 2	SMD (Odds Ratio or Raw Mean Difference When Indicated)	Sig	Clinical Importance	Strength of Evidence
Kirkley (1999)	VAS Pain on 6 minute walk-improvement	74	Yes	26	Kellgren and Lawrence Grade 1-4	NR	Unloader brace	Usual care	MD= 18.9 (p<.001)	Favors brace	Unclear	High
Kirkley (1999)	WOMAC Pain improvement	74	Yes	26	Kellgren and Lawrence Grade 1-4	NR	Unloader brace	Usual care	MD= 2.26 (p<.001)	Favors brace	Unclear	High

Table 109. Brace Plus Usual Care Versus Usual Care: Functional Tasks

Study	Outcome	N	Power	Week	Severity	Avg. BMI	Group 1	Group 2	SMD (Odds Ratio or Raw Mean Difference When Indicated)	Sig	Clinical Importance	Strength of Evidence
Kirkley (1999)	30 second stair climb improvement	74	Unclear	26	Kellgren and Lawrence Grade 1-4	NR	Unloader brace	Usual care	MD=16.21	No	N/A	High
Kirkley (1999)	6 minute walk distance-improvement	74	Unclear	26	Kellgren and Lawrence Grade 1-4	NR	Unloader brace	Usual care	MD= 4.1 meters	No	N/A	High
Brouwer (2006)	Walking distance	117	Yes	13	Ahlback 1-2	28.5	Brace	Usual care	MD=1.21 (.12, 2.28)	Favors brace	N/A	High
Brouwer (2006)	Walking distance	117	Unclear	26	Ahlback 1-2	28.5	Brace	Usual care	MD=0.79 (-.4, 1.98)	No	N/A	High
Brouwer (2006)	Walking distance	117	Yes	52	Ahlback 1-2	28.5	Brace	Usual care	MD=1.34 (.05, 2.63)	Favors brace	N/A	High

Table 110. Brace Plus Usual Care Versus Usual Care: Function

Study	Outcome	N	Power	Week	Severity	Avg. BMI	Group 1	Group 2	SMD (Odds Ratio or Raw Mean Difference When Indicated)	Sig	Clinical Importance	Strength of Evidence
Brouwer (2006)	HSS Function	117	Yes	13	Ahlback 1-2	28.5	Brace	Usual care	MD=3.5 (-.24, 7.24)	No	N/A	High
Brouwer (2006)	HSS Function	117	Yes	26	Ahlback 1-2	28.5	Brace	Usual care	MD=3.2 (-.58, 6.98)	No	N/A	High
Brouwer (2006)	HSS Function	117	Yes	52	Ahlback 1-2	28.5	Brace	Usual care	MD=3 (-1.05, 7.05)	No	N/A	High
Kirkley (1999)	MACTAR improvement	74	Yes	26	Kellgren and Lawrence Grade 1-4	NR	Unloader brace	Usual care	MD= 11.6 (p=.017)	Favors brace	N/A	High
Kirkley (1999)	WOMAC Function improvement	74	Yes	26	Kellgren and Lawrence Grade 1-4	NR	Unloader brace	Usual care	MD= 6.54 (p=.001)	Favors brace	Unclear	High

Table 111. Brace plus Usual Care Versus Usual Care: Other Outcomes

Outcome type	Study	Outcome	N	Power	Week	Severity	Avg. BMI	Group 1	Group 2	SMD (Odds Ratio or Raw Mean Difference When Indicated)	Sig	Clinical Importance	Strength of Evidence
WOMAC Stiffness	Kirkley (1999)	WOMAC Stiffness improvement	74	Yes	26	Kellgren and Lawrence Grade 1-4	NR	Unloader brace	Usual care	MD= 1.47 (p<.001)	Favors brace	Unclear	High
WOMAC Total	Kirkley (1999)	WOMAC Total improvement	74	Yes	26	Kellgren and Lawrence Grade 1-4	NR	Unloader brace	Usual care	MD= 10.28 (p<.001)	Favors brace	Unclear	High
Quality of Life	Brouwer (2006)	EQ-5D	117	Unclear	13	Ahlback 1-2	28.5	Brace	Usual care	MD=0.03 (-.05, .12)	No	N/A	High
	Brouwer (2006)	EQ-5D	117	Unclear	26	Ahlback 1-2	28.5	Brace	Usual care	MD=0.01 (-.08, .1)	No	N/A	High
	Brouwer (2006)	EQ-5D	117	Unclear	52	Ahlback 1-2	28.5	Brace	Usual care	MD=0.01 (-.08, .1)	No	N/A	High

Table 112. Brace Versus Neoprene Sleeve

Outcome Type	Study	Outcome	N	Power	Week	Severity	BMI	Group 1	Group 2	SMD (Odds Ratio or Raw Mean Difference When Indicated)	Sig	Clinical Sig	Strength Of evidence
Pain	Kirkley (1999)	WOMAC Pain	77	Yes	26	Kellgren and Lawrence Grade 1-4	Not Reported (NR)	Unloader brace	Neoprene sleeve	MD=1.204 (P.045)	Favors brace	Unclear	High
	Kirkley (1999)	VAS Pain on 6 minute walk	77	Yes	26	Kellgren and Lawrence Grade 1-4	NR	Unloader brace	Neoprene sleeve	MD= (p=.021)	Favors brace	Unclear	High
	Kirkley (1999)	VAS Pain on 30 second stair climb	77	Yes	26	Kellgren and Lawrence Grade 1-4	NR	Unloader brace	Neoprene sleeve	MD=12.3 (p=.016)	Favors brace	Unclear	High
	Kirkley (1999)	1cm on VAS Pain after 6 minute walk	77	Yes	26	Kellgren and Lawrence Grade 1-4	NR	Unloader brace	Neoprene sleeve	OR= 1.95 (0.79, 4.85)	Favors brace	N/A	High

Outcome Type	Study	Outcome	N	Power	Week	Severity	BMI	Group 1	Group 2	SMD (Odds Ratio or Raw Mean Difference When Indicated)	Sig	Clinical Sig	Strength Of evidence
Function (Self-Reported)	Kirkley (1999)	WOMAC Function	77	Unclear	26	Kellgren and Lawrence Grade 1-4	NR	Unloader brace	Neoprene sleeve	MD=3.532 (P=.081)	No	Unclear	High
	Kirkley (1999)	MACTAR	77	Unclear	26	Kellgren and Lawrence Grade 1-4	NR	Unloader brace	Neoprene sleeve	MD=16.1(P=.174)	No	N/A	High
Function Task	Kirkley (1999)	6 minute walk distance	77	Unclear	26	Kellgren and Lawrence Grade 1-4	NR	Unloader brace	Neoprene sleeve	MD=26.9 m (NS)	No	N/A	High
	Kirkley (1999)	30 second stair climb	77	Unclear	26	Kellgren and Lawrence Grade 1-4	NR	Unloader brace	Neoprene sleeve	MD=5.59 Steps (NS)	No	N/A	High

Outcome Type	Study	Outcome	N	Power	Week	Severity	BMI	Group 1	Group 2	SMD (Odds Ratio or Raw Mean Difference When Indicated)	Sig	Clinical Sig	Strength Of evidence
WOMAC Stiffness	Kirkley (1999)	WOMAC Stiffness	77	Unclear	26	Kellgren and Lawrence Grade 1-4	NR	Unloader brace	Neoprene sleeve	MD=.524 (P=.91)	No	Unclear	High
WOMAC Total	Kirkley (1999)	WOMAC Total	77	Sufficient	26	Kellgren and Lawrence Grade 1-4	NR	Unloader brace	Neoprene sleeve	MD=5.26 (P=.062)	No	Unclear	High

Table 113. Braces Versus Insoles

Study	Outcome	N	Power	Week	Severity	BMI	Group 1	Group 2	SMD (Odds Ratio or Raw Mean Difference When Indicated)	Sig	Clinical Importance	Strength of Evidence
Van Raaij (2010)	VAS Pain	117	Yes	26	K-L Grade 1-4	29.2	Brace	Insole	-.82 (-1.247, -.39)	Favors brace	Possibly clinically important	High

RECOMMENDATION 5

We cannot suggest that lateral wedge insoles be used for patients with symptomatic medial compartment osteoarthritis of the knee.

Strength of Recommendation: Moderate

Description: Evidence from two or more "Moderate" strength studies with consistent findings, or evidence from a single "High" quality study for recommending for or against the intervention. A **Moderate** recommendation means that the benefits exceed the potential harm (or that the potential harm clearly exceeds the benefits in the case of a negative recommendation), but the quality/applicability of the supporting evidence is not as strong.

Implications: Practitioners should generally follow a **Moderate** recommendation but remain alert to new information and be sensitive to patient preferences.

RATIONALE

This recommendation is based on five studies. Four studies, one of high-strength[81] and three of moderate-strength, compared outcomes using lateral wedge insoles to neutral insoles.[82-84] No significant changes in pain, self-reported physical function, or Patient Global Assessment scores were seen between the two types of insoles. A fifth low-strength study compared urethane lateral wedge insoles to rubber lateral insoles, and found a statistically significant improvement in Lequesne score for urethane insoles, but this outcome was of uncertain clinical significance.[85]

SUPPORTING EVIDENCE

QUALITY

Relevant Tables: Table 114-Table 115, Table 117

There were four studies that compared lateral wedge insoles to neutral insoles. Bennell et al.[81] was of high strength; Baker et al., [82] Maillefert et al.[83] and Pham et al.[84] were moderate strength. Group assignment was not flawed in the Baker et al. and Bennell et al. studies[81;82]. The equality of treatment groups at baseline was acceptable in the Bennell et al.[81] study. The treatment integrity was a problem in the studies by Maillefert et al.[83] and Pham et al.[84] due to the use of concomitant NSAIDs. There was potential for investigator bias in the Baker et al. and Bennell et al.[81;82] studies. No lateral wedge insole studies had problems with the validity of the outcomes measurements.

Toda et al.[85] compared Lequesne index scores of rubber to urethane insoles. This low strength study was flawed in the group assignment, comparability, investigator bias and blinding domains.

APPLICABILITY

Relevant Tables: Table 114-Table 115, Table 117

Moderate applicability ratings were given to all studies. The delivery of treatment interventions might not have been representative of clinical practice in the studies. In four out of five studies, participants might not have been representative of the osteoarthritis of the knee patient population. [81;83-85] All enrolled patients were included in the final

analyses of each study. Compliance and adherence were typical of clinical practice in the studies by Toda et al. and Bennell et al. [81;85]

FINAL STRENGTH OF EVIDENCE

The moderate quality and moderate applicability ratings were the reasons four out of five studies were rated as moderate strength of evidence. One of the four studies had moderate quality but low applicability and received a low strength of evidence rating.

Table 114. Quality and Applicability Summary: Lateral Wedge Insole

Study	Outcome	Duration	Quality	Applicability	Strength of Evidence
Baker (2007)	WOMAC Pain	6 weeks	Moderate	Moderate	Moderate
Bennell (2011)	Health related quality of life	1 year	High	Moderate	High
Bennell (2011)	Number of daily steps	1 year	High	Moderate	High
Bennell (2011)	Physical activity scale or elderly (0-400)	1 year	High	Moderate	High
Bennell (2011)	WOMAC Function	1 year	High	Moderate	High
Bennell (2011)	WOMAC Function	1 year	High	Moderate	High
Maillefert (2001)	Analgesics taken in past 3 months	6 months	Moderate	Moderate	Moderate
Maillefert (2001)	NSAIDS taken in past 3 months	6 months	Moderate	Moderate	Moderate
Maillefert (2001)	WOMAC Pain	13 weeks	Moderate	Moderate	Moderate
Maillefert (2001)	WOMAC Stiffness	13 weeks	Moderate	Moderate	Moderate
Bennell (2011)	WOMAC Stiffness	1 year	High	Moderate	High
Pham(2004)	Global assessment	24 weeks	Moderate	Moderate	Moderate

Table 115. Quality and Applicability Summary: Rubber Versus Urethane Insole

Study	Outcome	Duration	Quality	Applicability	Strength of Evidence
Toda (2004)	Lequesne index	4 weeks	Moderate	Moderate	Moderate

RESULTS

Relevant Tables: Figure 27-Figure 30, Table 118-Table 120

There were 11 outcomes that compared lateral wedge insoles to neutral insoles. None of the differences in outcomes between treatment groups were statistically significant.

Toda et al.[85] found that participants who wore urethane insoles reported better Lequesne index scores than those who wore rubber insoles (see Figure 27 for a summary of the results).

Figure 27. Results Summary: Foot Orthotics

	Outcome	Week 4	6	12	13	24	26	52
Lateral Versus Neutral Insoles	Analgesics taken in past 3 months						●	
	Health related quality of life							●
	NSAIDS taken in past 3 months						●	
	Number of daily steps							●
	Physical activity scale for elderly							●
	WOMAC Function							●
	WOMAC Pain		●					●
	WOMAC Stiffness				●			●
	Global Assessment					●		
Urethane Versus Rubber Insoles	Lequesne index	●						

Key: ● =Not Significant; ● =Statistically Significant in Favor of Urethane Insoles

EVIDENCE TABLES AND FIGURES

QUALITY AND APPLICABILITY

Table 116. Quality and Applicability: Lateral Wedge Insole

●: Domain free of flaws

○: Domain flaws present

◐: Moderate power

Study	*Outcome*	Prospective	Power	Group Assignment	Blinding	Group Comparability	Treatment Integrity	Measurement	Investigator Bias	*Quality*	Participants	Intervention and Expertise	Compliance and Adherence	Analysis	*Applicability Study*
Baker (2007)	WOMAC Pain	●	●	●	●	○	●	●	○	**Moderate**	●	○	○	●	**Moderate**
Maillefert (2001)	13 week WOMAC Stiffness	●	●	○	●	○	○	●	●	**Moderate**	○	○	○	●	**Moderate**
Toda (2004)	Lequesne index	○	●	○	○	○	●	●	○	**Low**	○	○	●	●	**Moderate**
Bennell (2011)	Health related quality of life	●	◐	●	●	●	●	●	○	**High**	○	○	●	●	**Moderate**
Bennell (2011)	WOMAC Pain	●	●	●	●	●	●	●	○	**High**	○	○	●	●	**Moderate**
Bennell (2011)	WOMAC Function	●	●	●	●	●	●	●	○	**High**	○	○	●	●	**Moderate**
Bennell (2011)	WOMAC Stiffness	●	●	●	●	●	●	●	○	**High**	○	○	●	●	**Moderate**

●: Domain free of flaws

○: Domain flaws present

◐: Moderate power

Study	*Outcome*	**Prospective**	**Power**	**Group Assignment**	**Blinding**	**Group Comparability**	**Treatment Integrity**	**Measurement**	**Investigator Bias**	*Quality*	**Participants**	**Intervention and Expertise**	**Compliance and Adherence**	**Analysis**	*Applicability Study*
Bennell (2011)	Physical activity scale for elderly (0-400)	●	◐	●	●	●	●	●	○	**High**	○	○	●	●	**Moderate**
Bennell (2011)	Number of daily steps	●	◐	●	●	●	●	●	○	**High**	○	○	●	●	**Moderate**
Maillefert (2001)	NSAIDS taken in past 3 months	●	◐	○	●	○	○	●	●	**Moderate**	○	○	○	●	**Moderate**
Maillefert (2001)	NSAIDS taken in past 3 months	●	◐	○	●	○	○	●	●	**Moderate**	○	○	○	●	**Moderate**
Pham(2004)	Global Assessment	●	◐	○	●	○	○	●	●	**Moderate**	○	○	○	●	**Moderate**

Table 117 Quality and Applicability: Rubber versus Urethane Insoles

●: Domain free of flaws

○: Domain flaws present

◐: Moderate power

Study	*Outcome*	Prospective	Power	Group Assignment	Blinding	Group Comparability	Treatment Integrity	Measurement	Investigator Bias	*Quality*	Participants	Intervention and Expertise	Compliance and Adherence	Analysis	*Applicability Study*
Baker (2007)	WOMAC Pain	●	●	●	●	○	●	●	○	**Moderate**	●	○	○	●	**Moderate**

FINDINGS

Table 118. Lateral Wedge versus Neutral Insoles: Critical Outcomes

Study	Outcome	N	Sufficient Power	Week	Group 1	Group 2	Custom/Not Custom	SMD (Odds Ratio or Raw Mean Difference When Indicated)	Sig	Clinical Importance	Strength of Evidence
Baker (2007)	WOMAC Pain	86	Yes	6	Lateral wedge	Neutral insole	Not custom	-0.05 (-0.47, 0.38)	No	Inconclusive	Moderate
Bennell(2011)	WOMAC Pain	179	Yes	52	Lateral wedge	Neutral insole	Not custom	0.15 (-0.15, 0.44)	No	N/A	High
Bennell(2011)	Health related quality of life	179	Unclear	52	Lateral wedge	Neutral insole	Not custom	0.08 (-0.17, 0.42)	No	N/A	High
Bennell(2011)	WOMAC Function	179	Yes	52	Lateral wedge	Neutral insole	Not custom	0.07 (-0.22, 0.36)	No	True negative	High

Table 119. Lateral Wedge versus Neutral Insoles: other outcomes

Study	Outcome	N	Sufficient Power	Week	Group 1	Group 2	Custom/Not Custom	SMD (Odds Ratio or Raw Mean Difference When Indicated)	Sig	Clinical Importance	Strength of Evidence
Bennell(2011)	Physical activity scale for elderly (0-400)	179	Unclear	52	Lateral Wedge insole	Neutral insole	Not custom	-0.1 (-0.39, 0.19)	No	N/A	High

Study	Outcome	N	Sufficient Power	Week	Group 1	Group 2	Custom/Not Custom	SMD (Odds Ratio or Raw Mean Difference When Indicated)	Sig	Clinical Importance	Strength of Evidence
Bennell(2011)	Number of daily steps	179	Unclear	52	Lateral Wedge insole	Neutral insole	Not custom	0.2 (-0.09, 0.49)	No	N/A	High
Bennell(2011)	WOMAC Stiffness	179	Yes	52	Lateral Wedge insole	Neutral insole	Not custom	0.2 (-0.13, 0.46)	No	True negative	High
Maillifert (2001)	WOMAC Stiffness	147	Yes	13	Lateral Wedge insole	Neutral insole	Custom	0.20 (-0.13, 0.52)	No	Inconclusive	Low
Maillefert (2001)	Analgesics taken in past 3 months	147	Yes	26	Lateral Wedge insole	Neutral insole	Custom	-.059(-.37, .26)	No	N/A	Low
Maillefert (2001)	NSAIDS taken in past 3 months	147	Yes	26	Lateral Wedge insole	Neutral insole	Custom	-.19(-.5, .12)	No	N/A	Low
Pham(2004)	Patient Global Assessment of Disease Activity	156	Unclear	24	Lateral Wedge insole	Neutral insole	Custom	.05 (-0.27, 0.36)	No	N/A	Moderate

Table 120. Urethane Versus Rubber Insole (Both With Subtalar Strapping)

Study	Outcome	N	Sufficient Power	Week	Group 1	Group 2	Custom/Not Custom	SMD (Odds Ratio or Raw Mean Difference When Indicated)	Sig	Clinical Importance	Strength of Evidence
Toda (2008)	Lequesne index	84	Yes	4	Lateral urethane insole	Lateral rubber insole	Not custom	-0.44 (-0.01, -0.88)	Favors urethane	N/A	Moderate

Figure 28. Lateral Wedge Insole Versus Neutral Insoles: Critical Outcomes

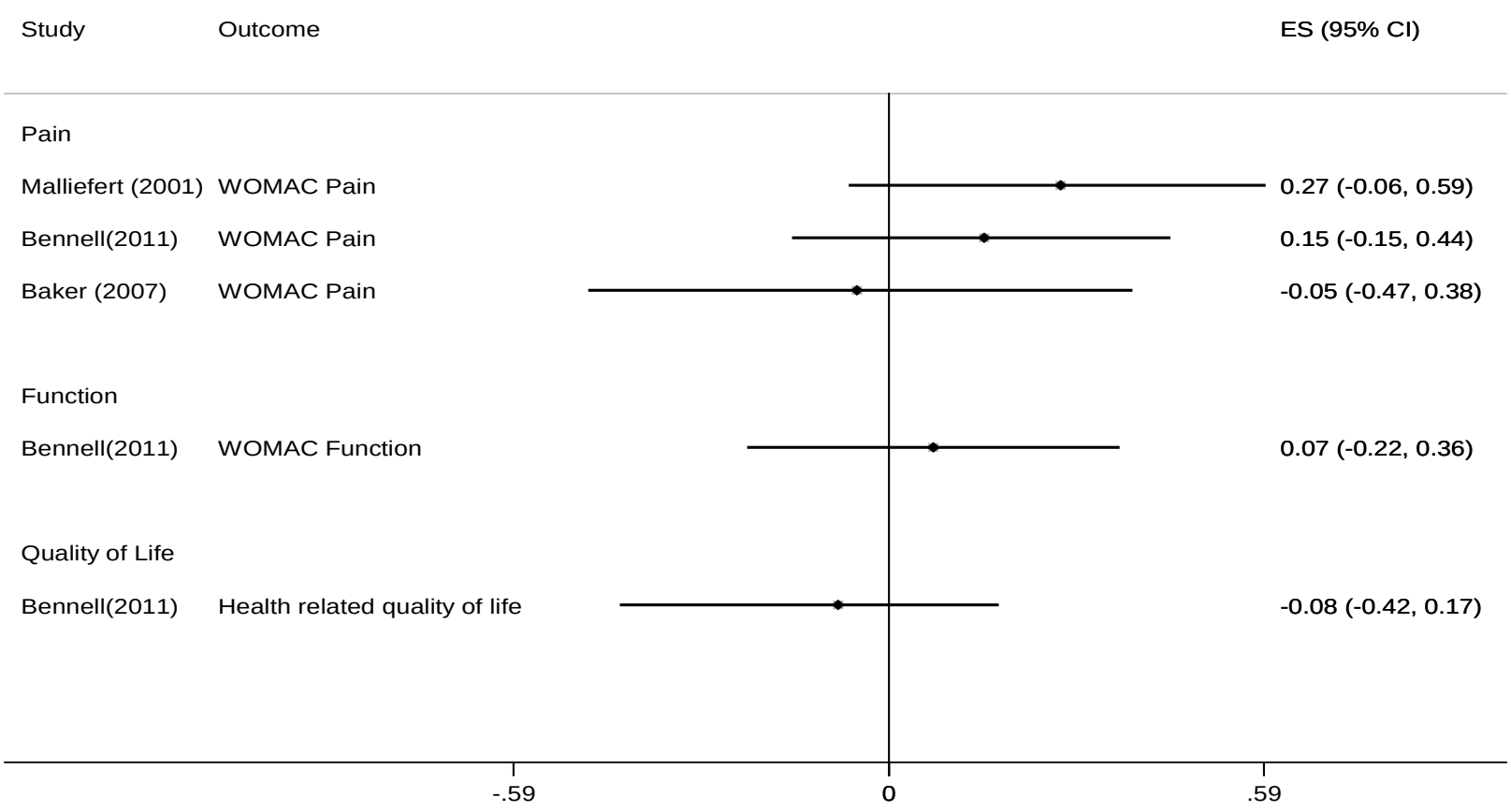


Figure 29. Lateral Wedge Insoles Versus Neutral Insoles: Other Outcomes

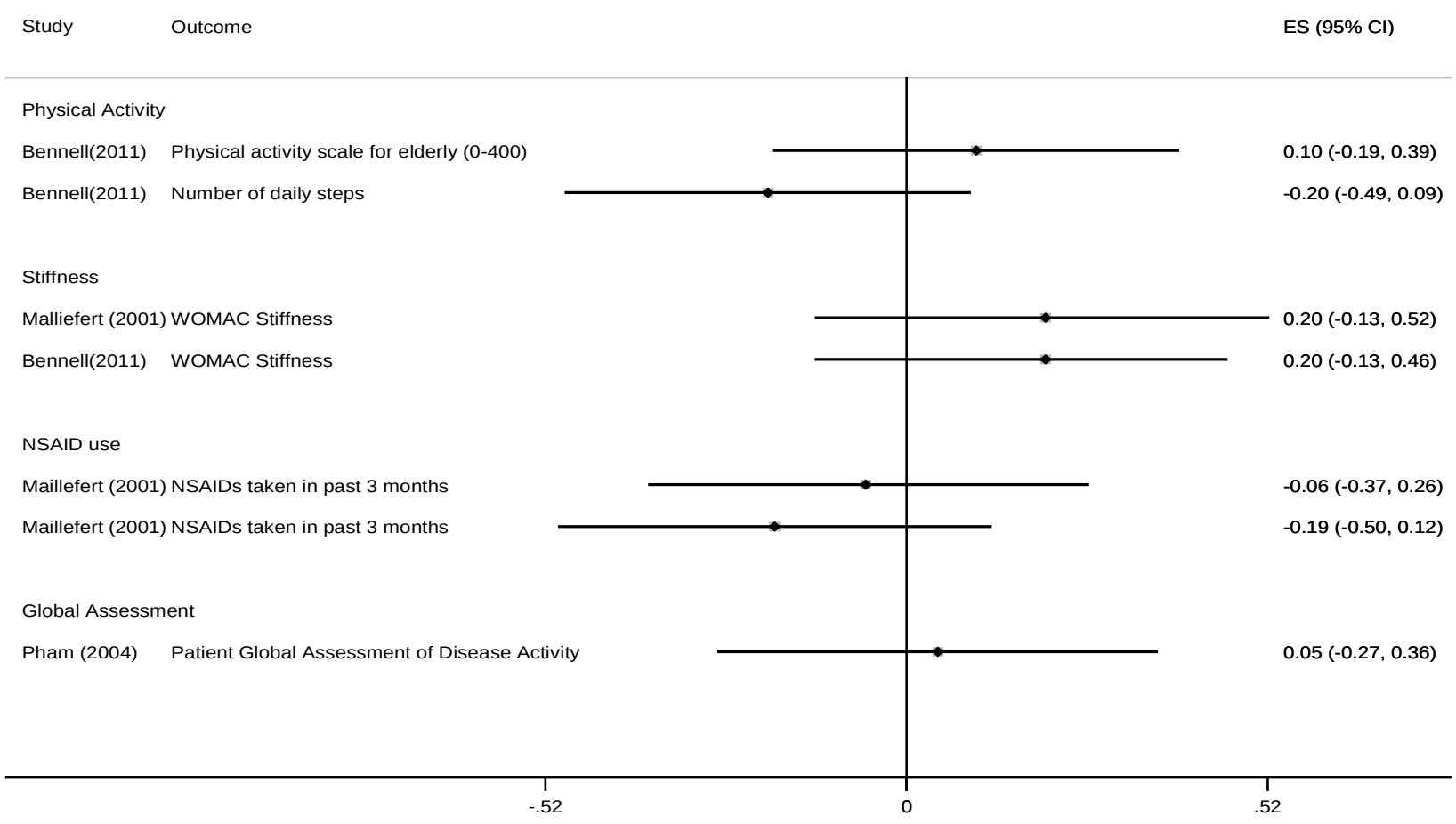
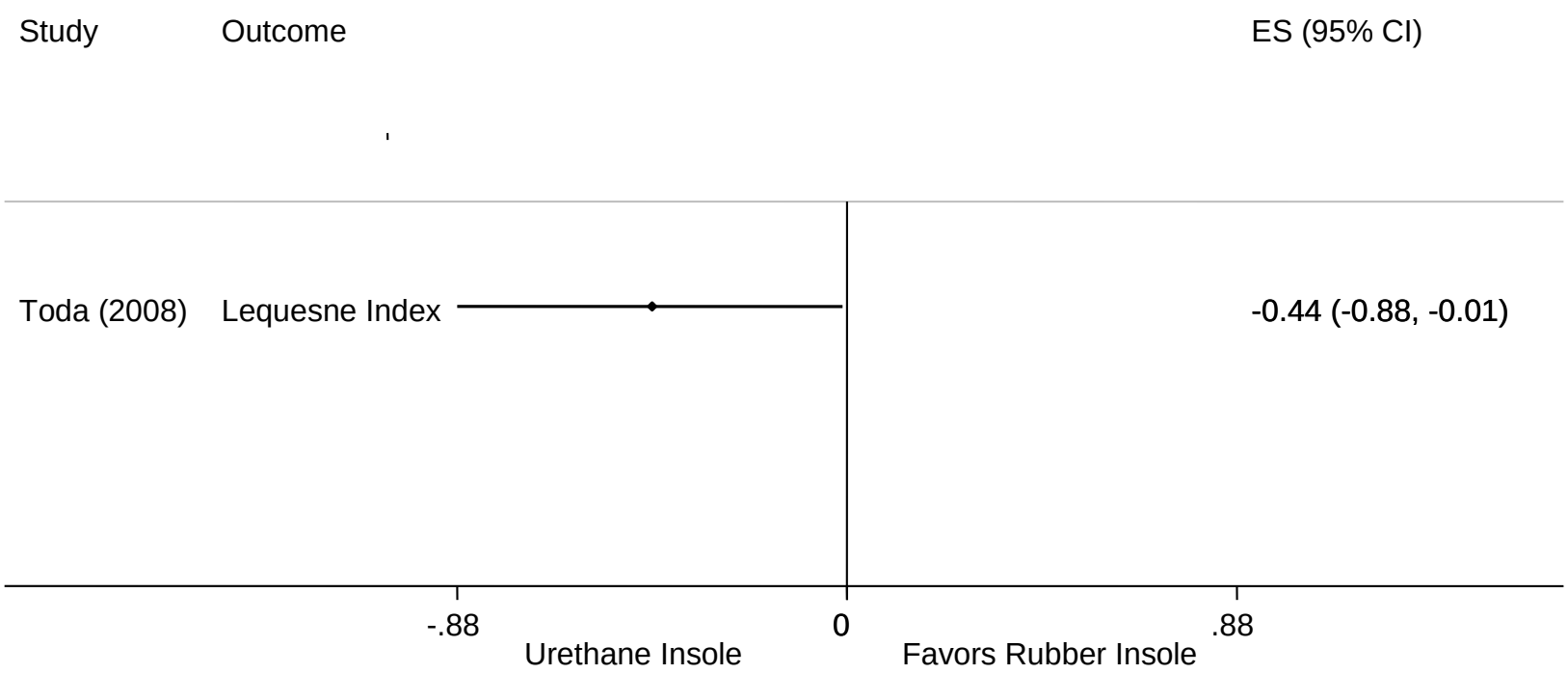


Figure 30. Urethane Versus Rubber Insoles



RECOMMENDATION 6

We cannot recommend using glucosamine and chondroitin for patients with symptomatic osteoarthritis of the knee.

Strength of Recommendation: Strong

Description: Evidence is based on two or more "High" strength studies with consistent findings for recommending for or against the intervention. A **Strong** recommendation means that the quality of the supporting evidence is high. A harms analysis on this recommendation was not performed.

Implications: Practitioners should follow a **Strong** recommendation unless a clear and compelling rationale for an alternative approach is present.

RATIONALE

Twenty-one studies were included as evidence for this recommendation; all were prospective. Twelve focused on glucosamine alone, eight on chondroitin sulfate alone, and one (Clegg et. al[86]) assessed both. Sixteen were of moderate-strength and five were of high-strength.

Among the studies, eleven of 52 outcomes were statistically significant in favor of glucosamine when compared to placebo. WOMAC pain and function subscales scores and VAS pain were the critical outcomes and were not associated with statistical significance at any treatment duration period. When meta-analyses were run for WOMAC pain, function, stiffness and total subscale scores, all meta-analyses showed that the overall effect of glucosamine compared to placebo was not statistically significant.

Two studies compared glucosamine to active treatments. Glucosamine was compared to reparagen[87] (a poly-herbal supplement), and enzymatic hydrolyzed collagen.[88] Glucosamine was found to have no significant effect on pain compared to these treatments.

Figure 33 presents the meta-analysis results comparing chondroitin sulfate to placebo in pain scores on the VAS. The weighted mean difference revealed that scores were 11.89 points lower in the chondroitin group than in the placebo group. However, the difference was not clinically important.

At this time, both glucosamine and chondroitin sulfate have been extensively studied. Despite the availability of the literature, there is essentially no evidence that minimum clinically important outcomes have been achieved compared to placebo, whether evaluated alone or in combination. The strength of the recommendation is based on lack of efficacy, not on potential harm.

One of our search terms was neutraceuticals and we initially maintained a broad focus. However, the original guidance was to evaluate methylsulfonylmethane, omega-3, gelatin, vitamin D, dimethylsulfoxide, antioxidants, and coenzyme Q10. The general term was intended to guide the search of the specific terms. Additionally, the evidence for neutraceuticals was variable and could not be easily summarized. Two moderate-strength

studies[89;90] comparing ginger extract to placebo arose in the included evidence. The only improvement in pain associated with both statistical significance and clinical importance was measured using WOMAC stiffness. Clinical importance could not be determined for four other pain measures, or they did not meet the minimum clinically important improvement threshold. The findings on outcomes of function were contradictory and low in count, which rendered them inconclusive. Glycosaminoglycan polysulfuric acid (GAGPS)[91] produced a true negative finding statistically and clinically, and gubitong was associated with higher WOMAC total scores than glucosamine in a non-control matched study where clinical importance could not be determined.

SUPPORTING EVIDENCE

QUALITY

Relevant Tables: Table 121-Table123

Twenty one studies were included as evidence for this recommendation. Schnitzer et al. was the only study that was not prospective. Fifteen studies were flawed in the group assignment domain. The studies and outcomes were all blinded. Ten studies were flawed in group comparability. With the exception of studies by Cibere et al.[92] and Mazierez et al.,[93] treatment integrity was maintained. Three studies did not have investigator bias as a concern, and all studies used valid outcome measurement instruments. In all, there were five high quality studies, one low quality study and 15 moderate quality studies included in this recommendation.

APPLICABILITY

Relevant Tables: Table 121-Table123

Seventeen studies enrolled patients who might not have been representative of the osteoarthritis of the knee population. Treatment administration was atypical of regular clinical practice in all studies and compliance and adherence were typical in 18 out of 21 studies. Finally, five studies did not include all enrolled patients in the final analyses.

FINAL STRENGTH OF EVIDENCE

All strength of evidence ratings were the same as the quality ratings since every outcome was of moderate applicability.

Table 121. Quality and Applicability Summary: Dietary Supplements

Study	Outcome	Quality	Applicability	Strength of Evidence
Bourgeois (1998)	VAS Pain (1200mg) 6 weeks	Moderate	Moderate	Moderate
Bourgeois (1998)	VAS Pain (400mg tid) 6 weeks	Moderate	Moderate	Moderate
Bourgeois (1998)	VAS Pain (1200mg) 13 weeks	Moderate	Moderate	Moderate
Bourgeois (1998)	VAS Pain (400mg tid) 13 weeks	Moderate	Moderate	Moderate
Bourgeois (1998)	Lequesne index (1200mg) 6 weeks	Moderate	Moderate	Moderate
Bourgeois (1998)	Lequesne index (400mg tid) 6 weeks	Moderate	Moderate	Moderate
Bourgeois (1998)	Lequesne index (1200mg) 13 weeks	Moderate	Moderate	Moderate
Bourgeois (1998)	Lequesne index (400mg tid) 13 weeks	Moderate	Moderate	Moderate
Bourgeois (1998)	VAS Pain (1200mg) 6 weeks	Moderate	Moderate	Moderate
Bucsi and Poor (1998)	VAS Pain 1 month	Moderate	Moderate	Moderate
Bucsi and Poor (1998)	VAS Pain 3 months	Moderate	Moderate	Moderate
Bucsi and Poor (1998)	VAS Pain 6 months	Moderate	Moderate	Moderate
Cibere (2004)	WOMAC Pain on walking	High	Moderate	High

Study	Outcome	Quality	Applicability	Strength of Evidence
Cibere (2004)	WOMAC Pain	High	Moderate	High
Cibere (2004)	WOMAC Function	High	Moderate	High
Cibere (2004)	WOMAC Stiffness	High	Moderate	High
Cibere (2004)	WOMAC Total	High	Moderate	High
Clegg (2006)	WOMAC Pain	Moderate	Moderate	Moderate
Clegg (2006)	Health Assessment Questionnaire-Pain	Moderate	Moderate	Moderate
Clegg (2006)	WOMAC Function	Moderate	Moderate	Moderate
Clegg (2006)	HAQ Alternative Disability	Moderate	Moderate	Moderate
Clegg (2006)	WOMAC Stiffness	Moderate	Moderate	Moderate
Clegg (2006)	WOMAC Total	Moderate	Moderate	Moderate
Clegg (2006)	Acetaminophen consumption	Moderate	Moderate	Moderate
Clegg (2006)	Patient Global Assessment of Response to Therapy	Moderate	Moderate	Moderate
Clegg (2006)	Patient Global Assessment of Disease Status	Moderate	Moderate	Moderate
Clegg (2006)	Physician Global Assessment of Disease Status	Moderate	Moderate	Moderate
Das (2000)	Lequesne index 4 weeks	Moderate	Moderate	Moderate
Das (2000)	Lequesne index 8 weeks	Moderate	Moderate	Moderate

Study	Outcome	Quality	Applicability	Strength of Evidence
Das (2000)	Lequesne index 13 weeks	Moderate	Moderate	Moderate
Das (2000)	Patient Global Assessment 4 weeks	Moderate	Moderate	Moderate
Das (2000)	Patient Global Assessment 8 weeks	Moderate	Moderate	Moderate
Giordano (2009)	Daily consumption of NSAIDS 4 weeks	Moderate	Moderate	Moderate
Giordano (2009)	Daily consumption of NSAIDS 8 weeks	Moderate	Moderate	Moderate
Giordano (2009)	Daily consumption of NSAIDS 12 weeks	Moderate	Moderate	Moderate
Giordano (2009)	Daily consumption of NSAIDS 16 weeks	Moderate	Moderate	Moderate
Giordano (2009)	Daily consumption of NSAIDS 20 weeks	Moderate	Moderate	Moderate
Giordano (2009)	Daily consumption of NSAIDS 24 weeks	Moderate	Moderate	Moderate
Houpt (1999)	WOMAC Pain	Moderate	Moderate	Moderate
Houpt (1999)	WOMAC Function	Moderate	Moderate	Moderate
Houpt (1999)	WOMAC Stiffness	Moderate	Moderate	Moderate
Houpt (1999)	WOMAC Total	Moderate	Moderate	Moderate

Study	Outcome	Quality	Applicability	Strength of Evidence
Hughes (2002)	WOMAC Pain	High	Moderate	High
Hughes (2002)	WOMAC Function	High	Moderate	High
Hughes (2002)	WOMAC Stiffness	High	Moderate	High
Kahan (2009)	Patient Global Assessment 26 weeks	High	Moderate	High
Kahan (2009)	Physician Global Assessment 26 weeks	High	Moderate	High
Mazieres (2001)	VAS Effect of OAK on Daily Living	Moderate	Moderate	Moderate
Mazieres (2001)	Change in Lequesne index	Moderate	Moderate	Moderate
Mazieres (2001)	VAS Pain with Activity	Moderate	Moderate	Moderate
Mazieres (2001)	Change in VAS Pain at rest	Moderate	Moderate	Moderate
Mazieres (2006)	VAS Pain during activity 4 weeks	Moderate	Moderate	Moderate
Mazieres (2006)	VAS Pain during activity 12 weeks	Moderate	Moderate	Moderate
Mazieres (2006)	VAS Pain during activity 24 weeks	Moderate	Moderate	Moderate
Mazieres (2006)	Lequesne index 4 weeks	Moderate	Moderate	Moderate
Mazieres (2006)	Lequesne index 12 weeks	Moderate	Moderate	Moderate
Mazieres (2006)	Lequesne index 24 weeks	Moderate	Moderate	Moderate

Study	Outcome	Quality	Applicability	Strength of Evidence
Mazieres (2006)	Change in pain at rest (VAS; 24 weeks	Moderate	Moderate	Moderate
Mazieres (2006)	Patient Global Assessment 24 weeks	Moderate	Moderate	Moderate
Mazieres (2006)	Physician Global Assessment 3.1 (2.7) 24 weeks	Moderate	Moderate	Moderate
Mazieres (2006)	Consumption of analgesics 24 weeks	Moderate	Moderate	Moderate
Mazieres (2006)	Days requiring NSAIDS 24 weeks	Moderate	Moderate	Moderate
Mazieres (2006)	Mental SF-12 24 weeks	Moderate	Moderate	Moderate
Mazieres (2006)	Physical SF-12 24 weeks	Moderate	Moderate	Moderate
Mazieres (2006)	OARSI Responders 24 weeks	Moderate	Moderate	Moderate
Mazieres (2006)	Adverse Events 24 weeks	Moderate	Moderate	Moderate
McAlindon (2004)	WOMAC Pain	High	Moderate	High
McAlindon (2004)	WOMAC Function	High	Moderate	High
McAlindon (2004)	WOMAC Stiffness	High	Moderate	High
McAlindon (2004)	WOMAC Total	High	Moderate	High
Moller (2010)	VAS Pain 1 month	Moderate	Moderate	Moderate

Study	Outcome	Quality	Applicability	Strength of Evidence
Moller (2010)	VAS Pain 2 months	Moderate	Moderate	Moderate
Moller (2010)	VAS Pain 3 months	Moderate	Moderate	Moderate
Moller (2010)	Lequesne index 1 month	Moderate	Moderate	Moderate
Moller (2010)	Lequesne index 2 months	Moderate	Moderate	Moderate
Moller (2010)	Lequesne index 3 months	Moderate	Moderate	Moderate
Moller (2010)	SF-36 Mental Function	Moderate	Moderate	Moderate
Moller (2010)	SF-36 Physical Function	Moderate	Moderate	Moderate
Noack (1994)	Lequesne index 4 weeks	Moderate	Moderate	Moderate
Noack (1994)	Responder (3pt reduction in Lequesne and positive investigator global assessment) 4 weeks	Moderate	Moderate	Moderate
Noack (1994)	Gastrointestinal disturbances 4 weeks	Moderate	Moderate	Moderate
Noack (1994)	Pruritus or skin reaction 4 weeks	Moderate	Moderate	Moderate
Noack (1994)	Headache 4 weeks	Moderate	Moderate	Moderate
Noack (1994)	Circulatory disturbances 4 weeks	Moderate	Moderate	Moderate

Study	Outcome	Quality	Applicability	Strength of Evidence
Noack (1994)	Total adverse events 4 weeks	Moderate	Moderate	Moderate
Pavelka (2002)	WOMAC Total	Moderate	Moderate	Moderate
Pavelka (2002)	Lequesne index	Moderate	Moderate	Moderate
Rindone (2000)	VAS Walking Pain week 4	Moderate	Moderate	Moderate
Rindone (2000)	VAS Walking Pain week 8	Moderate	Moderate	Moderate
Rindone (2000)	VAS Resting Pain week 4	Moderate	Moderate	Moderate
Rindone (2000)	VAS Resting Pain week 8	Moderate	Moderate	Moderate
Trc (2010)	VAS improvement 20mm	Moderate	Moderate	Moderate
Trc (2010)	WOMAC Total 15 or more points	Moderate	Moderate	Moderate
Trc (2010)	VAS Pain	Moderate	Moderate	Moderate
Trc (2010)	VAS typical or average pain	Moderate	Moderate	Moderate
Trc (2010)	VAS Pain level at its best	Moderate	Moderate	Moderate
Trc (2010)	VAS Pain level at its worst	Moderate	Moderate	Moderate
Uebelhart (2004)	VAS Pain 3 months	High	Moderate	High
Uebelhart (2004)	VAS Pain 6 months	High	Moderate	High
Uebelhart (2004)	VAS Pain 9 months	High	Moderate	High
Uebelhart (2004)	VAS Pain 12 months	High	Moderate	High

Study	Outcome	Quality	Applicability	Strength of Evidence
Uebelhart (2004)	Lequesne index 3 months	High	Moderate	High
Uebelhart (2004)	Lequesne index 6 months	High	Moderate	High
Uebelhart (2004)	Lequesne index 9 months	High	Moderate	High
Uebelhart (2004)	Lequesne index 12 months	High	Moderate	High
Pavelka (2010)	WOMAC Total week 4	Moderate	Moderate	Moderate
Pavelka (2010)	WOMAC Total week 8	Moderate	Moderate	Moderate
Pavelka (2010)	WOMAC Total week 12	Moderate	Moderate	Moderate
Pavelka (2010)	WOMAC Total week 24	Moderate	Moderate	Moderate
Pavelka (2010)	WOMAC Total week 32	Moderate	Moderate	Moderate
Pavelka (2010)	WOMAC Stiffness week 4	Moderate	Moderate	Moderate
Pavelka (2010)	WOMAC Stiffness week 8	Moderate	Moderate	Moderate
Pavelka (2010)	WOMAC Stiffness week 12	Moderate	Moderate	Moderate
Pavelka (2010)	WOMAC Stiffness week 24	Moderate	Moderate	Moderate
Pavelka (2010)	WOMAC Stiffness week 32	Moderate	Moderate	Moderate
Pavelka (2010)	WOMAC Pain week 4	Moderate	Moderate	Moderate
Pavelka (2010)	WOMAC Pain week 8	Moderate	Moderate	Moderate
Pavelka (2010)	WOMAC Pain week 12	Moderate	Moderate	Moderate
Pavelka (2010)	WOMAC Pain week 24	Moderate	Moderate	Moderate
Pavelka (2010)	WOMAC Pain week 32	Moderate	Moderate	Moderate
Pavelka (2010)	WOMAC Function week 4	Moderate	Moderate	Moderate
Pavelka (2010)	WOMAC Function week 8	Moderate	Moderate	Moderate

Study	Outcome	Quality	Applicability	Strength of Evidence
Pavelka (2010)	WOMAC Function week 12	Moderate	Moderate	Moderate
Pavelka (2010)	WOMAC Function week 24	Moderate	Moderate	Moderate
Pavelka (2010)	WOMAC Function week 32	Moderate	Moderate	Moderate
Pavelka (2010)	Pain on movement (VAS) week 4	Moderate	Moderate	Moderate
Pavelka (2010)	Pain on movement (VAS) week 8	Moderate	Moderate	Moderate
Pavelka (2010)	Pain on movement (VAS) week 12	Moderate	Moderate	Moderate
Pavelka (2010)	Pain on movement (VAS) week 24	Moderate	Moderate	Moderate
Pavelka (2010)	Pain on movement (VAS) week 32	Moderate	Moderate	Moderate
Pavelka (2010)	Lequesne index week 4	Moderate	Moderate	Moderate
Pavelka (2010)	Lequesne index week 8	Moderate	Moderate	Moderate
Pavelka (2010)	Lequesne index week 12	Moderate	Moderate	Moderate
Pavelka (2010)	Lequesne index week 24	Moderate	Moderate	Moderate
Pavelka (2010)	Lequesne index week 32	Moderate	Moderate	Moderate
Pavelka (2010)	Rescue medication, mean tablets/day week 4	Moderate	Moderate	Moderate
Pavelka (2010)	Rescue medication, mean tablets/day week 8	Moderate	Moderate	Moderate
Pavelka (2010)	Rescue medication, mean tablets/day week 12	Moderate	Moderate	Moderate

Study	Outcome	Quality	Applicability	Strength of Evidence
Pavelka (2010)	Rescue medication, mean tablets/day week 24	Moderate	Moderate	Moderate
Pavelka (2010)	Rescue medication, mean tablets/day week 32	Moderate	Moderate	Moderate
Pavelka (2010)	VAS Pain at rest week 4	Moderate	Moderate	Moderate
Pavelka (2010)	VAS Pain at rest week 8	Moderate	Moderate	Moderate
Pavelka (2010)	VAS Pain at rest week 12	Moderate	Moderate	Moderate
Pavelka (2010)	VAS Pain at rest week 24	Moderate	Moderate	Moderate
Pavelka (2010)	VAS Pain at rest week 32	Moderate	Moderate	Moderate
Rai (2004)	Lequesne index week 52	Moderate	Moderate	Moderate

RESULTS

Relevant Tables: Figure 31-Figure 41, Table 124-Table 143

Eleven out of 52 outcomes were statistically significant in favor of glucosamine when compared to placebo (see Figure 31). WOMAC pain, WOMAC function, and VAS pain were the critical outcomes. None were associated with statistical significance at any time duration (Figure 31).

Meta-analyses were run for WOMAC pain, WOMAC function, WOMAC stiffness and WOMAC total. All meta-analyses showed statistically insignificant differences between glucosamine and placebo (Figures 38-41).

Two studies compared glucosamine to active treatments. Glucosamine was compared to reparagen[87] and enzymatic hydrolyzed collagen (EHC).[88] It was found to have no statistically significant effect on pain compared to reparagen.

Enzymatic hydrolyzed collagen (EHC) was compared to glucosamine sulfate by Trc et al.[88] All pain outcomes were statistically significant in favor of EHC. However, two outcomes—VAS pain and VAS pain at its worst—were not clinically important.

Figure 32 presents a summary of the results for chondroitin sulfate. Twenty four out of 64 outcomes were significantly higher for chondroitin over placebo. The critical outcomes presented in the studies were pain and function. Pain was significantly lower in the glucosamine group for 12 out of 22 outcomes. Of those 12, four outcomes were

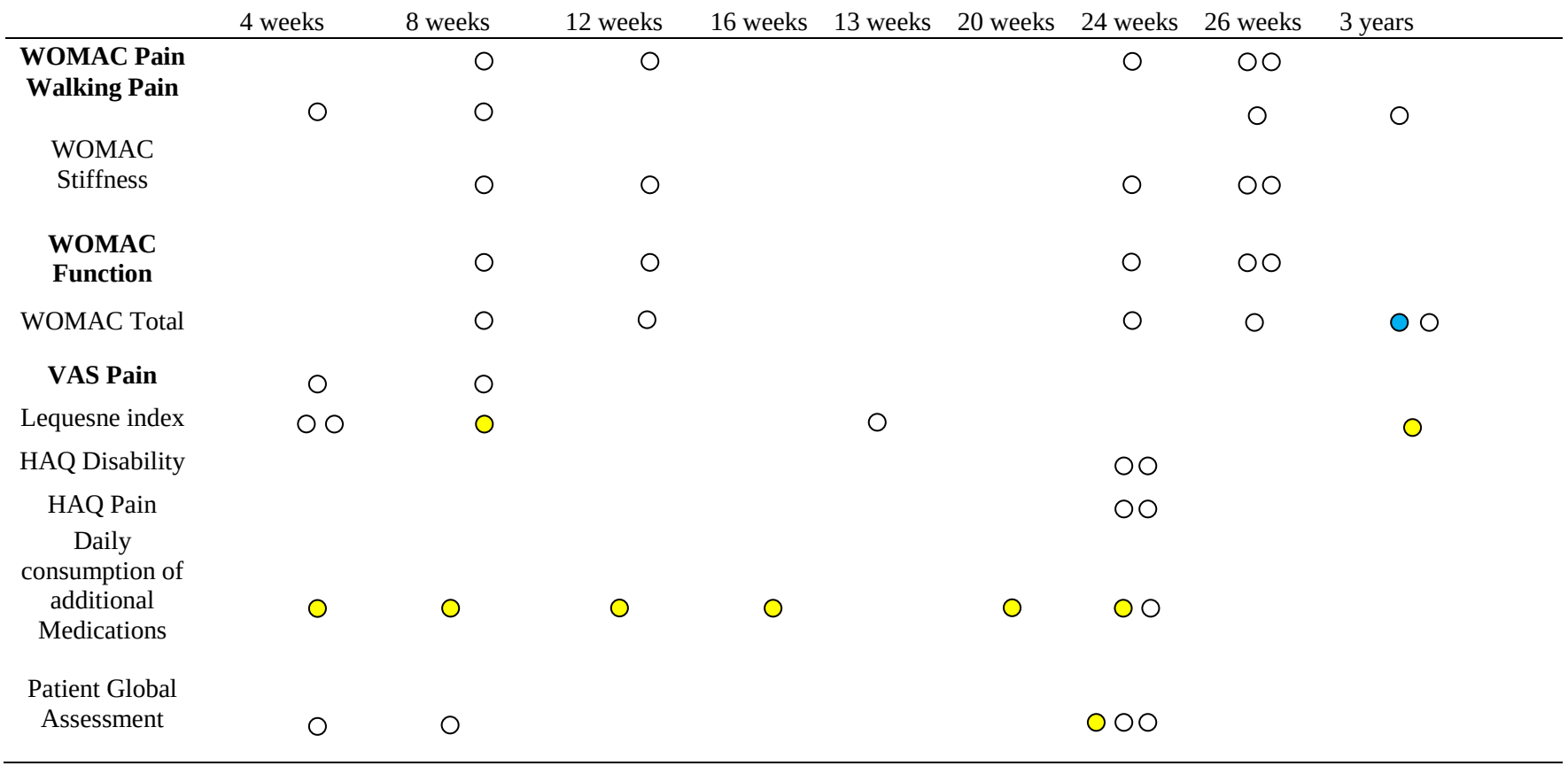
clinically important and six were possibly clinically important. No statistically significant results were found for any functional outcome.

Figure 33 presents the meta-analysis results comparing VAS chondroitin sulfate to placebo in VAS pain scores. The weighted mean difference revealed that VAS pain was 11.89 points lower in the chondroitin group than in the placebo group. However, the difference was not clinically important.

Pavelka et al.[94] compared piascledine (avocado soybean unsaponifiable) to chondroitin sulfate. The authors measured WOMAC total and subscale scores, as well as VAS pain, Lequesne index, and concomitant medication use at four, eight, 12, 24 and 32 weeks. None of the 40 outcomes were associated with significant differences between treatment groups.

Two studies compared combined chondroitin and glucosamine to placebo. Only two of 11 outcomes were statistically significant in favor of the treatment group. However, one study by Clegg et al.[86] also did a subgroup analysis stratified by severity. For the moderate to severe osteoarthritis subgroup, the authors found the treatment group to have significantly higher odds of being OARSI responders. Moderate to severe osteoarthritic patients were more likely to achieve 20% to 50% reductions in WOMAC pain scores than those who received a placebo. The outcomes were not statistically significant in the total sample or in the mild severity subgroup.

Figure 31. Results Summary: Glucosamine Versus Placebo

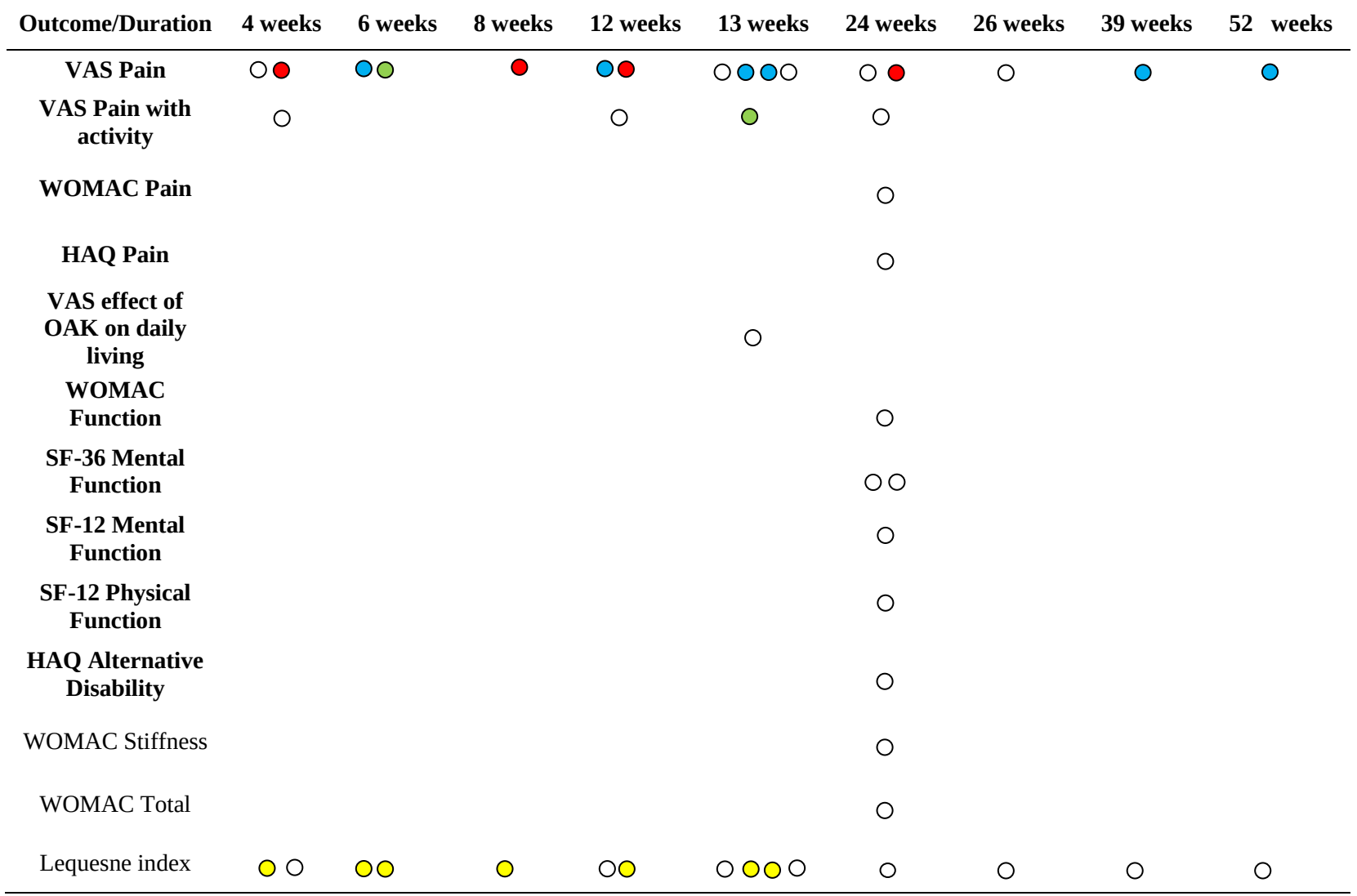


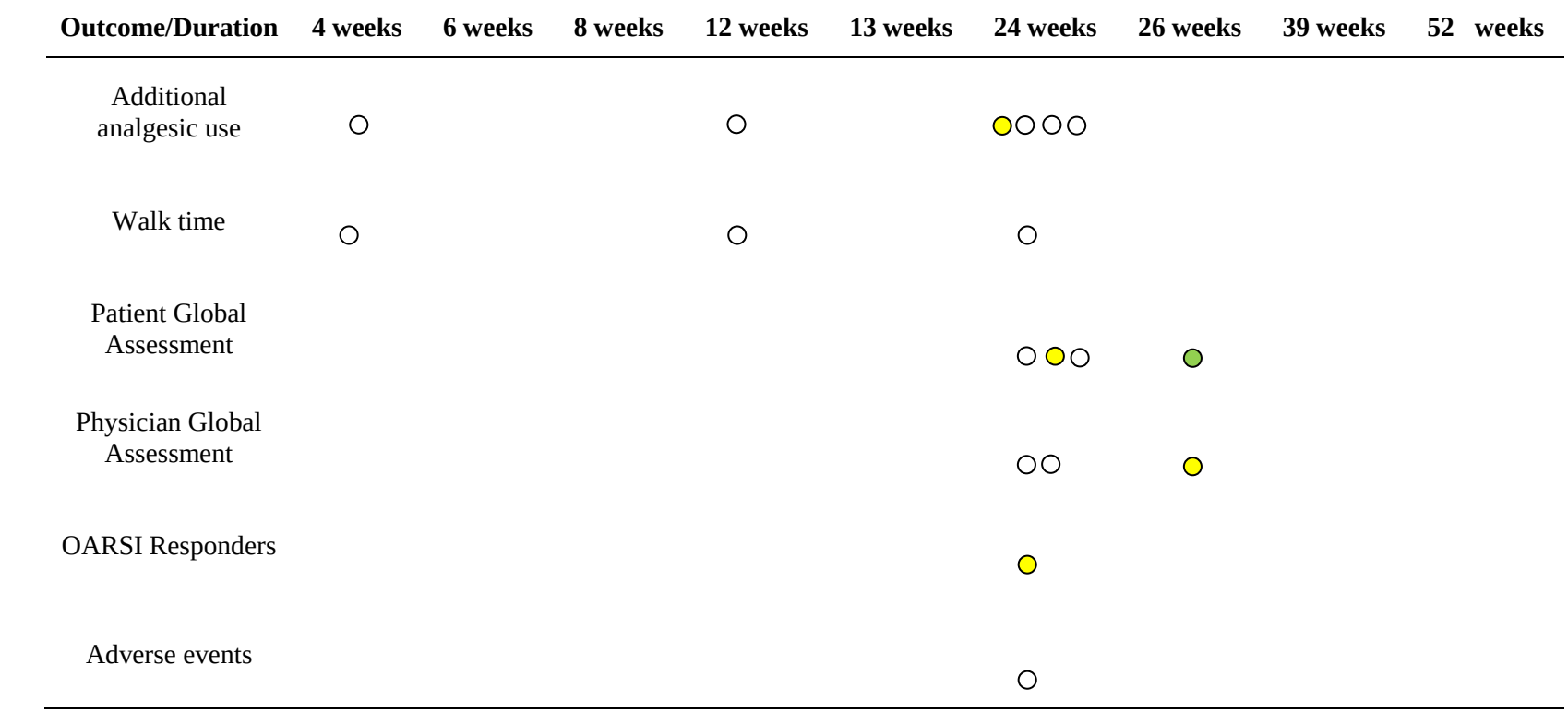
	4 weeks	8 weeks	12 weeks	16 weeks	13 weeks	20 weeks	24 weeks	26 weeks	3 years
responder (3pt reduction in Lequesne and positive investigator global assessment)	●								
Gastrointestinal disturbances	○								
Pruritus or skin reaction	○								
Headache	○								
Circulatory disturbances	○								
Total adverse events	○								

***Each shape represents the result of one study at each time period.**

○ **Insignificant treatment effect**
● **Possibly clinically significant in favor of Glucosamine**
● **Statistically significant in favor of Glucosamine**

Figure 32. Results Summary: Chondroitin Sulfate Versus Placebo





***Note: each shape represents a finding from one study at each time point**

Indicates a statistically insignificant treatment effect between Chondroitin Sulfate and control.

Indicates a statistically significant treatment effect in favor of Chondroitin Sulfate.

Indicates a possibly clinically significant treatment effect in favor of Chondroitin Sulfate.

Indicates a clinically significant treatment effect in favor of Chondroitin Sulfate.

Statistically significant, but not clinically important effect in favor of Chondroitin Sulfate

EVIDENCE TABLES AND FIGURES

QUALITY AND APPLICABILITY

Table 122. Quality And Applicability: Glucosamine Versus Control

●: Domain free of flaws

○: Domain flaws present

◐: Moderate power

Study	*Outcome*	Prospective	Power	Group Assignment	Blinding	Group Comparability	Treatment Integrity	Measurement	Investigator Bias	*Quality*	Participants	Intervention and Expertise	Compliance and Adherence	Analysis	*Applicability Study*
Cibere (2004)	WOMAC Pain on Walking	●	◐	●	●	●	○	●	●	**High**	○	○	●	●	**Moderate**
Cibere (2004)	WOMAC Pain	●	○	●	●	●	○	●	●	**High**	○	○	●	●	**Moderate**
Cibere (2004)	WOMAC Function	●	○	●	●	●	○	●	●	**High**	○	○	●	●	**Moderate**
Cibere (2004)	WOMAC Stiffness	●	○	●	●	●	○	●	●	**High**	○	○	●	●	**Moderate**
Cibere (2004)	WOMAC Total	●	○	●	●	●	○	●	●	**High**	○	○	●	●	**Moderate**
Clegg (2006)	WOMAC Pain	●	●	○	●	○	●	●	●	**Moderate**	○	○	○	●	**Moderate**

●: Domain free of flaws

○: Domain flaws present

◐: Moderate power

Study	*Outcome*	**Prospective**	**Power**	**Group Assignment**	**Blinding**	**Group Comparability**	**Treatment Integrity**	**Measurement**	**Investigator Bias**	*Quality*	**Participants**	**Intervention and Expertise**	**Compliance and Adherence**	**Analysis**	*Applicability Study*
Clegg (2006)	WOMAC Stiffness	●	●	○	●	○	●	●	●	**Moderate**	○	○	○	●	**Moderate**
Clegg (2006)	WOMAC Function	●	●	○	●	○	●	●	●	**Moderate**	○	○	○	●	**Moderate**
Clegg (2006)	Normalized WOMAC	●	●	○	●	○	●	●	●	**Moderate**	○	○	○	●	**Moderate**
Clegg (2006)	HAQ Alternative Disability	●	◐	○	●	○	●	●	●	**Moderate**	○	○	○	●	**Moderate**
Clegg (2006)	HAQ Pain	●	◐	○	●	○	●	●	●	**Moderate**	○	○	○	●	**Moderate**
Clegg (2006)	Patient Global Assessment of Response to Therapy	●	◐	○	●	○	●	●	●	**Moderate**	○	○	○	●	**Moderate**
Clegg (2006)	Patient Global Assessment of Disease Status	●	◐	○	●	○	●	●	●	**Moderate**	○	○	○	●	**Moderate**

●: Domain free of flaws

○: Domain flaws present

◐: Moderate power

Study	*Outcome*	**Prospective**	**Power**	**Group Assignment**	**Blinding**	**Group Comparability**	**Treatment Integrity**	**Measurement**	**Investigator Bias**	*Quality*	**Participants**	**Intervention and Expertise**	**Compliance and Adherence**	**Analysis**	*Applicability Study*
Clegg (2006)	Physician Global Assessment of Disease Status	●	◐	○	●	○	●	●	●	**Moderate**	○	○	○	●	**Moderate**
Hughes (2002)	WOMAC Pain	●	◐	●	●	●	●	●	○	**High**	○	○	●	●	**Moderate**
Hughes (2002)	WOMAC Function	●	◐	●	●	●	●	●	○	**High**	○	○	●	●	**Moderate**
Hughes (2002)	WOMAC Stiffness	●	◐	●	●	●	●	●	○	**High**	○	○	●	●	**Moderate**
Rindone (2000)	VAS Walking Pain week 4	●	●	○	●	●	●	●	○	**Moderate**	●	○	●	○	**Moderate**
Rindone (2000)	VAS Walking Pain week 8	●	●	○	●	●	●	●	○	**Moderate**	●	○	●	○	**Moderate**
Rindone (2000)	VAS Resting Pain week 4	●	●	○	●	●	●	●	○	**Moderate**	●	○	●	○	**Moderate**

●: Domain free of flaws

○: Domain flaws present

◐: Moderate power

Study	*Outcome*	**Prospective**	**Power**	**Group Assignment**	**Blinding**	**Group Comparability**	**Treatment Integrity**	**Measurement**	**Investigator Bias**	*Quality*	**Participants**	**Intervention and Expertise**	**Compliance and Adherence**	**Analysis**	*Applicability Study*
Rindone (2000)	VAS Resting Pain week 8	●	●	○	●	●	●	●	○	**Moderate**	●	○	●	○	**Moderate**
Pavelka (2002)	WOMAC Total	●	●	●	●	○	●	●	○	**Moderate**	○	○	●	●	**Moderate**
Pavelka (2002)	Lequesne index	●	◐	●	●	○	●	●	○	**Moderate**	○	○	●	●	**Moderate**
McAlindon (2004)	WOMAC Pain	●	●	●	●	●	●	●	●	**High**	●	○	●	●	**Moderate**
McAlindon (2004)	WOMAC Function	●	●	●	●	●	●	●	●	**High**	●	○	●	●	**Moderate**
McAlindon (2004)	WOMAC Stiffness	●	●	●	●	●	●	●	●	**High**	●	○	●	●	**Moderate**
McAlindon (2004)	WOMAC Total	●	●	●	●	●	●	●	●	**High**	●	○	●	●	**Moderate**
Houpt (1999)	WOMAC Pain	●	○	○	●	○	●	●	○	**Moderate**	●	○	●	○	**Moderate**

●: Domain free of flaws

○: Domain flaws present

◐: Moderate power

Study	*Outcome*	**Prospective**	**Power**	**Group Assignment**	**Blinding**	**Group Comparability**	**Treatment Integrity**	**Measurement**	**Investigator Bias**	*Quality*	**Participants**	**Intervention and Expertise**	**Compliance and Adherence**	**Analysis**	*Applicability Study*
Houpt (1999)	WOMAC Function	●	●	○	●	○	●	●	○	**Moderate**	●	○	●	○	**Moderate**
Houpt (1999)	WOMAC Stiffness	●	○	○	●	○	●	●	○	**Moderate**	●	○	●	○	**Moderate**
Houpt (1999)	WOMAC Total	●	○	○	●	○	●	●	○	**Moderate**	●	○	●	○	**Moderate**
Trc (2010)	VAS improvement 20mm	●	●	○	●	●	●	●	○	**Moderate**	○	○	●	●	**Moderate**
Trc (2010)	WOMAC Total 15mm improvement	●	●	○	●	●	●	●	○	**Moderate**	○	○	●	●	**Moderate**
Trc (2010)	VAS Pain	●	●	○	●	●	●	●	○	**Moderate**	○	○	●	●	**Moderate**
Trc (2010)	VAS typical or	●	●	○	●	●	●	●	○	**Moderate**	○	○	●	●	**Moderate**

●: Domain free of flaws

○: Domain flaws present

◐: Moderate power

Study	*Outcome*	**Prospective**	**Power**	**Group Assignment**	**Blinding**	**Group Comparability**	**Treatment Integrity**	**Measurement**	**Investigator Bias**	*Quality*	**Participants**	**Intervention and Expertise**	**Compliance and Adherence**	**Analysis**	*Applicability Study*
	average pain														
Trc (2010)	VAS Pain level at its best	●	●	○	●	●	●	●	○	**Moderate**	○	○	●	●	**Moderate**
Trc (2010)	VAS Pain level at its worst	●	●	○	●	●	●	●	○	**Moderate**	○	○	●	●	**Moderate**
Giordano (2009)	Daily consumption of NSAIDS 4 weeks	●	◐	○	●	○	●	●	○	**Moderate**	○	○	●	●	**Moderate**
Giordano (2009)	Daily consumption of NSAIDS 8 weeks	●	◐	○	●	○	●	●	○	**Moderate**	○	○	●	●	**Moderate**

●: Domain free of flaws

○: Domain flaws present

◐: Moderate power

Study	*Outcome*	**Prospective**	**Power**	**Group Assignment**	**Blinding**	**Group Comparability**	**Treatment Integrity**	**Measurement**	**Investigator Bias**	*Quality*	**Participants**	**Intervention and Expertise**	**Compliance and Adherence**	**Analysis**	*Applicability Study*
Giordano (2009)	Daily consumption of NSAIDS 12 weeks	●	◐	○	●	○	●	●	○	**Moderate**	○	○	●	●	**Moderate**
Giordano (2009)	Daily consumption of NSAIDS 16 weeks	●	◐	○	●	○	●	●	○	**Moderate**	○	○	●	●	**Moderate**
Giordano (2009)	Daily consumption of NSAIDS 20 weeks	●	◐	○	●	○	●	●	○	**Moderate**	○	○	●	●	**Moderate**
Giordano (2009)	Daily consumption of NSAIDS 24 weeks	●	◐	○	●	○	●	●	○	**Moderate**	○	○	●	●	**Moderate**

●: Domain free of flaws

○: Domain flaws present

◐: Moderate power

Study	*Outcome*	**Prospective**	**Power**	**Group Assignment**	**Blinding**	**Group Comparability**	**Treatment Integrity**	**Measurement**	**Investigator Bias**	*Quality*	**Participants**	**Intervention and Expertise**	**Compliance and Adherence**	**Analysis**	*Applicability Study*
Noack (1994)	Lequesne index 4 weeks	●	●	○	●	○	●	●	○	**Moderate**	○	○	●	●	**Moderate**
Noack (1994)	Responder (3pt reduction in Lequesne and positive investigator global assessment) 4 weeks	●	◐	○	●	○	●	●	○	**Moderate**	○	○	●	●	**Moderate**
Noack (1994)	Gastrointestinal disturbances 4 weeks	●	◐	○	●	○	●	●	○	**Moderate**	○	○	●	●	**Moderate**
Noack (1994)	Pruritus or skin reaction 4 weeks	●	◐	○	●	○	●	●	○	**Moderate**	○	○	●	●	**Moderate**

●: Domain free of flaws

○: Domain flaws present

◐: Moderate power

Study	*Outcome*	**Prospective**	**Power**	**Group Assignment**	**Blinding**	**Group Comparability**	**Treatment Integrity**	**Measurement**	**Investigator Bias**	*Quality*	**Participants**	**Intervention and Expertise**	**Compliance and Adherence**	**Analysis**	*Applicability Study*
Noack (1994)	Headache 4 weeks	●	◐	○	●	○	●	●	○	**Moderate**	○	○	●	●	**Moderate**
Noack (1994)	Circulatory disturbances 4 weeks	●	◐	○	●	○	●	●	○	**Moderate**	○	○	●	●	**Moderate**
Noack (1994)	Total adverse events 4 weeks	●	◐	○	●	○	●	●	○	**Moderate**	○	○	●	●	**Moderate**
Das (2000)	Lequesne index 4 weeks	●	◐	○	●	○	●	●	○	**Moderate**	○	○	●	●	**Moderate**
Das (2000)	Lequesne index 8 weeks	●	●	○	●	○	●	●	○	**Moderate**	○	○	●	●	**Moderate**
Das (2000)	Lequesne index 13 weeks	●	◐	○	●	○	●	●	○	**Moderate**	○	○	●	●	**Moderate**
Das (2000)	Patient Global Assessment 4 weeks	●	●	○	●	○	●	●	○	**Moderate**	○	○	●	●	**Moderate**

●: Domain free of flaws

○: Domain flaws present

◐: Moderate power

Study	*Outcome*	**Prospective**	**Power**	**Group Assignment**	**Blinding**	**Group Comparability**	**Treatment Integrity**	**Measurement**	**Investigator Bias**	*Quality*	**Participants**	**Intervention and Expertise**	**Compliance and Adherence**	**Analysis**	*Applicability Study*
Das (2000)	Patient Global Assessment 8 weeks	●	●	○	●	○	●	●	○	**Moderate**	○	○	●	●	**Moderate**
Rai (2004)	Lequesne index week 52	●	●	○	●	○	●	●	○	**Moderate**	○	○	●	●	**Moderate**
Reginster (2001)	WOMAC Total week 156	●	●	●	●	○	●	●	●	**High**	○	○	○	●	**Moderate**
Reginster (2001)	WOMAC Pain week 156	●	●	●	●	○	●	●	●	**High**	○	○	○	●	**Moderate**

Table 123. Quality and Applicability: Chondroitin

●: Domain free of flaws

○: Domain flaws present

◐: Moderate power

Study	*Outcome*	**Prospective**	**Power**	**Group Assignment**	**Blinding**	**Group Comparability**	**Treatment Integrity**	**Measurement**	**Investigator Bias**	*Quality*	**Participants**	**Intervention and Expertise**	**Compliance and Adherence**	**Analysis**	*Applicability Study*
Bourgeois (1998)	VAS Pain (1200mg) 6 weeks	●	●	○	●	●	●	●	○	**Moderate**	○	○	●	●	**Moderate**
Bourgeois (1998)	VAS Pain (400mg tid) 6 weeks	●	●	○	●	●	●	●	○	**Moderate**	○	○	●	●	**Moderate**
Bourgeois (1998)	VAS Pain (1200mg) 13 weeks	●	●	○	●	●	●	●	○	**Moderate**	○	○	●	●	**Moderate**
Bourgeois (1998)	VAS Pain (400mg tid) 13 weeks	●	●	○	●	●	●	●	○	**Moderate**	○	○	●	●	**Moderate**
Bourgeois (1998)	Lequesne index (1200mg) 6 weeks	●	●	○	●	●	●	●	○	**Moderate**	○	○	●	●	**Moderate**

●: Domain free of flaws

○: Domain flaws present

◐: Moderate power

Study	*Outcome*	**Prospective**	**Power**	**Group Assignment**	**Blinding**	**Group Comparability**	**Treatment Integrity**	**Measurement**	**Investigator Bias**	*Quality*	**Participants**	**Intervention and Expertise**	**Compliance and Adherence**	**Analysis**	*Applicability Study*
Clegg (2006)	WOMAC Pain	●	●	○	●	○	●	●	●	**Moderate**	○	○	○	●	**Moderate**
Clegg (2006)	WOMAC Stiffness	●	●	○	●	○	●	●	●	**Moderate**	○	○	○	●	**Moderate**
Clegg (2006)	WOMAC Function	●	●	○	●	○	●	●	●	**Moderate**	○	○	○	●	**Moderate**
Clegg (2006)	Normalized WOMAC	●	●	○	●	○	●	●	●	**Moderate**	○	○	○	●	**Moderate**
Clegg (2006)	HAQ Alternative Disability	●	◐	○	●	○	●	●	●	**Moderate**	○	○	○	●	**Moderate**
Clegg (2006)	HAQ Pain	●	◐	○	●	○	●	●	●	**Moderate**	○	○	○	●	**Moderate**
Clegg (2006)	Patient Global Assessment of Response to	●	◐	○	●	○	●	●	●	**Moderate**	○	○	○	●	**Moderate**

●: Domain free of flaws

○: Domain flaws present

◐: Moderate power

Study	*Outcome*	**Prospective**	**Power**	**Group Assignment**	**Blinding**	**Group Comparability**	**Treatment Integrity**	**Measurement**	**Investigator Bias**	*Quality*	**Participants**	**Intervention and Expertise**	**Compliance and Adherence**	**Analysis**	*Applicability Study*
	Therapy														
Clegg (2006)	Patient Global Assessment of Disease Status	●	◐	○	●	○	●	●	●	**Moderate**	○	○	○	●	**Moderate**
Clegg (2006)	Physician Global Assessment of Disease Status	●	◐	○	●	○	●	●	●	**Moderate**	○	○	○	●	**Moderate**
Clegg (2006)	Acetaminophen consumption	●	◐	○	●	○	●	●	●	**Moderate**	○	○	○	●	**Moderate**
Mazieres (2006)	VAS Pain during activity 4 weeks	●	●	○	●	●	○	●	○	**Moderate**	○	○	○	●	**Moderate**
Mazieres (2006)	VAS Pain during activity 12 weeks	●	●	○	●	●	○	●	○	**Moderate**	○	○	○	●	**Moderate**

●: Domain free of flaws

○: Domain flaws present

◐: Moderate power

Study	*Outcome*	**Prospective**	**Power**	**Group Assignment**	**Blinding**	**Group Comparability**	**Treatment Integrity**	**Measurement**	**Investigator Bias**	*Quality*	**Participants**	**Intervention and Expertise**	**Compliance and Adherence**	**Analysis**	*Applicability Study*
Mazieres (2006)	VAS Pain during activity 24 weeks	●	●	○	●	●	○	●	○	**Moderate**	○	○	○	●	**Moderate**
Mazieres (2006)	Lequesne index 4 weeks	●	◐	○	●	●	○	●	○	**Moderate**	○	○	○	●	**Moderate**
Mazieres (2006)	Lequesne index 12 weeks	●	◐	○	●	●	○	●	○	**Moderate**	○	○	○	●	**Moderate**
Mazieres (2006)	Lequesne index 24 weeks	●	◐	○	●	●	○	●	○	**Moderate**	○	○	○	●	**Moderate**
Mazieres (2006)	VAS change in pain at rest 24 weeks	●	●	○	●	●	○	●	○	**Moderate**	○	○	○	●	**Moderate**
Mazieres (2006)	Patient Global Assessment 24 weeks	●	◐	○	●	●	○	●	○	**Moderate**	○	○	○	●	**Moderate**
Mazieres (2006)	Physician Global Assessment 3.1 (2.7) 24 weeks	●	◐	○	●	●	○	●	○	**Moderate**	○	○	○	●	**Moderate**

●: Domain free of flaws

○: Domain flaws present

◐: Moderate power

Study	*Outcome*	**Prospective**	**Power**	**Group Assignment**	**Blinding**	**Group Comparability**	**Treatment Integrity**	**Measurement**	**Investigator Bias**	*Quality*	**Participants**	**Intervention and Expertise**	**Compliance and Adherence**	**Analysis**	*Applicability Study*
Mazieres (2006)	Consumption of analgesics 24 weeks	●	◐	○	●	●	○	●	○	**Moderate**	○	○	○	●	**Moderate**
Mazieres (2006)	days requiring NSAIDS 24 weeks	●	◐	○	●	●	○	●	○	**Moderate**	○	○	○	●	**Moderate**
Mazieres (2006)	Mental SF-12 24 weeks	●	◐	○	●	●	○	●	○	**Moderate**	○	○	○	●	**Moderate**
Mazieres (2006)	Physical SF-12 24 weeks	●	◐	○	●	●	○	●	○	**Moderate**	○	○	○	●	**Moderate**
Mazieres (2006)	OARSI Responders 24 weeks	●	●	○	●	●	○	●	○	**Moderate**	○	○	○	●	**Moderate**
Mazieres (2006)	Adverse events 24 weeks	●	◐	○	●	●	○	●	○	**Moderate**	○	○	○	●	**Moderate**
Bourgeois (1998)	Lequesne index (400mg tid) 6 weeks	●	●	○	●	●	●	●	○	**Moderate**	○	○	●	●	**Moderate**

●: Domain free of flaws

○: Domain flaws present

◐: Moderate power

Study	*Outcome*	**Prospective**	**Power**	**Group Assignment**	**Blinding**	**Group Comparability**	**Treatment Integrity**	**Measurement**	**Investigator Bias**	*Quality*	**Participants**	**Intervention and Expertise**	**Compliance and Adherence**	**Analysis**	*Applicability Study*
Bourgeois (1998)	Lequesne index (1200mg) 13 weeks	●	●	○	●	●	●	●	○	**Moderate**	○	○	●	●	**Moderate**
Bourgeois (1998)	Lequesne index (400mg tid) 13 weeks	●	●	○	●	●	●	●	○	**Moderate**	○	○	●	●	**Moderate**
Bucsi and Poor (1998)	VAS Pain 1 month	●	●	○	●	●	●	●	○	**Moderate**	○	○	●	●	**Moderate**
Bucsi and Poor (1998)	VAS Pain 3 months	●	●	○	●	●	●	●	○	**Moderate**	○	○	●	●	**Moderate**
Bucsi and Poor (1998)	VAS Pain 6 months	●	●	○	●	●	●	●	○	**Moderate**	○	○	●	●	**Moderate**
Mazieres	VAS effect of OAK	●	◐	○	●	●	●	●	○	**Moderate**	○	○	●	○	**Moderate**

●: Domain free of flaws

○: Domain flaws present

◐: Moderate power

Study	*Outcome*	**Prospective**	**Power**	**Group Assignment**	**Blinding**	**Group Comparability**	**Treatment Integrity**	**Measurement**	**Investigator Bias**	*Quality*	**Participants**	**Intervention and Expertise**	**Compliance and Adherence**	**Analysis**	*Applicability Study*
(2001)	on daily living														
Mazieres (2001)	Change in Lequesne index	●	●	○	●	●	●	●	○	**Moderate**	○	○	●	○	**Moderate**
Mazierez (2001)	VAS Pain with Activity	●	●	○	●	●	●	●	○	**Moderate**	○	○	●	○	**Moderate**
Mazierez (2001)	Change in VAS Pain at Rest	●	●	○	●	●	●	●	○	**Moderate**	○	○	●	○	**Moderate**
Moller (2010)	VAS Pain 1 month	●	●	○	●	○	●	●	○	**Moderate**	○	○	●	○	**Moderate**
Moller (2010)	VAS Pain 2 months	●	●	○	●	○	●	●	○	**Moderate**	○	○	●	○	**Moderate**
Moller (2010)	VAS Pain 3 months	●	●	○	●	○	●	●	○	**Moderate**	○	○	●	○	**Moderate**

●: Domain free of flaws

○: Domain flaws present

◐: Moderate power

Study	*Outcome*	**Prospective**	**Power**	**Group Assignment**	**Blinding**	**Group Comparability**	**Treatment Integrity**	**Measurement**	**Investigator Bias**	*Quality*	**Participants**	**Intervention and Expertise**	**Compliance and Adherence**	**Analysis**	*Applicability Study*
Moller (2010)	Lequesne index 1 month	●	●	○	●	○	●	●	○	**Moderate**	○	○	●	○	**Moderate**
Moller (2010)	Lequesne index 2 months	●	●	○	●	○	●	●	○	**Moderate**	○	○	●	○	**Moderate**
Moller (2010)	Lequesne index 3 months	●	●	○	●	○	●	●	○	**Moderate**	○	○	●	○	**Moderate**
Moller(2010)	SF-36 Mental Function	●	◐	○	●	○	●	●	○	**Moderate**	○	○	●	○	**Moderate**
Moller(2010)	SF-36 Physical Function	●	○	○	●	○	●	●	○	**Moderate**	○	○	●	○	**Moderate**
Uebelhart (2004)	VAS Pain 3 months	●	●	○	●	●	●	●	○	**High**	○	○	●	●	**Moderate**

●: Domain free of flaws

○: Domain flaws present

◐: Moderate power

Study	*Outcome*	**Prospective**	**Power**	**Group Assignment**	**Blinding**	**Group Comparability**	**Treatment Integrity**	**Measurement**	**Investigator Bias**	*Quality*	**Participants**	**Intervention and Expertise**	**Compliance and Adherence**	**Analysis**	*Applicability Study*
Uebelhart (2004)	VAS Pain 6 months	●	●	○	●	●	●	●	○	**High**	○	○	●	●	**Moderate**
Uebelhart (2004)	VAS Pain 9 months	●	●	●	●	●	●	●	○	**High**	○	○	●	●	**Moderate**
Uebelhart (2004)	VAS Pain 12 months	●	●	●	●	●	●	●	○	**High**	○	○	●	●	**Moderate**
Uebelhart (2004)	Lequesne index 3 months	●	◐	●	●	●	●	●	○	**High**	○	○	●	●	**Moderate**
Uebelhart (2004)	Lequesne index 6 months	●	◐	●	●	●	●	●	○	**High**	○	○	●	●	**Moderate**
Uebelhart (2004)	Lequesne index 9 months	●	◐	●	●	●	●	●	○	**High**	○	○	●	●	**Moderate**

●: Domain free of flaws

○: Domain flaws present

◐: Moderate power

Study	*Outcome*	**Prospective**	**Power**	**Group Assignment**	**Blinding**	**Group Comparability**	**Treatment Integrity**	**Measurement**	**Investigator Bias**	*Quality*	**Participants**	**Intervention and Expertise**	**Compliance and Adherence**	**Analysis**	*Applicability Study*
Uebelhart (2004)	Lequesne index 12 months	●	◐	●	●	●	●	●	○	**High**	○	○	●	●	**Moderate**
Bourgeois (1998)	VAS Pain (1200mg) 6 weeks	●	●	○	●	●	●	●	○	**Moderate**	○	○	●	●	**Moderate**
Kahan (2003)	Patient Global Assessment 26 weeks	●	●	●	●	●	●	●	○	**High**	○	○	○	●	**Moderate**
Kahan (2003)	Physician Global Assessment 26 weeks	●	◐	●	●	●	●	●	○	**High**	○	○	○	●	**Moderate**
Pavelka (2010)	WOMAC Total week 4	●	●	○	●	○	●	●	○	**Moderate**	○	○	●	●	**Moderate**
Pavelka (2010)	WOMAC Total week 8	●	●	○	●	○	●	●	○	**Moderate**	○	○	●	●	**Moderate**

●: Domain free of flaws

○: Domain flaws present

◐: Moderate power

Study	*Outcome*	**Prospective**	**Power**	**Group Assignment**	**Blinding**	**Group Comparability**	**Treatment Integrity**	**Measurement**	**Investigator Bias**	*Quality*	**Participants**	**Intervention and Expertise**	**Compliance and Adherence**	**Analysis**	*Applicability Study*
Pavelka (2010)	WOMAC Total week 12	●	●	○	●	○	●	●	○	**Moderate**	○	○	●	●	**Moderate**
Pavelka (2010)	WOMAC Total week 24	●	●	○	●	○	●	●	○	**Moderate**	○	○	●	●	**Moderate**
Pavelka (2010)	WOMAC Total week 32	●	●	○	●	○	●	●	○	**Moderate**	○	○	●	●	**Moderate**
Pavelka (2010)	WOMAC Stiffness week 4	●	●	○	●	○	●	●	○	**Moderate**	○	○	●	●	**Moderate**
Pavelka (2010)	WOMAC Stiffness week 8	●	●	○	●	○	●	●	○	**Moderate**	○	○	●	●	**Moderate**
Pavelka (2010)	WOMAC Stiffness week 12	●	●	○	●	○	●	●	○	**Moderate**	○	○	●	●	**Moderate**

●: Domain free of flaws

○: Domain flaws present

◐: Moderate power

Study	*Outcome*	**Prospective**	**Power**	**Group Assignment**	**Blinding**	**Group Comparability**	**Treatment Integrity**	**Measurement**	**Investigator Bias**	*Quality*	**Participants**	**Intervention and Expertise**	**Compliance and Adherence**	**Analysis**	*Applicability Study*
Pavelka (2010)	WOMAC Stiffness week 24	●	●	○	●	○	●	●	○	**Moderate**	○	○	●	●	**Moderate**
Pavelka (2010)	WOMAC Stiffness week 32	●	●	○	●	○	●	●	○	**Moderate**	○	○	●	●	**Moderate**
Pavelka (2010)	WOMAC Pain week 4	●	●	○	●	○	●	●	○	**Moderate**	○	○	●	●	**Moderate**
Pavelka (2010)	WOMAC Pain week 8	●	●	○	●	○	●	●	○	**Moderate**	○	○	●	●	**Moderate**
Pavelka (2010)	WOMAC Pain week 12	●	●	○	●	○	●	●	○	**Moderate**	○	○	●	●	**Moderate**
Pavelka (2010)	WOMAC Pain week 24	●	●	○	●	○	●	●	○	**Moderate**	○	○	●	●	**Moderate**

●: Domain free of flaws

○: Domain flaws present

◐: Moderate power

Study	*Outcome*	**Prospective**	**Power**	**Group Assignment**	**Blinding**	**Group Comparability**	**Treatment Integrity**	**Measurement**	**Investigator Bias**	*Quality*	**Participants**	**Intervention and Expertise**	**Compliance and Adherence**	**Analysis**	*Applicability Study*
Pavelka (2010)	WOMAC Pain week 32	●	●	○	●	○	●	●	○	**Moderate**	○	○	●	●	**Moderate**
Pavelka (2010)	WOMAC Function week 4	●	●	○	●	○	●	●	○	**Moderate**	○	○	●	●	**Moderate**
Pavelka (2010)	WOMAC Function week 8	●	●	○	●	○	●	●	○	**Moderate**	○	○	●	●	**Moderate**
Pavelka (2010)	WOMAC Function week 12	●	●	○	●	○	●	●	○	**Moderate**	○	○	●	●	**Moderate**
Pavelka (2010)	WOMAC Function week 24	●	●	○	●	○	●	●	○	**Moderate**	○	○	●	●	**Moderate**
Pavelka (2010)	WOMAC Function week 32	●	●	○	●	○	●	●	○	**Moderate**	○	○	●	●	**Moderate**

●: Domain free of flaws

○: Domain flaws present

◐: Moderate power

Study	*Outcome*	**Prospective**	**Power**	**Group Assignment**	**Blinding**	**Group Comparability**	**Treatment Integrity**	**Measurement**	**Investigator Bias**	*Quality*	**Participants**	**Intervention and Expertise**	**Compliance and Adherence**	**Analysis**	*Applicability Study*
Pavelka (2010)	Pain on movement (VAS) week 4	●	●	○	●	○	●	●	○	**Moderate**	○	○	●	●	**Moderate**
Pavelka (2010)	Pain on movement (VAS) week 8	●	●	○	●	○	●	●	○	**Moderate**	○	○	●	●	**Moderate**
Pavelka (2010)	Pain on movement (VAS) week 12	●	●	○	●	○	●	●	○	**Moderate**	○	○	●	●	**Moderate**
Pavelka (2010)	Pain on movement (VAS) week 24	●	●	○	●	○	●	●	○	**Moderate**	○	○	●	●	**Moderate**
Pavelka (2010)	Pain on movement (VAS) week 32	●	●	○	●	○	●	●	○	**Moderate**	○	○	●	●	**Moderate**
Pavelka (2010)	Lequesne index week 4	●	◐	○	●	○	●	●	○	**Moderate**	○	○	●	●	**Moderate**

●: Domain free of flaws

○: Domain flaws present

◐: Moderate power

Study	*Outcome*	**Prospective**	**Power**	**Group Assignment**	**Blinding**	**Group Comparability**	**Treatment Integrity**	**Measurement**	**Investigator Bias**	*Quality*	**Participants**	**Intervention and Expertise**	**Compliance and Adherence**	**Analysis**	*Applicability Study*
Pavelka (2010)	Lequesne index week 8	●	◐	○	●	○	●	●	○	**Moderate**	○	○	●	●	**Moderate**
Pavelka (2010)	Lequesne index week 12	●	◐	○	●	○	●	●	○	**Moderate**	○	○	●	●	**Moderate**
Pavelka (2010)	Lequesne index week 24	●	◐	○	●	○	●	●	○	**Moderate**	○	○	●	●	**Moderate**
Pavelka (2010)	Lequesne index week 32	●	◐	○	●	○	●	●	○	**Moderate**	○	○	●	●	**Moderate**
Pavelka (2010)	Rescue medication, mean tablets/day week 4	●	◐	○	●	○	●	●	○	**Moderate**	○	○	●	●	**Moderate**
Pavelka (2010)	Rescue medication, mean tablets/day	●	◐	○	●	○	●	●	○	**Moderate**	○	○	●	●	**Moderate**

●: Domain free of flaws

○: Domain flaws present

◐: Moderate power

Study	*Outcome*	**Prospective**	**Power**	**Group Assignment**	**Blinding**	**Group Comparability**	**Treatment Integrity**	**Measurement**	**Investigator Bias**	*Quality*	**Participants**	**Intervention and Expertise**	**Compliance and Adherence**	**Analysis**	*Applicability Study*
	week 8														
Pavelka (2010)	Rescue medication, mean tablets/day week 12	●	◐	○	●	○	●	●	○	**Moderate**	○	○	●	●	**Moderate**
Pavelka (2010)	Rescue medication, mean tablets/day week 24	●	◐	○	●	○	●	●	○	**Moderate**	○	○	●	●	**Moderate**
Pavelka (2010)	Rescue medication, mean tablets/day week 32	●	◐	○	●	○	●	●	○	**Moderate**	○	○	●	●	**Moderate**
Pavelka (2010)	VAS Pain at rest week 4	●	●	○	●	○	●	●	○	**Moderate**	○	○	●	●	**Moderate**

●: Domain free of flaws

○: Domain flaws present

◐: Moderate power

Study	*Outcome*	**Prospective**	**Power**	**Group Assignment**	**Blinding**	**Group Comparability**	**Treatment Integrity**	**Measurement**	**Investigator Bias**	*Quality*	**Participants**	**Intervention and Expertise**	**Compliance and Adherence**	**Analysis**	*Applicability Study*
Pavelka (2010)	VAS Pain at rest week 8	●	●	○	●	○	●	●	○	**Moderate**	○	○	●	●	**Moderate**
Pavelka (2010)	VAS Pain at rest week 12	●	●	○	●	○	●	●	○	**Moderate**	○	○	●	●	**Moderate**
Pavelka (2010)	VAS Pain at rest week 24	●	●	○	●	○	●	●	○	**Moderate**	○	○	●	●	**Moderate**
Pavelka (2010)	VAS Pain at rest week 32	●	●	○	●	○	●	●	○	**Moderate**	○	○	●	●	**Moderate**

FINDINGS

Table 124. Glucosamine Versus Placebo: Pain

Study	Outcome	N	Power to Detect MCII	Week	Group 1	Group 2	SMD (Odds Ratio When Indicated)	Sig	Clinical Importance	Strength of Evidence
Cibere (2004)	WOMAC Pain on walking	137	Unclear	26	Glucosamine Sulfate	Placebo	.13 (-.21,.47)	No	N/A	High
Cibere (2004)	WOMAC Pain	137	No	26	Glucosamine Sulfate	Placebo	.03 (-.31,.36)	No	Inconclusive	High
Hughes (2002)	WOMAC Pain	75	Unclear	26	Glucosamine Sulfate	Placebo	.06 (-.39, .52)	No	Inconclusive	High
Rindone (2000)	VAS Walking Pain	98	Yes	4	Glucosamine	Placebo	.08 (-.32, .48)	No	N/A	Moderate
Rindone (2000)	VAS Walking Pain	98	Yes	8	Glucosamine	Placebo	.00 (-.4, .4)	No	N/A	Moderate
Rindone (2000)	VAS Resting Pain	98	Yes	4	Glucosamine	Placebo	-.08 (-.47, .32)	No	N/A	Moderate
Rindone (2000)	VAS Resting Pain	98	Yes	8	Glucosamine	Placebo	-.08 (-.48 , .32)	No	N/A	Moderate
McAlindon (2004)	WOMAC Pain	205	Yes	12	Glucosamine Sulfate/Glucosamine HCL	Placebo	-.14 (-.41, .14)	No	Inconclusive	High
Reginster (2001)	WOMAC Pain	212	Yes	156	Glucosamine Sulfate	Placebo	-.21 (-.48, .06)	No	Inconclusive	High
Houpt	WOMAC Pain	98	No	8	Glucosamine HCL	Placebo	-.12 (-.52, .27)	No	Inconclusive	Moderate

Study	Outcome	N	Power to Detect MCII	Week	Group 1	Group 2	SMD (Odds Ratio When Indicated)	Sig	Clinical Importance	Strength of Evidence
Clegg (2006)	WOMAC Pain	630	Yes	24	Glucosamine	Placebo	0.03 (-0.13,0.18)	No	True negative	Moderate
Clegg (2006)	Health Assessment Questionnaire-Pain	630	Yes	24	Glucosamine	Placebo	0.03 (-0.13, .18)	No	True negative	Moderate

Table 125. Glucosamine Versus Placebo: Function

Study	Outcome	N	Power to Detect MCII	Week	Group 1	Group 2	SMD (Odds Ratio When Indicated)	Sig	Clinical Importance	Strength of Evidence
McAlindon (2004)	WOMAC Function	205	Yes	12	Glucosamine Sulfate/Glucosamine HCL	Placebo	.06 (-.21, .34)	No	Negative	High
Hughes (2002)	WOMAC Function	75	Unclear	26	Glucosamine Sulfate	Placebo	.11(-.34, .57)	No	Inconclusive	High
Cibere (2004)	WOMAC Function	137	No	26	Glucosamine Sulfate	Placebo	-.02 (-.32, .35)	No	Negative	High
Houpt (1999)	WOMAC Function	98	Yes	8	Glucosamine HCL	Placebo	-.08 (-.48, .32)	No	Inconclusive	Moderate

Study	Outcome	N	Power to Detect MCII	Week	Group 1	Group 2	SMD (Odds Ratio When Indicated)	Sig	Clinical Importance	Strength of Evidence
Clegg (2006)	WOMAC Function	630	Yes	24	Glucosamine	Placebo	0.01 (-0.14,0.17)	No	True negative	Moderate
Clegg (2006)	HAQ Alternative Disability Score	630	Yes	24	Glucosamine	Placebo	-0.06 (-0.21, 0.1)	No	Unclear	Moderate

Table 126. Glucosamine Versus Placebo: WOMAC Stiffness

Study	Outcome	N	Power to Detect MCII	Week	Group 1	Group 2	SMD (Odds Ratio When Indicated)	Sig	Clinical Importance	Strength of Evidence
Cibere (2004)	WOMAC Function	137	No	26	Glucosamine Sulfate	Placebo	-.09(-.42, .25)	No	Inconclusive	High
Hughes (2002)	WOMAC Stiffness	75	Unclear	26	Glucosamine Sulfate	Placebo	.14(-.32, .59)	No	Inconclusive	High
McAlindon (2004)	WOMAC Stiffness	205	Yes	12	Glucosamine Sulfate/Glucosamine HCL	Placebo	-.06(-.34, .21)	No	Negative	High
Houpt (1999)	WOMAC Stiffness	98	No	8	Glucosamine HCL	Placebo	-.19(-.59, .21)	No	Inconclusive	Moderate
Clegg (2006)	WOMAC Stiffness	630	Yes	24	Glucosamine	Placebo	0.03 (-0.12, 0.19)	No	True negative	Moderate

Table 127. Glucosamine Versus Placebo: WOMAC Total

Study	Outcome	N	Power to Detect MCII	Week	Group 1	Group 2	SMD (Odds Ratio When Indicated)	Sig	Clinical Importance	Strength of Evidence
Pavelka (2002)	WOMAC Total	203	Yes	156	Glucosamine Sulfate	Placebo	-.35(-.63, -.08)	Favors Glucosamine Sulfate	Possibly clinically important	Moderate
Cibere (2004)	WOMAC Total	137	No	26	Glucosamine Sulfate	Placebo	.01(-.33, .34)	No	Negative	High
McAlindon (2004)	WOMAC Total	205	Yes	12	Glucosamine Sulfate/ Glucosamine HCL	Placebo	.00	No	Negative	High
Houpt	WOMAC Total	98	No	8	Glucosamine HCL	Placebo	-.10(-.50, .30)	No	Inconclusive	Moderate
Reginster (2001)	WOMAC Total	212	yes	156	Glucosamine Sulfate	Placebo	-.19 (-.46, .08)	No	Inconclusive	High
Clegg (2006)	WOMAC Total	630	Yes	24	Glucosamine	Placebo	0.03 (-0.13, 0.18)	No	True negative	Moderate

Table 128. Glucosamine Versus Placebo: Other Outcomes

Study	Outcome	N	Power	Week	Group 1	Group 2	SMD (Odds Ratio When Indicated)	Sig	Clinical Importance	Strength of Evidence
Pavelka (2002)	Lequesne index	101	Yes	156	Glucosamine Sulfate	Placebo	-.42(-.70, -.14)	Favors GS	N/A	Moderate
Noack (1994)	Lequesne index	252	Unclear	4	Glucosamine Sulfate	Placebo	-0.2 (-0.44, 0.05)	No	N/A	Moderate
Das (2000)	Lequesne index	72	Unclear	4	Glucosamine HCL plus Sodium Chondroitin plus Manganese Ascorbate	Placebo	-.23(-.695, .235)	No	N/A	Moderate
Das (2000)	Lequesne index	72	Unclear	8	Glucosamine HCL plus Sodium Chondroitin plus Manganese Ascorbate	Placebo	-.55(-1.02, -.075)	Yes	N/A	Moderate
Das (2000)	Lequesne index	72	Unclear	13	Glucosamine HCL plus Sodium Chondroitin plus Manganese Ascorbate	Placebo	-.44(-.907, .031)	No	N/A	Moderate

Study	Outcome	N	Power	Week	Group 1	Group 2	SMD (Odds Ratio When Indicated)	Sig	Clinical Importance	Strength of Evidence
Clegg (2006)	Patient Global Assessment of Response to Therapy	630	Yes	24	Glucosamine	Placebo	2.9 (2.68, 3.12)	Yes	Unclear	Moderate
Clegg (2006)	Patient Global Assessment of Disease Status	630	Unclear	24	Glucosamine	Placebo	0.05 (-0.11, 0.2)	No	Unclear	Moderate
Clegg (2006)	Physician Global Assessment of Disease Status	630	Unclear	24	Glucosamine	Placebo	0.1 (-0.06, 0.26)	No	Unclear	Moderate
Clegg (2006)	Number of 500-mg tablets of Acetaminophen	630	Unclear	24	Glucosamine	Placebo	-0.06 (-0.21, 0.1)	No	Unclear	Moderate

Table 129 Glucosamine HCL Plus Sodium Chondroitin Plus Manganese Ascorbate Versus Placebo: Patient Global Assessment

Study	Outcome	N	Power to Detect MCII	Week	Group 1	Group 2	SMD (Odds Ratio When Indicated)	Sig	Clinical Importance	Strength of Evidence
Das (2000)	Patient Global Assessment	72	Yes	4	Glucosamine HCL plus Sodium Chondroitin plus Manganese Ascorbate	Placebo	-.07(-.534, .394)	No	True negative	Moderate
Das (2000)	Patient Global Assessment	72	Yes	8	Glucosamine HCL plus Sodium Chondroitin plus Manganese Ascorbate	Placebo	-.294(-.76, .173)	No	True negative	Moderate

Table 130. Glucosamine Versus Placebo: NSAID Consumption

Study	Outcome	N	Power to Detect MCII	Week	Group 1	Group 2	SMD (Odds Ratio When Indicated)	Sig	Clinical Importance	Strength of Evidence
Novack (1994)	Daily consumption of NSAIDS	60	Unclear	4	Glucosamine	Placebo	-0.55 (-1.07, -0.04)	Favors Glucosamine	N/A	Moderate
Novack (1994)	Daily consumption of NSAIDS	60	Unclear	8	Glucosamine	Placebo	-0.9 (-1.43, -0.37)	Favors Glucosamine	N/A	Moderate

Novack (1994)	Daily consumption of NSAIDS	60	Unclear	12	Glucosamine	Placebo	-1.24 (-1.79, -0.68)	Favors Glucosamine	N/A	Moderate
Novack (1994)	Daily consumption of NSAIDS	60	Unclear	16	Glucosamine	Placebo	-1.13 (-1.68, -0.58)	Favors Glucosamine	N/A	Moderate
Novack (1994)	Daily consumption of NSAIDS	60	Unclear	20	Glucosamine	Placebo	-1.14 (-1.69, -0.59)	Favors Glucosamine	N/A	Moderate
Novack (1994)	Daily consumption of NSAIDS	60	Unclear	24	Glucosamine	Placebo	-0.82 (-1.35, -0.29)	Favors Glucosamine	N/A	Moderate

Table 131. Glucosamine Versus Placebo: Adverse Events

Study	Outcome	N	Power to Detect MCII	week	Group 1	Group 2	SMD (Odds Ratio When Indicated)	Sig	Clinical Importance	Strength of Evidence
Noack (1994)	Gastrointestinal disturbances	246	Unclear	4	Glucosamine	Placebo	OR=.83 (.24, 2.78)	No	N/A	Moderate
Noack (1994)	Pruritus or Skin reaction	249	Unclear	4	Glucosamine	Placebo	OR=.328 (.03, 3.19)	No	N/A	Moderate
Noack (1994)	Headache	250	Unclear	4	Glucosamine	Placebo	OR=1(.14, 7.21)	No	N/A	Moderate
Noack (1994)	Circulatory disturbances	250	Unclear	4	Glucosamine	Placebo	OR=.2(.009, 4.14)	No	N/A	Moderate
Noack (1994)	Total adverse events	239	Unclear	4	Glucosamine	Placebo	OR=.59 (.24 ,1.48)	No	N/A	Moderate

Table 132. Glucosamine Versus Reparagen: Pain

Study	Outcome	N	Power to Detect MCII	Week	Group 1	Group 2	SMD (Odds Ratio When Indicated)	Sig	Clinical Importance	Strength of Evidence
Mehta (2007)	20% decrease in WOMAC Pain and 10mm decrease in VAS Pain	95	Unclear	8	Glucosamine Sulfate	Reparagen	OR .88 (.37 ,2.08)	No	N/A	Moderate
Mehta (2007)	20% decrease in WOMAC Pain	95	Unclear	8	Glucosamine Sulfate	Reparagen	OR=.67 (.25 , 1.79)	No	N/A	Moderate

Table 133. Glucosamine Versus Enzymatic Hydrolyzed Collagen

Study	Outcome	N	Power to Detect MCII	Week	Group 1	Group 2	SMD (Odds Ratio When Indicated)	Sig	Clinical Importance	Strength of Evidence
Trc (2010)	VAS improvement 20mm	93	Yes	12	Glucosamine Sulfate	Enzymatic hydrolyzed collagen	OR= 0.27 (0.12, 0.65)	Favors enzymatic hydrolyzed collagen	N/A	Moderate
Trc (2010)	WOMAC Total 15 or more points	91	Yes	12	Glucosamine Sulfate	Enzymatic hydrolyzed collagen	OR= 0.29 (0.10, 0.83)	Favors enzymatic hydrolyzed collagen	N/A	Moderate
Trc (2010)	VAS Pain	93	Yes	12	Glucosamine Sulfate	Enzymatic hydrolyzed collagen	0.85 (0.42 ,1.27)	Favors enzymatic hydrolyzed collagen	Possibly clinically important	Moderate
Trc (2010)	VAS typical or average pain	93	Yes	12	Glucosamine Sulfate	Enzymatic hydrolyzed collagen	0.56 (0.14 ,0.97)	Favors enzymatic hydrolyzed collagen	Not clinically important	Moderate
Trc (2010)	VAS Pain level at its best	93	Yes	12	Glucosamine Sulfate	Enzymatic hydrolyzed collagen	0.43 (0.02 ,0.85)	Favors enzymatic hydrolyzed collagen	Not clinically important	Moderate
Trc (2010)	VAS Pain level at its worst	93	Yes	12	Glucosamine Sulfate	Enzymatic hydrolyzed collagen	0.83 (0.41 ,1.26)	Favors enzymatic hydrolyzed collagen	Possibly clinically important	Moderate

Table 134. Chondroitin Sulfate Versus Placebo: Pain

Study	Outcome	N	Sufficient Power	Week	Group 1	Group 2	SMD (Odds Ratio When Indicated)	Sig	Clinical Importance	Strength of Evidence
Bourgeois (1998)	VAS Pain	84	Yes	6	Chondroitin Sulfate (1200mg qd)	Placebo	-0.85 (-1.30, -0.40)	Favors CS	Possibly clinically significant	Moderate
Bourgeois (1998)	VAS Pain	87	Yes	6	Chondroitin Sulfate (400mg tid)	Placebo	-0.72 (-1.15, -0.28)	Favors CS	Not clinically significant	Moderate
Bourgeois (1998)	VAS Pain	84	Yes	13	Chondroitin Sulfate (1200mg qd)	Placebo	-0.90 (-1.35, -0.45)	Favors CS	Possibly clinically significant	Moderate
Bourgeois (1998)	VAS Pain	87	Yes	13	Chondroitin Sulfate (400mg tid)	Placebo	-0.89 (-1.33, -0.45)	Favors CS	Possibly clinically significant	Moderate
Moller (2010)	VAS Pain	116	Yes	4	Chondroitin Sulfate	Placebo	-2.58 (-3.08 ,-2.09)	Favors CS	Clinically important	Moderate
Moller (2010)	VAS Pain	116	Yes	8	Chondroitin Sulfate	Placebo	-1.99(-2.44 , -1.54)	Favors CS	Clinically important	Moderate
Moller (2010)	VAS Pain	116	Yes	12	Chondroitin Sulfate	Placebo	-4.15(-4.80 , -3.5)	Favors CS	Clinically important	Moderate
Bucsi and Poor (1998)	VAS Pain	85	Yes	4	Chondroitin Sulfate	Placebo	-.28(-.71 , .15)	No	N/A	Moderate
Bucsi and Poor (1998)	VAS Pain	85	Yes	12	Chondroitin Sulfate	Placebo	-.64 (-1.07, -.20)	Favors CS	Possibly clinically significant	Moderate

Study	Outcome	N	Sufficient Power	Week	Group 1	Group 2	SMD (Odds Ratio When Indicated)	Sig	Clinical Importance	Strength of Evidence
Bucsi and Poor (1998)	VAS Pain	85	Yes	24	Chondroitin Sulfate	Placebo	-.92 (-1.37 , -.47)	Favors CS	Clinically important	Moderate
Uebelhart (2004)	VAS Pain	110	Yes	13	Chondroitin Sulfate	Placebo	-.26 (-.63 , .12)	No	True negative	High
Uebelhart (2004)	VAS Pain	110	Yes	26	Chondroitin Sulfate	Placebo	-.28(-.65 , .10)	No	N/A	High
Uebelhart (2004)	VAS Pain	110	Yes	39	Chondroitin Sulfate	Placebo	-.45(-.83 , -.07)	Favors CS	Possibly clinically significant	High
Uebelhart (2004)	VAS Pain	110	Yes	52	Chondroitin Sulfate	Placebo	-.42(-.79 , -.04)	Favors CS	Possibly clinically significant	High
Mazierez (2001)	VAS Pain with activity	130	Yes	13	Chondroitin Sulfate	Placebo	-.38 (-.73 , -.03)	Favors CS	Not clinically important	Moderate
Mazierez (2001)	Change in VAS Pain at rest	130	Yes	13	Chondroitin Sulfate	Placebo	-.25(-.6 , .09)	No	True negative	Moderate
Mazieres (2006)	VAS Pain during activity	153	Yes	4	Chondroitin Sulfate	Placebo	-0.14 (-0.36, 0.09)	No	True negative	Moderate
Mazieres (2006)	VAS Pain during activity	153	Yes	12	Chondroitin Sulfate	Placebo	-0.09 (-0.31, 0.13)	No	True negative	Moderate
Mazieres (2006)	VAS Pain during activity	153	Yes	24	Chondroitin Sulfate	Placebo	-0.21 (-0.44, 0.01)	No	True negative	Moderate
Mazieres (2006)	VAS Pain	153	Yes	24	Chondroitin Sulfate	Placebo	-0.14 (-0.36, 0.09)	No	True negative	Moderate

Study	Outcome	N	Sufficient Power	Week	Group 1	Group 2	SMD (Odds Ratio When Indicated)	Sig	Clinical Importance	Strength of Evidence
Clegg (2006)	WOMAC Pain	631	Yes	24	Chondroitin Sulfate	Placebo	0.02 (-0.14, 0.18)	No	True negative	Moderate
Clegg (2006)	HAQ Pain Score	631	Unclear	24	Chondroitin Sulfate	Placebo	0.04 (-0.11, 0.2)	No	Unclear	Moderate

Table 135. Chondroitin Sulfate Versus Placebo: Function

Study	Outcome	N	Power to Detect MCII	Week	Group 1	Group 2	SMD (Odds Ratio When Indicated)	Sig	Clinical Importance	Strength of Evidence
Mazieres (2001)	VAS effect of OAK on daily living	130	Unclear	12.85	Chondroitin Sulfate	Placebo	-.24 (-.59, .10)	No	N/A	Moderate
Moller(2010)	SF-36 Mental Function	129	Unclear	24	Chondroitin Sulfate	Placebo	-.07(-.43, .30)	No	N/A	Moderate
Mazieres (2006)	SF-12 Physical Function	24	Yes	24	Chondroitin Sulfate	Placebo	0.08 (-0.14, 0.31)	No	N/A	Moderate
Mazieres (2006)	SF-36 Mental Function	24	Yes	24	Chondroitin Sulfate	Placebo	0.21 (-0.02, 0.43)	No	N/A	Moderate
Bucsi (1998)	Walk time	85	Unclear	4	Chondroitin Sulfate	Placebo	-0.20 (-0.63, 0.23)	No	N/A	Moderate
Bucsi (1998)	Walk time	85	Unclear	12	Chondroitin Sulfate	Placebo	-0.17 (-0.60, 0.26)	No	N/A	Moderate
Bucsi (1998)	Walk time	85	Unclear	24	Chondroitin Sulfate	Placebo	-0.33 (-0.76, 0.10)	No	N/A	Moderate

Clegg (2006)	WOMAC Function	631	Yes	24	Chondroitin Sulfate	Placebo	-0.02 (-0.18, 0.13)	No	True negative	Moderate
Clegg (2006)	HAQ Alternative Disability	631	Unclear	24	Chondroitin Sulfate	Placebo	-0.03 (-0.18, 0.13)	No	Unclear	Moderate

Table 136. Chondroitin Sulfate Versus Placebo: WOMAC Stiffness

Study	Outcome	N	Power to Detect MCII	Week	Group 1	Group 2	SMD (Odds Ratio When Indicated)	Sig	Clinical Importance	Strength of Evidence
Clegg (2006)	WOMAC Stiffness	631	Yes	24	Chondroitin Sulfate	Placebo	0.1 (-0.06, 0.26)	No	True negative	Moderate

Table 137. Chondroitin Sulfate Versus Placebo: WOMAC Total

Study	Outcome	N	Power to Detect MCII	Week	Group 1	Group 2	SMD (Odds Ratio When Indicated)	Sig	Clinical Importance	Strength of Evidence
Clegg (2006)	WOMAC Total	631	Yes	24	Chondroitin Sulfate	Placebo	0.04 (-0.12, 0.2)	No	True negative	Moderate

Table 138. Chondroitin Sulfate Versus Placebo: Lequesne Index

Study	Outcome	N	Sufficient Power	Week	Group 1	Group 2	SMD (Odds Ratio When Indicated)	Sig	Clinical Importance	Strength of Evidence
Mazieres (2001)	Change in Lequesne index	130	Yes	13	Chondroitin Sulfate	Placebo	-.27(-.62, .07)	No	N/A	Moderate
Uebelhart (2004)	Lequesne index	110	Yes	13	Chondroitin Sulfate	Placebo	-.15(-.53, .22)	No	N/A	High
Uebelhart (2004)	Lequesne index	110	Yes	26	Chondroitin Sulfate	Placebo	-.21(-.59, .16)	No	N/A	High
Uebelhart (2004)	Lequesne index	110	Yes	39	Chondroitin Sulfate	Placebo	-.26(-.63, .12)	No	N/A	High
Uebelhart (2004)	Lequesne index	110	Yes	52	Chondroitin Sulfate	Placebo	-.32(-.69, .06)	No	N/A	High
Moller (2010)	Lequesne index	110	Yes	4	Chondroitin Sulfate	Placebo	.66(.29, 1.04)	Favors Placebo	N/A	Moderate
Moller (2010)	Lequesne index	110	Yes	8	Chondroitin Sulfate	Placebo	-2.24(-2.70, -1.77)	Favors CS	N/A	Moderate
Moller (2010)	Lequesne index	110	Yes	12	Chondroitin Sulfate	Placebo	-3.50(-4.08, -2.91)	Favors CS	N/A	Moderate
Mazieres (2006)	Lequesne index	4	Yes	4	Chondroitin Sulfate	Placebo	-0.04 (-0.26, 0.19)	No	N/A	Moderate
Mazieres (2006)	Lequesne index	12	Yes	12	Chondroitin Sulfate	Placebo	-0.03 (-0.25, 0.19)	No	N/A	Moderate
Mazieres (2006)	Lequesne index	24	Yes	24	Chondroitin Sulfate	Placebo	-0.14 (-0.37, 0.08)	No	N/A	Moderate

Study	Outcome	N	Sufficient Power	Week	Group 1	Group 2	SMD (Odds Ratio When Indicated)	Sig	Clinical Importance	Strength of Evidence
Bourgeois (1998)	Lequesne index	84	Yes	6	Chondroitin Sulfate (1200mg qd)	Placebo	-0.66 (-1.10, -0.22)	Favors CS	N/A	Moderate
Bourgeois (1998)	Lequesne index	87	Yes	6	Chondroitin Sulfate (400mg tid)	Placebo	-0.78 (-1.21, -0.34)	Favors CS	N/A	Moderate
Bourgeois (1998)	Lequesne index	84	Yes	13	Chondroitin Sulfate (1200mg qd)	Placebo	-0.84 (-1.28, -0.39)	Favors CS	N/A	Moderate
Bourgeois (1998)	Lequesne index	87	Yes	13	Chondroitin Sulfate (400mg tid)	Placebo	-0.84 (-1.28, -0.40)	Favors CS	N/A	Moderate

Table 139. Chondroitin Versus Placebo: Additional Analgesic Use

Study	Outcome	N	Sufficient Power	Week	Group 1	Group 2	SMD (Odds Ratio When Indicated)	Sig	Clinical Importance	Strength of Evidence
Bucsi (1998)	Paracetamol consumption	85	Unclear	4	Chondroitin Sulfate	Placebo	-0.20 (-0.63, 0.22)	No	Unclear	Moderate
Bucsi (1998)	Paracetamol consumption	85	Unclear	12	Chondroitin Sulfate	Placebo	-0.20 (-0.63, 0.23)	No	Unclear	Moderate
Bucsi (1998)	Paracetamol consumption	85	Unclear	24	Chondroitin Sulfate	Placebo	-0.44 (-0.88, -.01)	Favors Chondroitin Sulfate	Unclear	Moderate
Mazieres (2006)	Analgesic consumption	4	Yes	24	Chondroitin Sulfate	Placebo	0 (-0.22, 0.22)	No	N/A	Moderate
Mazieres (2006)	Number of days NSAIDS were taken	12	Yes	24	Chondroitin Sulfate	Placebo	-0.1 (-0.33, 0.12)	No	N/A	Moderate
Clegg (2006)	Acetaminophen consumption	631	Yes	24	Chondroitin Sulfate	Placebo	0.05 (-0.1, 0.21)	No	Unclear	Moderate

Table 140. Chondroitin Sulfate Versus Placebo: Other Outcomes

Study	Outcome	N	Sufficient Power	Week	Group 1	Group 2	SMD (Odds Ratio When Indicated)	Sig	Clinical Importance	Strength of Evidence
Mazieres (2006)	Patient Global Assessment	307	Unclear	24	Chondroitin Sulfate	Placebo	0.2 (-0.03, 0.42)	No	True negative	Moderate
Mazieres (2006)	Physician Global Assessment	307	Unclear	24	Chondroitin Sulfate	Placebo	0.21 (-0.01, 0.43)	No	N/A	Moderate

Study	Outcome	N	Sufficient Power	Week	Group 1	Group 2	SMD (Odds Ratio When Indicated)	Sig	Clinical Importance	Strength of Evidence
Mazieres (2006)	OARSI Responders	307	Yes	24	Chondroitin Sulfate	Placebo	OR= 1.67 (1.05, 2.67)	Favors Chondroitin Sulfate	Unclear	Moderate
Mazieres (2006)	Adverse Events	307	Unclear	24	Chondroitin Sulfate	Placebo	OR=.98 (.63,1.54)	No	N/A	Moderate
Kahan (2009)	Patient Global Assessment	622	Yes	26	Chondroitin Sulfate	Placebo	0.18 (0.02, 0.34)	Favors Chondroitin Sulfate	Not Clinically important	High
Kahan (2009)	Physician Global Assessment	622	Unclear	26	Chondroitin Sulfate	Placebo	0.16 (0.01, 0.32)	Favors Chondroitin Sulfate	N/A	High
Clegg (2006)	Patient Global Assessment of Response to Therapy	631	Yes	24	Chondroitin Sulfate	Placebo	2.95 (2.73, 3.18)	Yes	Unclear	Moderate
Clegg (2006)	Patient Global Assessment of Disease Status	631	Yes	24	Chondroitin Sulfate	Placebo	0.05 (-0.11, 0.2)	No	Unclear	Moderate
Clegg (2006)	Physician Global Assessment of Disease Status	631	Yes	24	Chondroitin Sulfate	Placebo	0.04 (-0.12, 0.19)	No	Unclear	Moderate

Table 141. Chondroitin Sulfate Plus Glucosamine Versus Placebo

Study	Outcome	N	Sufficient Power	Week	Group 1	Group 2	SMD (Odds Ratio When Indicated)	Sig	Clinical Importance	Strength of Evidence
Rai (2004)	Lequesne index	50	Yes	52	Chondroitin Sulfate plus Glucosamine	Placebo	Mean Difference=7.78 (p<.01)	Yes	Unclear	Moderate
Clegg (2006)	WOMAC Pain	631	Yes	24	Chondroitin Sulfate plus Glucosamine	Placebo	-0.13 (-0.28, 0.03)	No	True negative	Moderate
Clegg (2006)	WOMAC Stiffness	631	Yes	24	Chondroitin Sulfate plus Glucosamine	Placebo	-0.05 (-0.21, 0.1)	No	True negative	Moderate
Clegg (2006)	WOMAC Function	631	Yes	24	Chondroitin Sulfate plus Glucosamine	Placebo	-0.14 (-0.29, 0.02)	No	True negative	Moderate
Clegg (2006)	Normalized WOMAC	631	Yes	24	Chondroitin Sulfate plus Glucosamine	Placebo	-0.11 (-0.27, 0.04)	No	True negative	Moderate
Clegg (2006)	HAQ Alternative Disability	631	Yes	24	Chondroitin Sulfate plus Glucosamine	Placebo	-0.11 (-0.26, 0.05)	No	Unclear	Moderate
Clegg (2006)	HAQ Pain	631	Yes	24	Chondroitin Sulfate plus Glucosamine	Placebo	-0.15 (-0.3, 0.01)	No	Unclear	Moderate
Clegg (2006)	Patient Global Assessment of Response to Therapy	631	Yes	24	Chondroitin Sulfate plus Glucosamine	Placebo	2.9 (2.67, 3.12)	Yes	Unclear	Moderate

Clegg (2006)	Patient Global Assessment of Disease Status	631	Unclear	24	Chondroitin Sulfate plus Glucosamine	Placebo	-0.08 (-0.23, 0.08)	No	Unclear	Moderate
Clegg (2006)	Physician Global Assessment of Disease Status	631	Unclear	24	Chondroitin Sulfate plus Glucosamine	Placebo	-0.04 (-0.2, 0.12)	No	Unclear	Moderate
Clegg (2006)	Acetaminophen consumption	631	Unclear	24	Chondroitin Sulfate plus Glucosamine	Placebo	-0.06 (-0.21, 0.1)	No	Unclear	Moderate

Table 142. Chondroitin Sulfate Plus Glucosamine: Stratified By Severity (Clegg 2006)

Severity Subgroup	Outcome	N	Sufficient Power	Week	Group 1	Group 2	Odds Ratio	Sig	Strength of Evidence
Mild (WOMAC Pain 5-12)	20% WOMAC decrease	558	Unclear	24	Chondroitin Sulfate plus Glucosamine	Placebo	1.13 (0.8, 1.59)	No	Moderate
	OMERACT-OARSI Response	488	Unclear	24	Chondroitin Sulfate plus Glucosamine	Placebo	1.16 (0.81, 1.67)	No	Moderate
	50% decrease in WOMAC Pain score	488	Unclear	24	Chondroitin Sulfate plus Glucosamine	Placebo	0.99 (0.69, 1.41)	No	Moderate
Moderate to Severe (WOMAC > 12)	20% WOMAC decrease	142	Yes	24	Chondroitin Sulfate plus Glucosamine	Placebo	3.2 (1.53, 6.69)	No	Moderate
	OMERACT-OARSI response	142	Yes	24	Chondroitin Sulfate plus Glucosamine	Placebo	3.18 (1.56, 6.46)	No	Moderate

Severity Subgroup	Outcome	N	Sufficient Power	Week	Group 1	Group 2	Odds Ratio	Sig	Strength of Evidence
	50% decrease in WOMAC Pain score	142	Yes	24	Chondroitin Sulfate plus Glucosamine	Placebo	2.28 (1.16, 4.51)	No	Moderate

Table 143. Piascledine Versus Chondroitin Sulfate

Study	Outcome	N	Sufficient Power	Week	Group 1	Group 2	SMD (Odds Ratio When Indicated)	Sig	Clinical Importance	Strength of Evidence
Pavelka (2010)	WOMAC Total	357	Yes	4	Avocado soybean unsaponifiable (Piascledine)	Chondroitin Sulfate	0.09 (-0.12, 0.3)	No	True negative	Moderate
Pavelka (2010)	WOMAC Total	357	Yes	8	Avocado soybean unsaponifiable (Piascledine)	Chondroitin Sulfate	0.09 (-0.12, 0.3)	No	True negative	Moderate
Pavelka (2010)	WOMAC Total	357	Yes	12	Avocado soybean unsaponifiable (Piascledine)	Chondroitin Sulfate	0.09 (-0.12, 0.3)	No	True negative	Moderate
Pavelka (2010)	WOMAC Total	357	Yes	24	Avocado soybean unsaponifiable (Piascledine)	Chondroitin Sulfate	0.08 (-0.12, 0.29)	No	True negative	Moderate

Study	Outcome	N	Sufficient Power	Week	Group 1	Group 2	SMD (Odds Ratio When Indicated)	Sig	Clinical Importance	Strength of Evidence
Pavelka (2010)	WOMAC Total	357	Yes	32	Avocado soybean unsaponifiable (Piascledine)	Chondroitin Sulfate	0.08 (-0.13, 0.28)	No	True negative	Moderate
Pavelka (2010)	WOMAC Stiffness	357	Yes	4	Avocado soybean unsaponifiable (Piascledine)	Chondroitin Sulfate	0.03 (-0.17, 0.24)	No	True negative	Moderate
Pavelka (2010)	WOMAC Stiffness	357	Yes	8	Avocado soybean unsaponifiable (Piascledine)	Chondroitin Sulfate	0.06 (-0.14, 0.27)	No	True negative	Moderate
Pavelka (2010)	WOMAC Stiffness	357	Yes	12	Avocado soybean unsaponifiable (Piascledine)	Chondroitin Sulfate	0.04 (-0.17, 0.25)	No	True negative	Moderate
Pavelka (2010)	WOMAC Stiffness	357	Yes	24	Avocado soybean unsaponifiable (Piascledine)	Chondroitin Sulfate	0.03 (-0.18, 0.23)	No	True negative	Moderate
Pavelka (2010)	WOMAC Stiffness	357	Yes	32	Avocado soybean unsaponifiable (Piascledine)	Chondroitin Sulfate	0.12 (-0.09, 0.33)	No	True negative	Moderate

Study	Outcome	N	Sufficient Power	Week	Group 1	Group 2	SMD (Odds Ratio When Indicated)	Sig	Clinical Importance	Strength of Evidence
Pavelka (2010)	WOMAC Pain	357	Yes	4	Avocado soybean unsaponifiable (Piascledine)	Chondroitin Sulfate	0.1 (-0.11, 0.3)	No	True negative	Moderate
Pavelka (2010)	WOMAC Pain	357	Yes	8	Avocado soybean unsaponifiable (Piascledine)	Chondroitin Sulfate	0.1 (-0.11, 0.31)	No	True negative	Moderate
Pavelka (2010)	WOMAC Pain	357	Yes	12	Avocado soybean unsaponifiable (Piascledine)	Chondroitin Sulfate	0.06 (-0.15, 0.26)	No	True negative	Moderate
Pavelka (2010)	WOMAC Pain	357	Yes	24	Avocado soybean unsaponifiable (Piascledine)	Chondroitin Sulfate	0.1 (-0.1, 0.31)	No	True negative	Moderate
Pavelka (2010)	WOMAC Pain	357	Yes	32	Avocado soybean unsaponifiable (Piascledine)	Chondroitin Sulfate	0.08 (-0.12, 0.29)	No	True negative	Moderate
Pavelka (2010)	WOMAC Function	357	Yes	4	Avocado soybean unsaponifiable (Piascledine)	Chondroitin Sulfate	0.09 (-0.12, 0.3)	No	True negative	Moderate

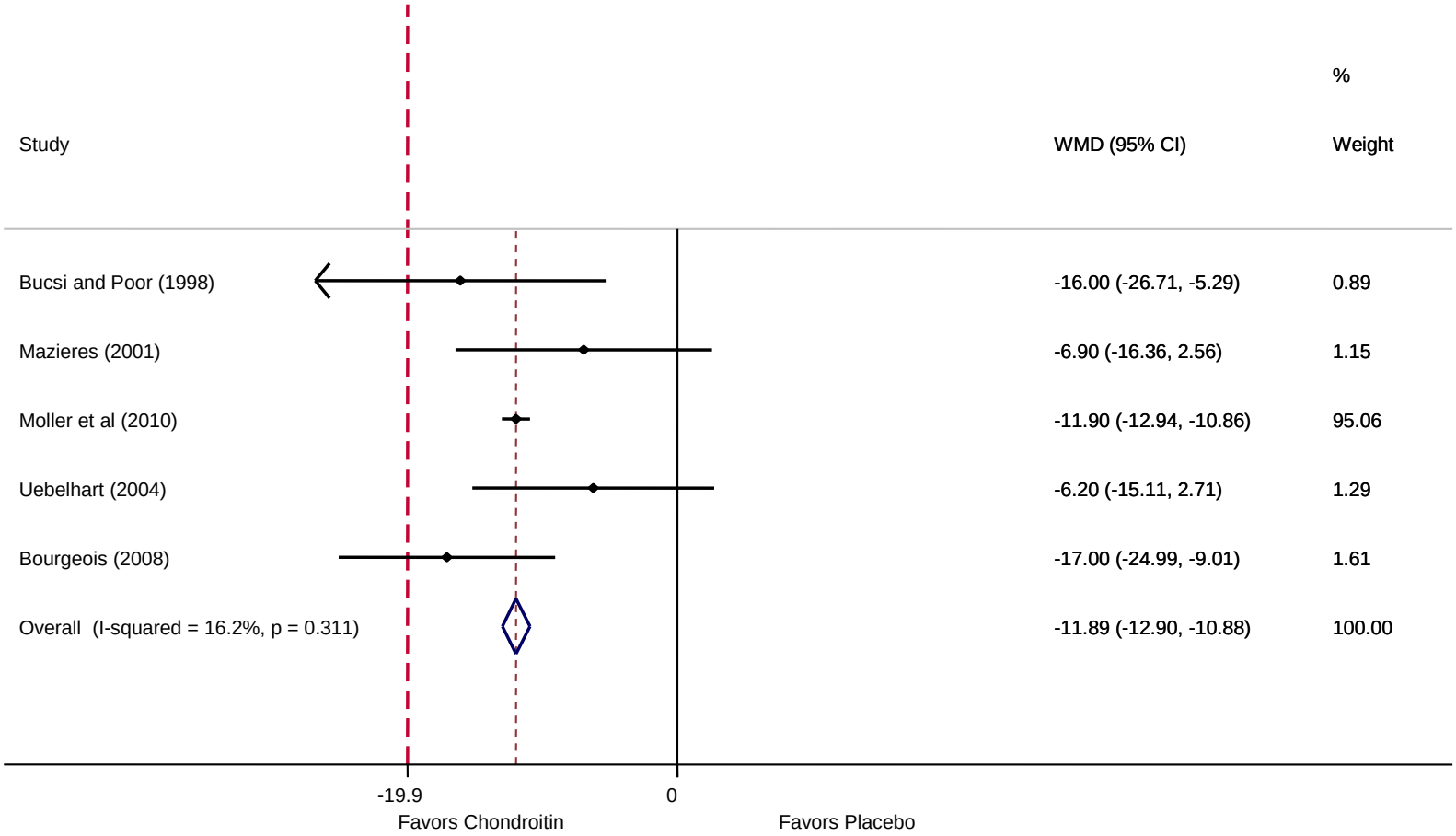
Study	Outcome	N	Sufficient Power	Week	Group 1	Group 2	SMD (Odds Ratio When Indicated)	Sig	Clinical Importance	Strength of Evidence
Pavelka (2010)	WOMAC Function	357	Yes	8	Avocado soybean unsaponifiable (Piascledine)	Chondroitin Sulfate	0.09 (-0.12, 0.29)	No	True negative	Moderate
Pavelka (2010)	WOMAC Function	357	Yes	12	Avocado soybean unsaponifiable (Piascledine)	Chondroitin Sulfate	0.1 (-0.11, 0.31)	No	True negative	Moderate
Pavelka (2010)	WOMAC Function	357	Yes	24	Avocado soybean unsaponifiable (Piascledine)	Chondroitin Sulfate	0.08 (-0.13, 0.29)	No	True negative	Moderate
Pavelka (2010)	WOMAC Function	357	Yes	32	Avocado soybean unsaponifiable (Piascledine)	Chondroitin Sulfate	0.07 (-0.14, 0.27)	No	True negative	Moderate
Pavelka (2010)	Pain on movement (VAS)	357	Yes	4	Avocado soybean unsaponifiable (Piascledine)	Chondroitin Sulfate	0.17 (-0.04, 0.38)	No	True negative	Moderate
Pavelka (2010)	Pain on movement (VAS)	357	Yes	8	Avocado soybean unsaponifiable (Piascledine)	Chondroitin Sulfate	0.09 (-0.12, 0.3)	No	True negative	Moderate

Study	Outcome	N	Sufficient Power	Week	Group 1	Group 2	SMD (Odds Ratio When Indicated)	Sig	Clinical Importance	Strength of Evidence
Pavelka (2010)	Pain on movement (VAS)	357	Yes	12	Avocado soybean unsaponifiable (Piascledine)	Chondroitin Sulfate	0.11 (-0.1, 0.32)	No	True negative	Moderate
Pavelka (2010)	Pain on movement (VAS)	357	Yes	24	Avocado soybean unsaponifiable (Piascledine)	Chondroitin Sulfate	0.1 (-0.1, 0.31)	No	True negative	Moderate
Pavelka (2010)	Pain on movement (VAS)	357	Yes	32	Avocado soybean unsaponifiable (Piascledine)	Chondroitin Sulfate	0.02 (-0.19, 0.23)	No	True negative	Moderate
Pavelka (2010)	Lequesne index	357	Unclear	4	Avocado soybean unsaponifiable (Piascledine)	Chondroitin Sulfate	0.08 (-0.13, 0.29)	No	Unclear	Moderate
Pavelka (2010)	Lequesne index	357	Unclear	8	Avocado soybean unsaponifiable (Piascledine)	Chondroitin Sulfate	0.04 (-0.17, 0.24)	No	Unclear	Moderate
Pavelka (2010)	Lequesne index	357	Unclear	12	Avocado soybean unsaponifiable (Piascledine)	Chondroitin Sulfate	0 (-0.21, 0.21)	No	Unclear	Moderate

Study	Outcome	N	Sufficient Power	Week	Group 1	Group 2	SMD (Odds Ratio When Indicated)	Sig	Clinical Importance	Strength of Evidence
Pavelka (2010)	Lequesne index	357	Unclear	24	Avocado soybean unsaponifiable (Piascledine)	Chondroitin Sulfate	0.03 (-0.18, 0.24)	No	Unclear	Moderate
Pavelka (2010)	Lequesne index	357	Unclear	32	Avocado soybean unsaponifiable (Piascledine)	Chondroitin Sulfate	0 (-0.21, 0.21)	No	Unclear	Moderate
Pavelka (2010)	Rescue medication, mean tablets/day	357	Unclear	4	Avocado soybean unsaponifiable (Piascledine)	Chondroitin Sulfate	0.03 (-0.18, 0.24)	No	Unclear	Moderate
Pavelka (2010)	Rescue medication, mean tablets/day	357	Unclear	8	Avocado soybean unsaponifiable (Piascledine)	Chondroitin Sulfate	0.03 (-0.18, 0.24)	No	Unclear	Moderate
Pavelka (2010)	Rescue medication, mean tablets/day	357	Unclear	12	Avocado soybean unsaponifiable (Piascledine)	Chondroitin Sulfate	0.02 (-0.19, 0.23)	No	Unclear	Moderate
Pavelka (2010)	Rescue medication, mean tablets/day	357	Unclear	24	Avocado soybean unsaponifiable (Piascledine)	Chondroitin Sulfate	0 (-0.21, 0.21)	No	Unclear	Moderate

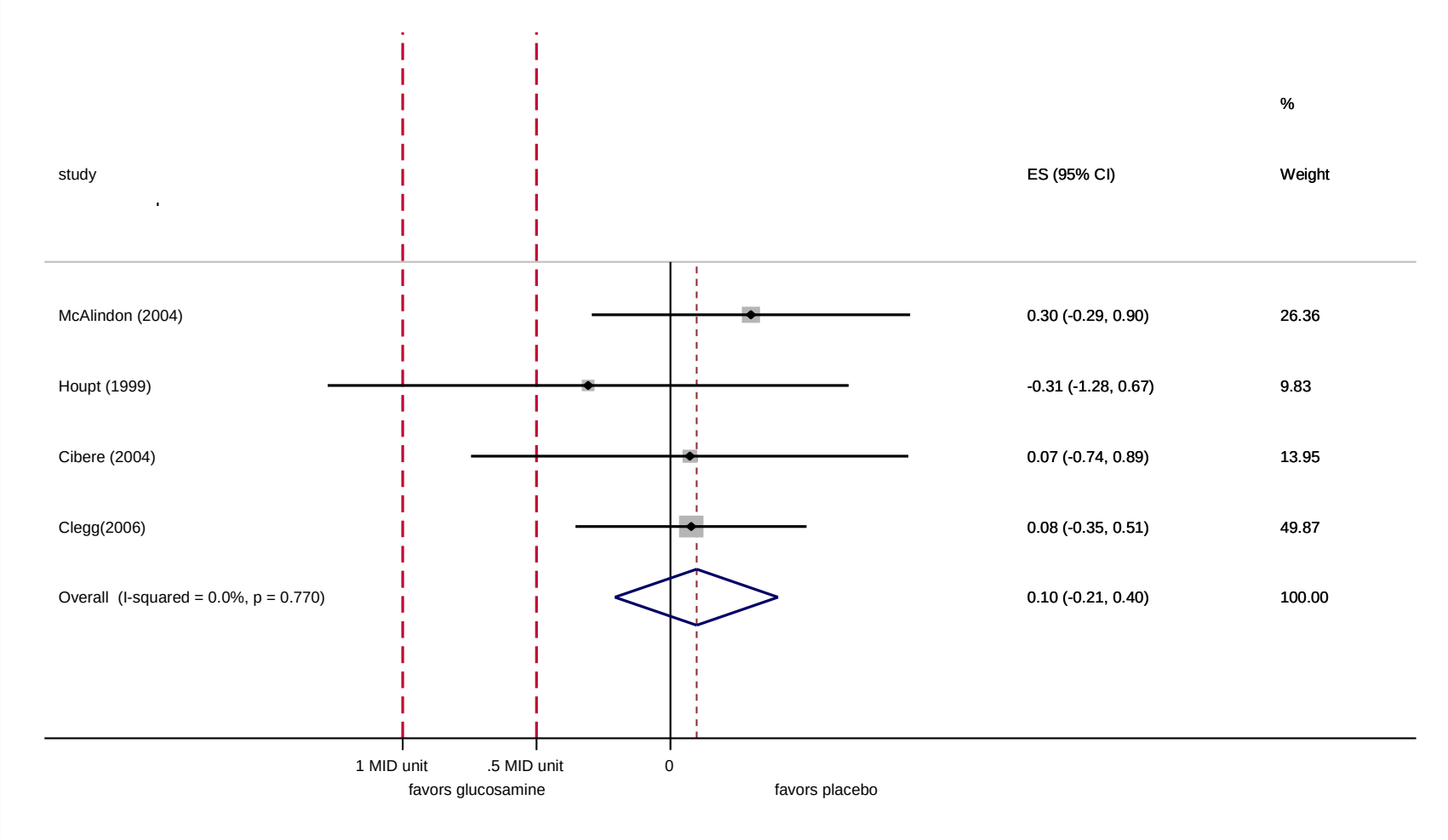
Study	Outcome	N	Sufficient Power	Week	Group 1	Group 2	SMD (Odds Ratio When Indicated)	Sig	Clinical Importance	Strength of Evidence
Pavelka (2010)	Rescue medication, mean tablets/day	357	Unclear	32	Avocado soybean unsaponifiable (Piascledine)	Chondroitin Sulfate	-0.01 (-0.22, 0.2)	No	Unclear	Moderate
Pavelka (2010)	Pain at rest (VAS)	357	Yes	4	Avocado soybean unsaponifiable (Piascledine)	Chondroitin Sulfate	0.1 (-0.11, 0.31)	No	True negative	Moderate
Pavelka (2010)	Pain at rest (VAS)	357	Yes	8	Avocado soybean unsaponifiable (Piascledine)	Chondroitin Sulfate	0.13 (-0.08, 0.33)	No	True negative	Moderate
Pavelka (2010)	Pain at rest (VAS)	357	Yes	12	Avocado soybean unsaponifiable (Piascledine)	Chondroitin Sulfate	0.16 (-0.04, 0.37)	No	True negative	Moderate
Pavelka (2010)	Pain at rest (VAS)	357	Yes	24	Avocado soybean unsaponifiable (Piascledine)	Chondroitin Sulfate	0.03 (-0.17, 0.24)	No	True negative	Moderate
Pavelka (2010)	Pain at rest (VAS)	357	Yes	32	Avocado soybean unsaponifiable (Piascledine)	Chondroitin Sulfate	0.01 (-0.2, 0.22)	No	True negative	Moderate

Figure 33. Chondroitin Sulfate Versus Placebo: VAS Pain



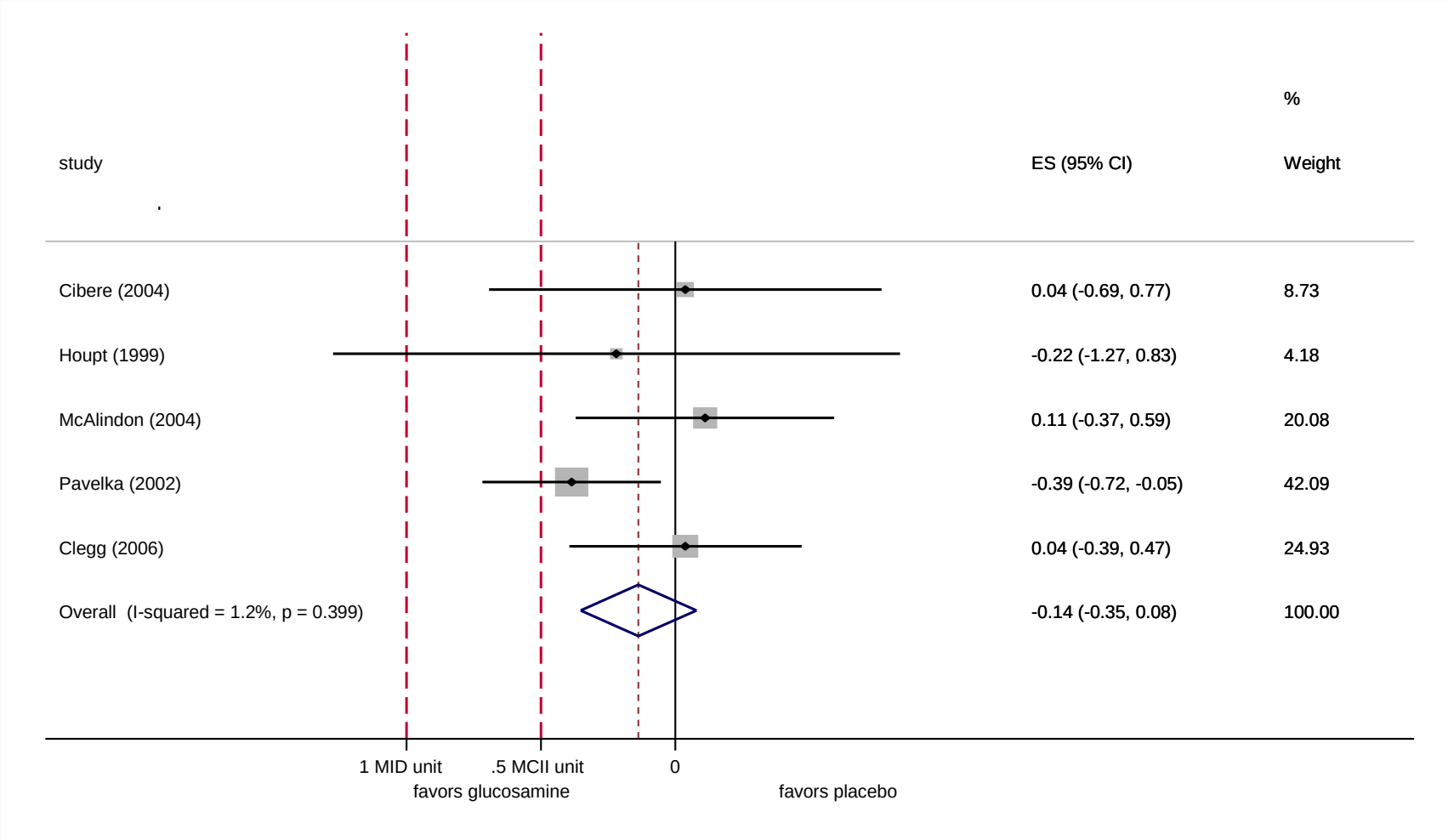
The red line indicates the MCII

Figure 34. Glucosamine Versus Placebo: WOMAC Pain in MID Units*



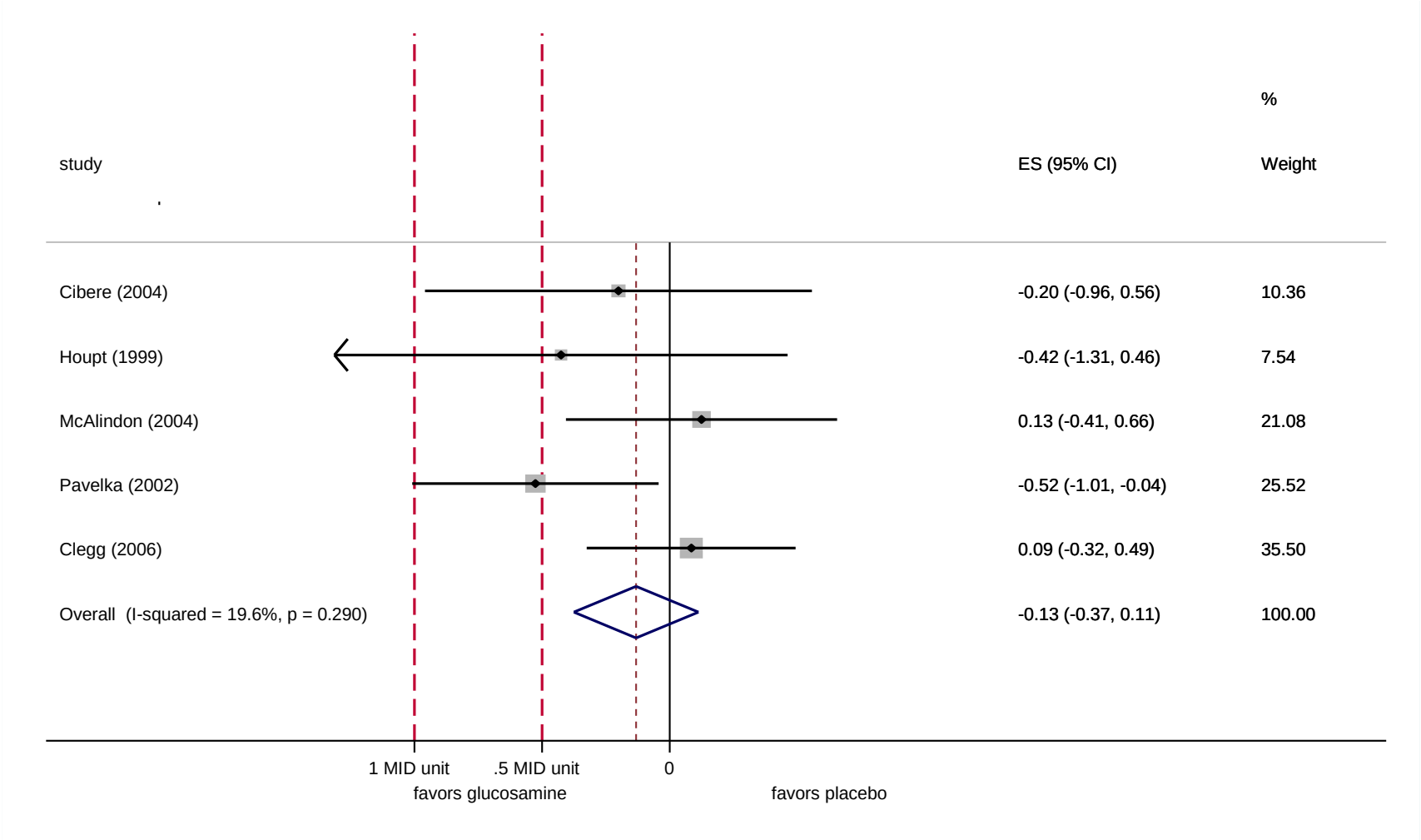
*All WOMAC scores are presented in 100mm VAS units

Figure 35. Glucosamine Versus Placebo: WOMAC Function in MID Units*



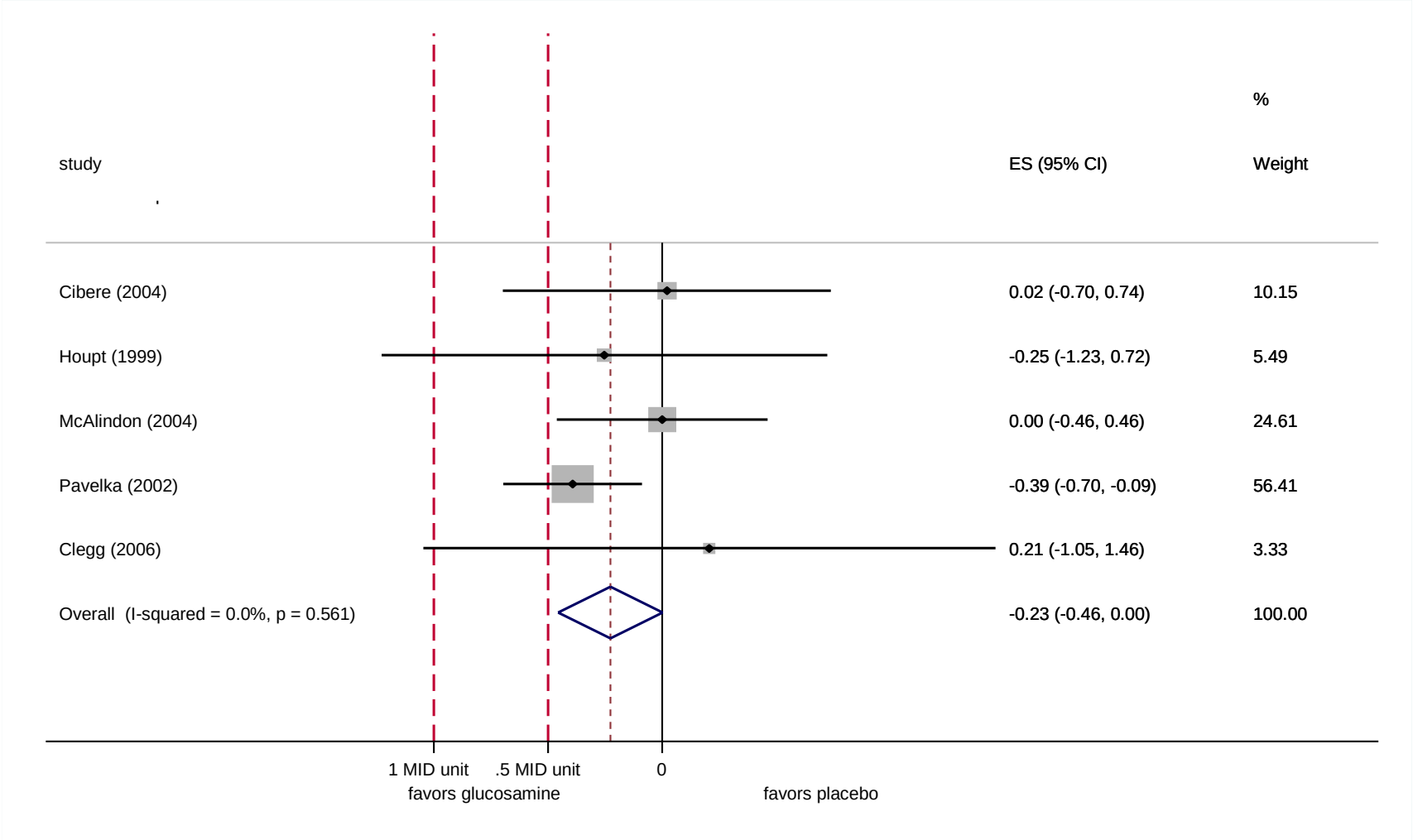
*All WOMAC scores are presented in 100mm VAS units

Figure 36. Glucosamine Versus Placebo: WOMAC Stiffness in MID Units*



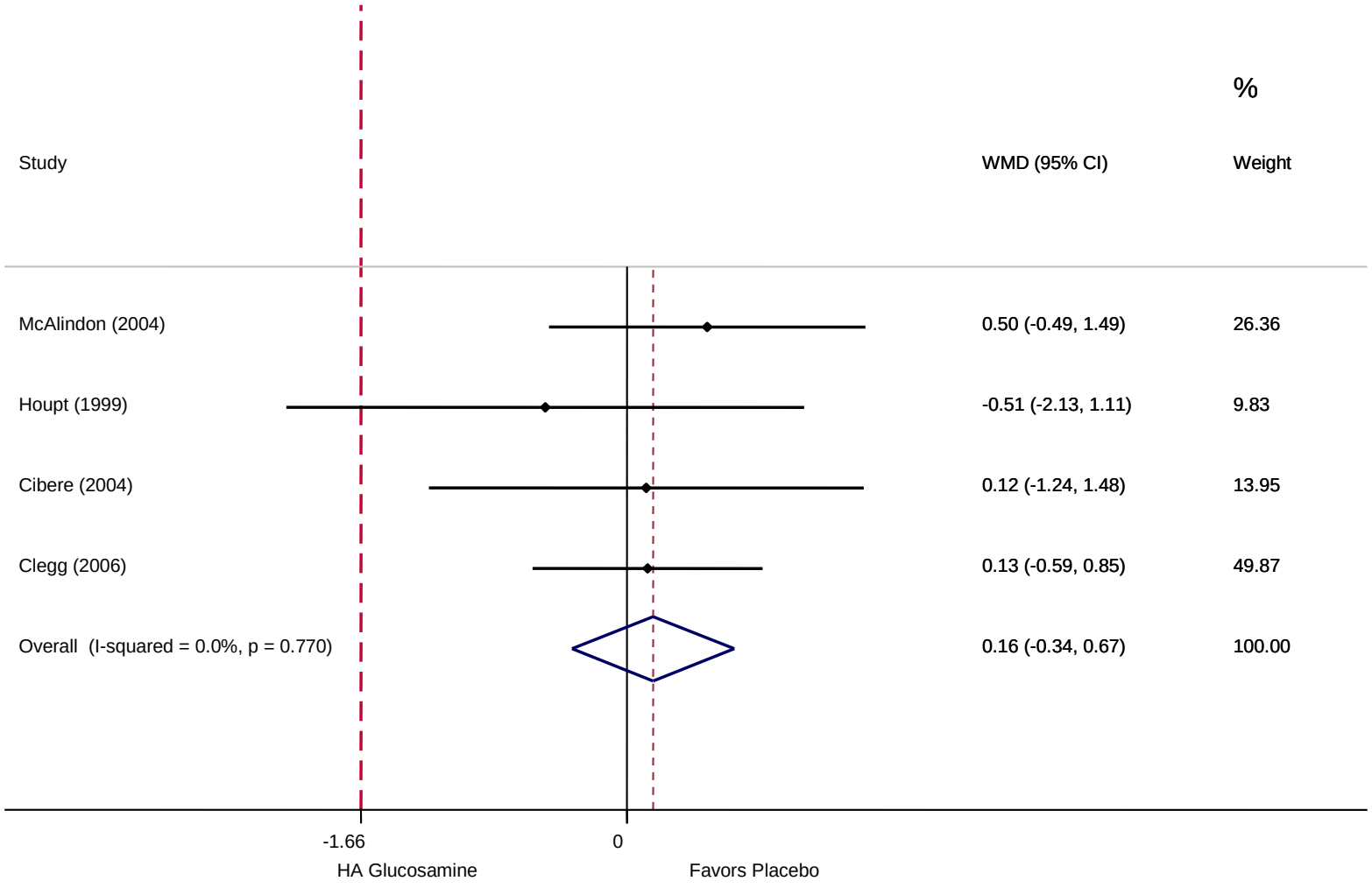
*All WOMAC scores are presented in 100 mm VAS units

Figure 37. Glucosamine Versus Placebo: WOMAC Total in MID Units*



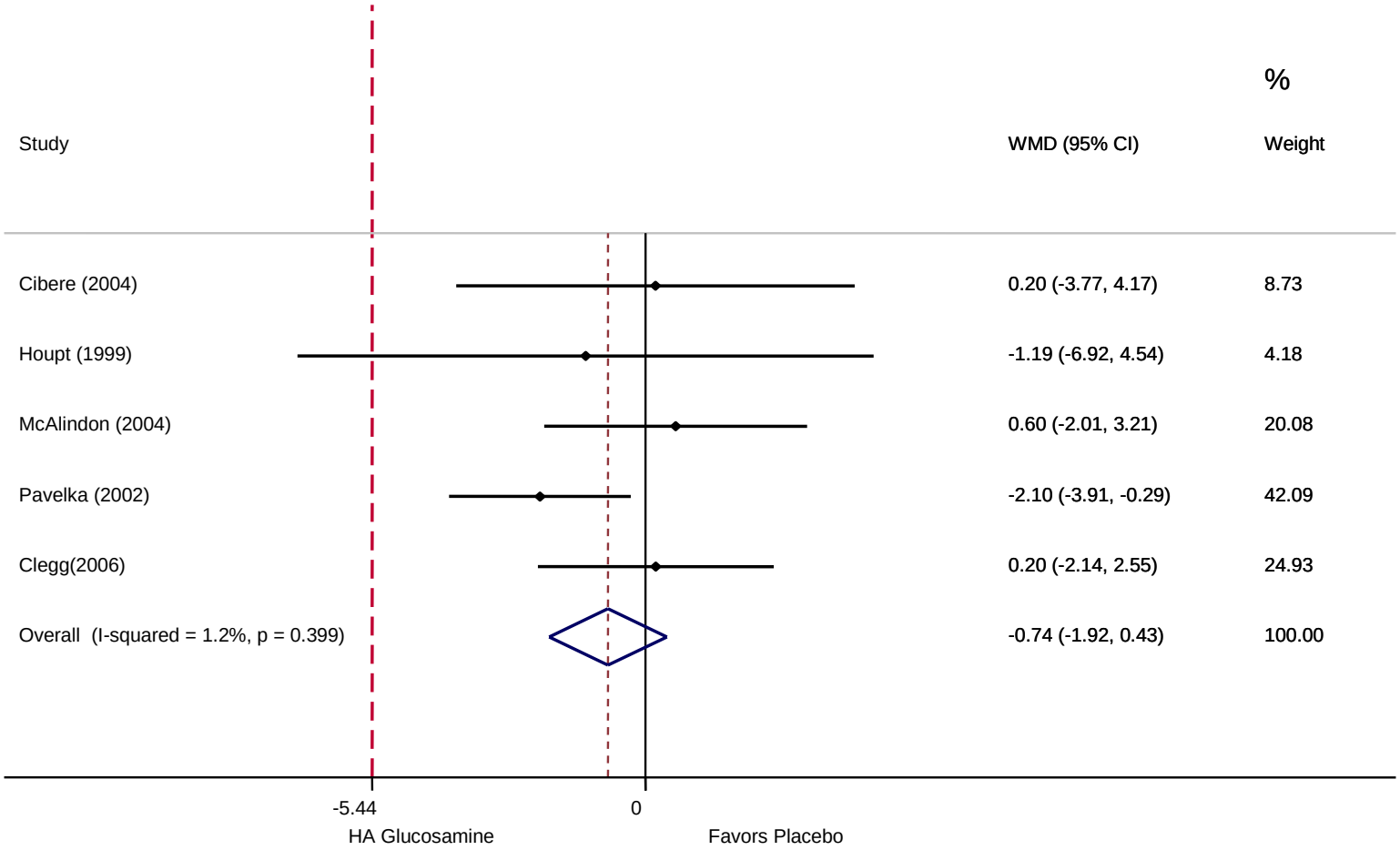
*All WOMAC scores are presented in 100mm VAS units

Figure 38. Glucosamine Versus Placebo: WOMAC Pain



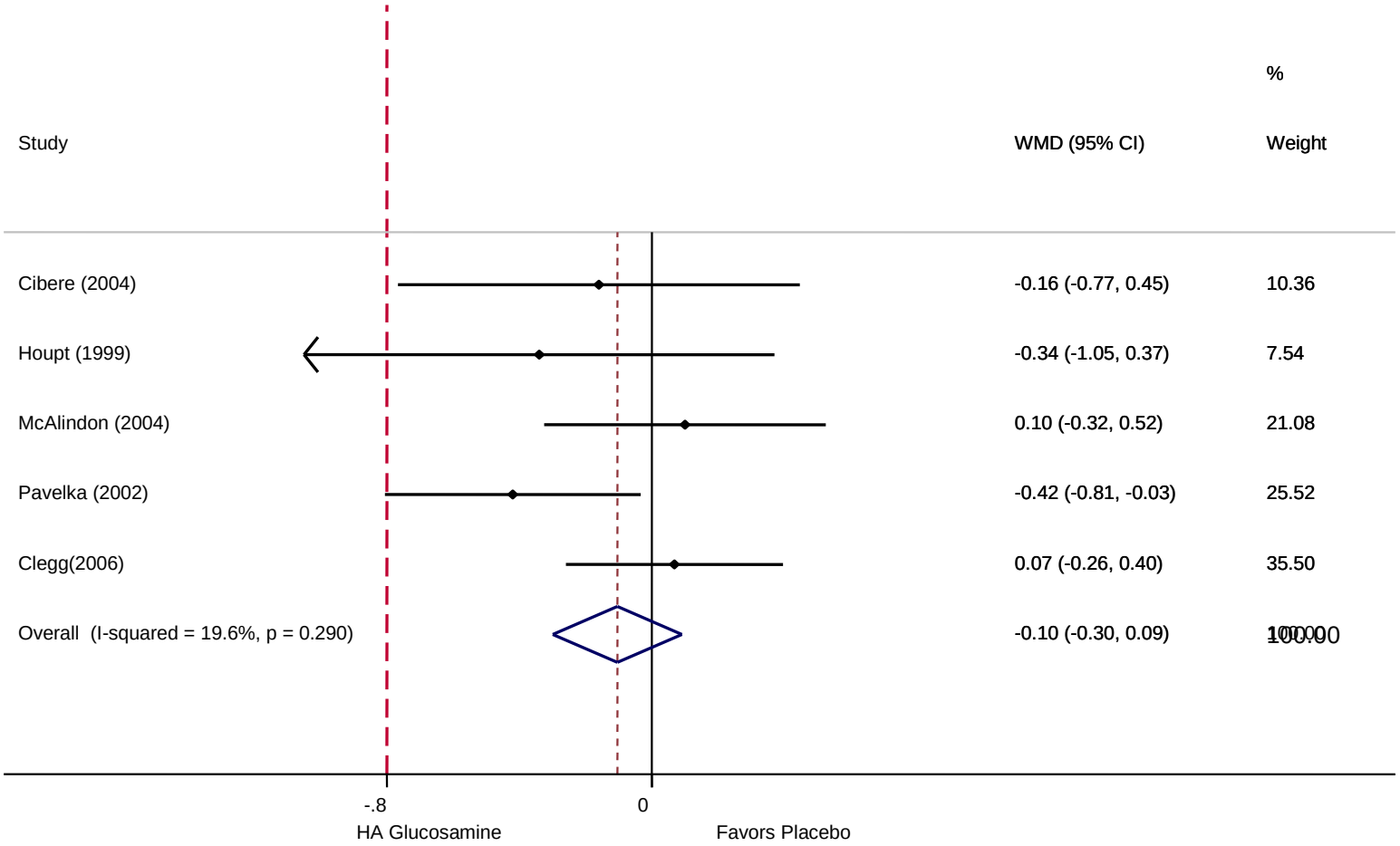
The red line indicates the MCII

Figure 39. Glucosamine Versus Placebo: WOMAC Function



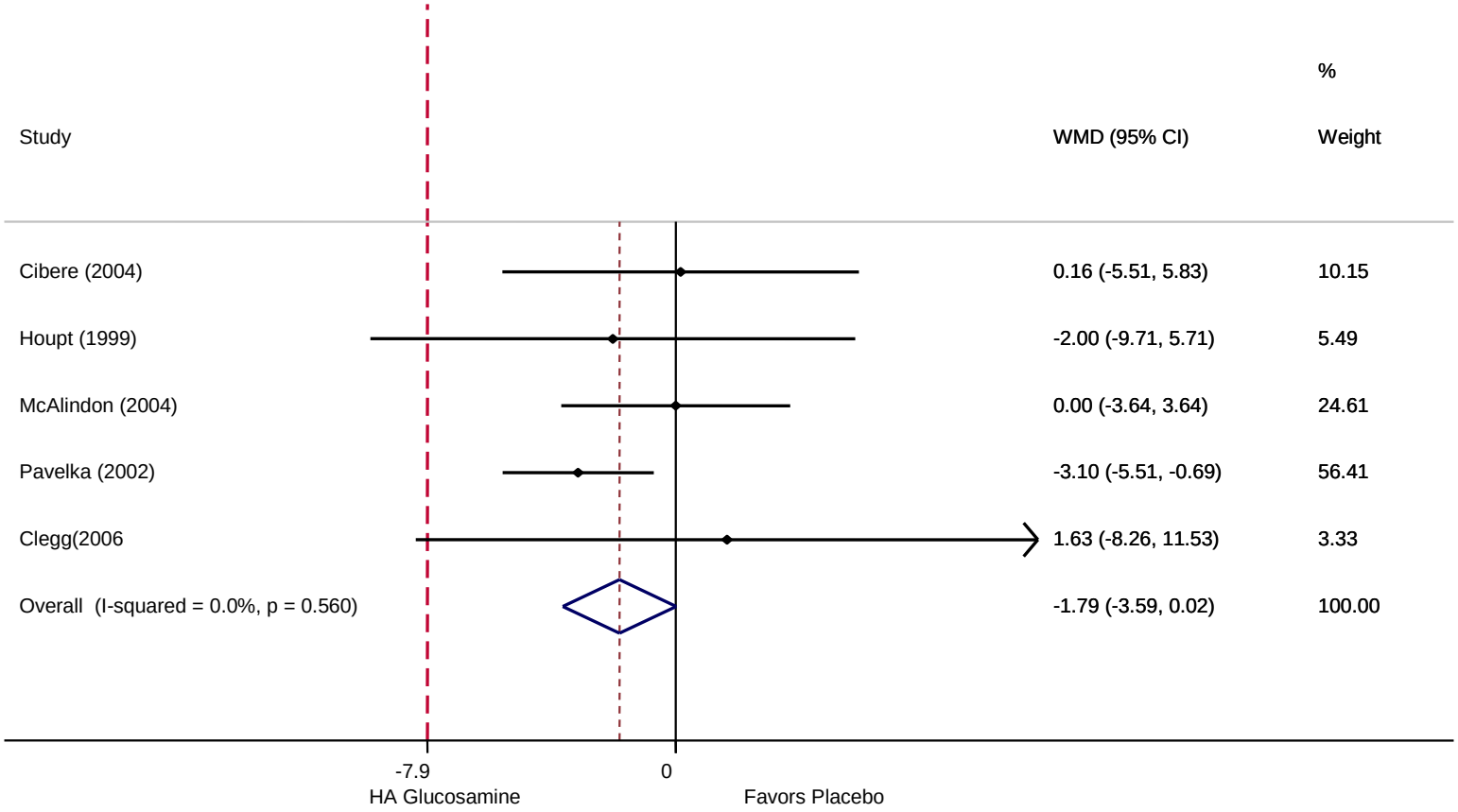
The red line indicates the MCII

Figure 40. Glucosamine Versus Placebo: WOMAC Stiffness



The red line indicates the MCII

Figure 41. Glucosamine Versus Placebo: WOMAC Total



The red line indicates the MCII

RECOMMENDATION 7A

We recommend nonsteroidal anti-inflammatory drugs (NSAIDs; oral or topical) or Tramadol for patients with symptomatic osteoarthritis of the knee.

Strength of Recommendation: Strong

Description: Evidence is based on two or more "High" strength studies with consistent findings for recommending for or against the intervention. A **Strong** recommendation means that the quality of the supporting evidence is high. A harms analysis on this recommendation was not performed.

Implications: Practitioners should follow a **Strong** recommendation unless a clear and compelling rationale for an alternative approach is present.

RECOMMENDATION 7B

We are unable to recommend for or against the use of acetaminophen, opioids, or pain patches for patients with symptomatic osteoarthritis of the knee.

Strength of Recommendation: Inconclusive

Description: Evidence from a single low quality study or conflicting findings that do not allow a recommendation for or against the intervention. An **Inconclusive** recommendation means that there is a lack of compelling evidence that has resulted in an unclear balance between benefits and potential harm.

Implications: Practitioners should feel little constraint in following a recommendation labeled as **Inconclusive,** exercise clinical judgment, and be alert for emerging evidence that clarifies or helps to determine the balance between benefits and potential harm. Patient preference should have a substantial influencing role.

RATIONALE

This recommendation included studies of both selective (cyclo-oxygenase-2, COX-2 inhibitors) and non-selective NSAIDs. The endorsement for NSAIDs was based on 202 favorable outcomes from 19 studies comparing either the selective, non-selective or topical analgesics to placebo. Twelve studies were of selective NSAIDs, four were of non-selective oral NSAIDs, and six were of topical NSAIDs. (Three studies compared multiple types of analgesics to placebo.) Three were high-strength studies, 14 were moderate, and two were of low-strength. The moderate and low strength studies were included because they examined different outcomes than the high strength articles. Out of 202 total outcomes, 171 were statistically significant in favor of the experimental group. Fifteen outcomes were above the MCII threshold and 63 outcomes were possibly clinically significant. The remaining outcomes were neither statistically nor clinically significant.

Two high- and three moderate- strength studies examining the various outcome measures in this recommendation compared tramadol to placebo. They included outcome measurements with follow up periods that ranged from 8 to 13 weeks in duration. Ten of 14 outcomes were statistically significant in favor of the treatment group. Two statistically significant outcomes (WOMAC pain and stiffness subscale scores) were possibly clinically significant and the other eight outcomes could not be evaluated. Fishman et al.[95] did not find any statistically significant improvements in pain efficacy between tramadol contramid doses of 100mg, 200mg and 300mg. Beaulieu et al.[96] found

similar treatment effects in tramadol and diclofenac in using WOMAC pain, stiffness and function subscale scales.

The recommendation on acetaminophen was downgraded from level B (i.e. Moderate) in the 2008 edition of the guideline to inconclusive in our current guideline. As opposed to the selection criteria previously used, our current systematic review examined acetaminophen separately and found only one relevant study that tested it against placebo (Miceli-Richard et al.[97]). Their study found no statistical significance or minimum clinically important improvement to patients compared to placebo. In addition, their findings and the previous clinical guideline were based on the usage of a maximum of 4000 mg of acetaminophen per day, and there has been a recent change to consider reducing the amount of the daily dosage to 3000 mg for over-the-counter patient use; for example, see this April 2012 reference from the Nevada Medicaid Services: Acetaminophen Dosage Announcement. The maximum prescription dose remains at 4000 mg per day.

The work group realizes that many practitioners prefer to start with acetaminophen prior to NSAIDs due to the side effect profile of NSAIDs. However, we found it unreasonable to recommend a treatment that does not show benefit over placebo.

Our literature review found no relevant studies meeting our inclusion criteria on opioids or pain patches for the treatment of knee osteoarthritis.

SUPPORTING EVIDENCE

QUALITY

Relevant Tables: Table 144, Table 148-Table 154

To summarize, this recommendation included 731 outcomes from 52 studies of which 107 outcomes were rated as high quality, 571 were moderate, and 53 were of low quality. The study by Schnitzer et al.[98] was retrospective and evaluated 20 outcomes that were flawed in the hypothesis and blinding domains. One other study with six outcomes was not sufficiently blinded.[99] Forty-seven studies and 624 outcomes were flawed in the group assignment domain. Twenty-nine studies were flawed in terms of group comparability, and five studies had treatment integrity flaws. There were no flaws in how outcomes were measured in any of the studies. The potential for investigator bias was present in all but one study.

APPLICABILITY

Relevant Tables: Table 144, Table 148-Table 154

All included studies in this recommendation was of moderate applicability. The enrolled patients in 48 of the 52 studies may not have been representative of the osteoarthritis of the knee population seen in clinical practice. Also, the treatment intervention was administered in a manner not consistent with clinical practice in all of the studies. Since 675 out of 731 outcomes were measured on an intent-to-treat basis, a sufficient percentage of enrolled patients were included in the final analysis.

FINAL STRENGTH OF EVIDENCE

Every study was assigned a moderate applicability rating. The strength of evidence ratings were the same as the quality ratings. A total of 107 outcomes had high strength of evidence, 571 had moderate strength, and 53 had low ratings.

Table 144. Quality and Applicability Summary: Analgesics

Study	Outcome	Weeks	Comparison	Quality	Applicability	Strength of Evidence
Astorga (1991)	Time to walk 50ft	4	Etodolac 300mg versus Piroxicam 20mg	Moderate	Moderate	Moderate
Astorga (1991)	Time to walk 50ft	6	Etodolac 300mg versus Piroxicam 20mg	Moderate	Moderate	Moderate
Astorga (1991)	Time to walk 50ft	8	Etodolac 300mg versus Piroxicam 20mg	Moderate	Moderate	Moderate
Astorga (1991)	Morning stiffness	4	Etodolac 300mg versus Piroxicam 20mg	Moderate	Moderate	Moderate
Astorga (1991)	Morning stiffness	6	Etodolac 300mg versus Piroxicam 20mg	Moderate	Moderate	Moderate
Astorga (1991)	Morning stiffness	8	Etodolac 300mg versus Piroxicam 20mg	Moderate	Moderate	Moderate

Astorga (1991)	Morning stiffness		Etodolac 300mg versus Piroxicam 20mg	Moderate	Moderate	Moderate
Ayral (2003)	Change in WOMAC averaged VAS Function	52	Tenidap 120mg versus Piroxicam 20mg	Moderate	Moderate	Moderate
Ayral (2003)	Change in WOMAC averaged VAS Pain	52	Tenidap 40mg versus Tenidap 120mg	Moderate	Moderate	Moderate
Ayral (2003)	Change in WOMAC averaged VAS Pain	52	Tenidap 40mg versus Piroxicam 20mg	Moderate	Moderate	Moderate
Ayral (2003)	Change in WOMAC averaged VAS Pain	52	Tenidap 120mg versus Piroxicam 20mg	Moderate	Moderate	Moderate
Ayral (2003)	Change in WOMAC averaged VAS Stiffness	52	Tenidap 40mg versus Tenidap 120mg	Moderate	Moderate	Moderate
Ayral (2003)	Change in WOMAC averaged VAS Stiffness	52	Tenidap 40mg versus Piroxicam 20mg	Moderate	Moderate	Moderate

Ayral (2003)	Change in WOMAC averaged VAS Stiffness	52	Tenidap 120mg versus Piroxicam 20mg	Moderate	Moderate	Moderate
Ayral (2003)	Change in WOMAC averaged VAS Total	52	Tenidap 40mg versus Tenidap 120mg	Moderate	Moderate	Moderate
Ayral (2003)	Change in WOMAC averaged VAS Total	52	Tenidap 40mg versus Piroxicam 20mg	Moderate	Moderate	Moderate
Ayral (2003)	Change in WOMAC averaged VAS Total	52	Tenidap 120mg versus Piroxicam 20mg	Moderate	Moderate	Moderate
Ayral (2003)	Physician Global Assessment	52	Tenidap 120mg versus Piroxicam 20mg	Moderate	Moderate	Moderate
Ayral (2003)	Physician Global Assessment	52	Tenidap 40mg versus Piroxicam 20mg	Moderate	Moderate	Moderate
Ayral (2003)	Patient Global Assessment	52	Tenidap 120mg versus Piroxicam 20mg	Moderate	Moderate	Moderate
Ayral (2003)	Patient Global	52	Tenidap 40mg	Moderate	Moderate	Moderate

	Assessment		versus Placebo			
Ayral (2003)	Physician Global Assessment	52	Tenidap 40mg versus Tenidap 120mg	Moderate	Moderate	Moderate
Ayral (2003)	Patient Global Assessment	52	Tenidap 40mg versus vehicle control	Moderate	Moderate	Moderate
Babul (2004)	WOMAC Function	12	Tramadol ER versus Placebo	Moderate	Moderate	Moderate
Babul (2004)	Patient Global Assessment	12	Tramadol ER versus Placebo	Moderate	Moderate	Moderate
Babul (2004)	VAS	12	Tramadol ER versus Placebo	Moderate	Moderate	Moderate
Babul (2004)	WOMAC Pain	12	Tramadol ER versus Placebo	Moderate	Moderate	Moderate
Babul (2004)	WOMAC Stiffness	12	Tramadol ER versus Placebo	Moderate	Moderate	Moderate
Baer (2005)	WOMAC Function	6	Pennsaid (topical Diclofenac solution) versus vehicle control solution	High	Moderate	High
Baer (2005)	WOMAC Pain	6	Pennsaid (topical Diclofenac solution) versus	High	Moderate	High

			vehicle control solution			
Baer (2005)	WOMAC Pain on walking	6	Pennsaid (topical Diclofenac solution) versus vehicle control solution	High	Moderate	High
Baer (2005)	WOMAC Stiffness	6	Pennsaid (topical Diclofenac solution) versus vehicle control solution	High	Moderate	High
Barthel (2009)	Weeks with no rescue drug	12	Diclofenac sodium 1% gel in DMSO versus DMSO vehicle	Moderate	Moderate	Moderate
Barthel (2009)	Weeks with no rescue drug	12	Diclofenac sodium 1% gel in DMSO versus DMSO vehicle	Moderate	Moderate	Moderate
Beaulieu (2008)	WOMAC Stiffness	6	CR Tramadol versus SR Diclofenac	Moderate	Moderate	Moderate
Beaulieu (2008)	WOMAC Function	6	CR Tramadol versus SR Diclofenac	Moderate	Moderate	Moderate

Beaulieu (2008)	Mean change in WOMAC Pain	6	Tramadol versus Diclofenac	Moderate	Moderate	Moderate
Bellamy (1993)	WOMAC Function	12	Tenoxicam versus Diclofenac	Moderate	Moderate	Moderate
Bellamy (1993)	WOMAC Pain	12	Tenoxicam versus Diclofenac	Moderate	Moderate	Moderate
Bellamy (1993)	WOMAC Stiffness	12	Tenoxicam versus Diclofenac	Moderate	Moderate	Moderate
Bookman (2004)	Mean WOMAC Stiffness (Likert)	4	Topical Diclofenac versus Placebo	High	Moderate	High
Bookman (2004)	Mean WOMAC Pain (Likert)	4	Topical Diclofenac versus Placebo gel	High	Moderate	High
Bookman (2004)	Mean WOMAC Function (Likert)	4	Topical Diclofenac versus vehicle control	High	Moderate	High
Bookman (2004)	Acetaminophen consumption	4	Topical Diclofenac versus vehicle control	High	Moderate	High
Bookman (2004)	Acetaminophen consumption	4	Topical Diclofenac versus Placebo	High	Moderate	High
Bookman (2004)	Acetaminophen	4	Topical Diclofenac versus	Moderate	Moderate	Moderate

	consumption		vehicle control			
Bookman (2004)	Acetaminophen consumption	4	Topical Diclofenac versus Placebo	Moderate	Moderate	Moderate
Bookman (2004)	WOMAC Function	4	Topical Diclofenac versus Placebo	High	Moderate	High
Bookman (2004)	WOMAC Function	4	Topical Diclofenac versus vehicle control	High	Moderate	High
Bookman (2004)	WOMAC Function	4	Topical Diclofenac versus Placebo	High	Moderate	High
Bookman (2004)	WOMAC Function	4	Topical Diclofenac versus vehicle control	High	Moderate	High
Bookman (2004)	WOMAC Pain	4	Topical Diclofenac versus vehicle control	High	Moderate	High
Bookman (2004)	WOMAC Pain	4	Topical Diclofenac versus Placebo	High	Moderate	High
Bookman (2004)	WOMAC Pain on walking	4	Topical Diclofenac versus vehicle control	High	Moderate	High

Bookman (2004)	WOMAC Pain on walking	4	Topical Diclofenac versus Placebo	High	Moderate	High
Bookman (2004)	WOMAC Pain	4	Topical Diclofenac versus vehicle control	High	Moderate	High
Bookman (2004)	WOMAC Pain	4	Topical Diclofenac versus Placebo	High	Moderate	High
Bookman (2004)	WOMAC Pain on walking	4	Topical Diclofenac versus vehicle control	High	Moderate	High
Bookman (2004)	WOMAC Pain on walking	4	Topical Diclofenac versus Placebo	High	Moderate	High
Bookman (2004)	WOMAC Stiffness	4	Topical Diclofenac versus Placebo	High	Moderate	High
Bookman (2004)	WOMAC Stiffness	4	Topical Diclofenac versus vehicle control	High	Moderate	High
Chubick (1987)	Improvement in morning weight-bearing pain	4	Sulindac 300-400mg Qd versus Sulindac 300-400mg Bid	Moderate	Moderate	Moderate

Chubick (1987)	Improvement in afternoon weight-bearing pain	4	Sulindac 300-400mg Qd versus Sulindac 300-400mg Bid	Moderate	Moderate	Moderate
Chubick (1987)	Improvement in night pain	4	Sulindac 300-400mg Qd versus Sulindac 300-400mg Bid	Moderate	Moderate	Moderate
Chubick (1987)	Improvement in tenderness	4	Sulindac 300-400mg Qd versus Sulindac 300-400mg Bid	Moderate	Moderate	Moderate
Dick (1992)	Time to walk 50ft	6	Etodolac 300mg x2 versus Piroxicam 20mg	Moderate	Moderate	Moderate
Dick (1992)	Morning stiffness	6	Etodolac 300mg x2 versus Piroxicam 20mg	Moderate	Moderate	Moderate
Ehrich (1999)	Patient Global Assessment of Response to Treatment	6	Rofecoxib 125mg versus Placebo	Moderate	Moderate	Moderate
Ehrich (1999)	Patient Global Assessment of Response to Treatment	6	Rofecoxib 25mg versus Placebo	Moderate	Moderate	Moderate

Ehrich (1999)	WOMAC Function	6	Rofecoxib versus Placebo	Moderate	Moderate	Moderate
Evcik (2003)	Health assessment questionnaire	26	Tenoxicam versus Placebo	Low	Moderate	Low
Evcik (2003)	Lequesne Index	26	Tenoxicam versus Placebo	Low	Moderate	Low
Evcik (2003)	VAS ascending stairs	26	Tenoxicam versus Placebo	Low	Moderate	Low
Evcik (2003)	VAS descending stairs	26	Tenoxicam versus Placebo	Low	Moderate	Low
Evcik (2003)	VAS Walking	26	Tenoxicam versus Placebo	Low	Moderate	Low
Evcik (2003)	VAS at rest	26	Tenoxicam versus Placebo	Low	Moderate	Low
Fishman (2007)	WOMAC Pain, percent improvement from baseline	12	Tramadol Contramid versus Placebo	High	Moderate	High
Fishman (2007)	WOMAC Pain, percent improvement from baseline	12	Tramadol Contramid versus Placebo	High	Moderate	High
Fishman (2007)	WOMAC Pain, percent improvement from	12	Tramadol Contramid versus	High	Moderate	High

	baseline		Placebo			
Fishman (2007)	WOMAC Pain, percent improvement from baseline	12	Tramadol Contramid 100mg versus Tramadol Contramid 200mg	High	Moderate	High
Fishman (2007)	WOMAC Pain, percent improvement from baseline	12	Tramadol Contramid 100mg versus Tramadol Contramid 300mg	High	Moderate	High
Fishman (2007)	WOMAC Pain, percent improvement from baseline	12	Tramadol Contramid 200mg versus Tramadol Contramid 300mg	High	Moderate	High
Fleischmann (2006)	Patient Global Assessment	13	Lumiracoxib 400mg versus Placebo	Low	Moderate	Low
Fleischmann (2006)	Patient Global Assessment	13	Lumiracoxib 200mg versus Placebo	Low	Moderate	Low
Fleischmann (2006)	VAS Pain improvement	13	Lumiracoxib versus Placebo	Low	Moderate	Low
Fleischmann (2006)	VAS Pain improvement	13	Lumiracoxib versus Placebo	Low	Moderate	Low
Fleischmann (2006)	WOMAC Pain	13	Lumiracoxib versus Placebo	Low	Moderate	Low

Fleischmann (2006)	WOMAC Pain	13	Lumiracoxib versus Placebo	Low	Moderate	Low
Fleischmann (2006)	Patient Global Assessment	13	Lumiracoxib 200mg versus Celecoxib 200mg	Low	Moderate	Low
Fleischmann (2006)	Patient Global Assessment	13	Lumiracoxib 400mg versus Celecoxib 200mg	Low	Moderate	Low
Fleischmann (2006)	Patient Global Assessment	13	Lumiracoxib 200mg versus Lumiracoxib 400mg	Low	Moderate	Low
Fleischmann (2006)	Physician Global Assessment	13	Celecoxib (Cox-2) versus Placebo	Low	Moderate	Low
Fleischmann (2006)	Physician Global Assessment	13	Lumiracoxib 200mg versus Placebo	Low	Moderate	Low
Fleischmann (2006)	Physician Global Assessment	13	Lumiracoxib 400mg versus Placebo	Low	Moderate	Low
Fleischmann (2006)	WOMAC Function	13	Lumiracoxib versus Placebo	Low	Moderate	Low
Fleischmann (2006)	WOMAC Function	13	Lumiracoxib versus Placebo	Low	Moderate	Low

Fleischmann (2006)	VAS Pain improvement	13	Celecoxib versus Placebo	Low	Moderate	Low
Fleischmann (2006)	WOMAC Pain	13	Celecoxib versus Placebo	Low	Moderate	Low
Fleischmann (2006)	WOMAC Stiffness	13	Kumiracoxib versus Placebo	Low	Moderate	Low
Fleischmann (2006)	WOMAC Stiffness	13	Lumiracoxib versus Placebo	Low	Moderate	Low
Fleischmann (2006)	WOMAC Total	13	Lumiracoxib versus Placebo	Low	Moderate	Low
Fleischmann (2006)	WOAMC Total	13	Lumiracoxib versus Placebo	Low	Moderate	Low
Fleischmann (2006)	Physician Global Assessment	13	Lumiracoxib 200mg versus Celecoxib 200mg	Low	Moderate	Low
Fleischmann (2006)	Physician Global Assessment	13	Lumiracoxib 400mg versus Celecoxib 200mg	Low	Moderate	Low
Fleischmann (2006)	Physician Global Assessment	13	Lumiracoxib 200mg versus Lumiracoxib 400mg	Low	Moderate	Low
Fleischmann (2006)	Adverse events	13	Lumiracoxib 200mg versus	Moderate	Moderate	Moderate

			Celecoxib 200mg			
Fleischmann (2006)	Adverse events	13	Lumiracoxib 400mg versus Celecoxib 200mg	Moderate	Moderate	Moderate
Fleischmann (2006)	Adverse events	13	Lumiracoxib 200mg versus Lumiracoxib 400mg	Moderate	Moderate	Moderate
Fleischmann (2006)	Adverse events	13	Lumiracoxib 200mg versus Placebo	Moderate	Moderate	Moderate
Fleischmann (2006)	Adverse events	13	Lumiracoxib 400mg versus Placebo	Moderate	Moderate	Moderate
Fleischmann (2001)	WOMAC Function	13	Tramadol versus Placebo	High	Moderate	High
Fleischmann (2001)	WOMAC Pain	13	Tramadol versus Placebo	High	Moderate	High
Fleischmann (2001)	WOMAC Stiffness	13	Tramadol versus Placebo	High	Moderate	High
Gibofsky (2003)	WOMAC Function	6	Celecoxib versus Placebo	Moderate	Moderate	Moderate
Gibofsky (2003)	WOMAC Function	6	Rofecoxib versus Placebo	Moderate	Moderate	Moderate

Gibofsky (2003)	VAS Pain on walking improvement	6	Celecoxib versus Placebo	Moderate	Moderate	Moderate
Gibofsky (2003)	VAS Pain on walking improvement	6	Rofecoxib versus Placebo	Moderate	Moderate	Moderate
Gibofsky (2003)	WOMAC Pain	6	Rofecoxib versus Placebo	Moderate	Moderate	Moderate
Gibofsky (2003)	WOMAC Pain	6	Celecoxib versus Placebo	Moderate	Moderate	Moderate
Gibofsky (2003)	WOMAC Stiffness	6	Celecoxib versus Placebo	Moderate	Moderate	Moderate
Gibofsky (2003)	WOMAC Stiffness	6	Rofecoxib versus Placebo	Moderate	Moderate	Moderate
Gibofsky (2003)	WOMAC Function improvement	6	Celecoxib 200mg versus Rofecoxib	Moderate	Moderate	Moderate
Gibofsky (2003)	VAS Pain on walking improvement	6	Celecoxib 200mg versus Rofecoxib	Moderate	Moderate	Moderate
Gibofsky (2003)	WOMAC Pain improvement	6	Celecoxib 200mg versus Rofecoxib	Moderate	Moderate	Moderate
Gibofsky (2003)	WOMAC Stiffness	6	Celecoxib 200mg versus Rofecoxib	Moderate	Moderate	Moderate

	improvement					
Gibofsky (2003)	Adverse events	6	Celecoxib 200mg versus Placebo	Moderate	Moderate	Moderate
Gibofsky (2003)	Adverse events	6	Rofecoxib 25mg versus Placebo	Moderate	Moderate	Moderate
Gibofsky (2003)	Adverse events	6	Celecoxib 200mg versus Aceclofenac	Moderate	Moderate	Moderate
Gibofsky (2003)	Any adverse event	6	Rofecoxib 25mg versus Placebo	Moderate	Moderate	Moderate
Gibofsky (2003)	Adverse events	6	Celecoxib 200mg versus Aceclofenac	Moderate	Moderate	Moderate
Gibofsky (2003)	Adverse events	6	Celecoxib 200mg versus Aceclofenac	Moderate	Moderate	Moderate
Gibofsky (2003)	Patient Global Assessment	6	Celecoxib 200mg versus Placebo	Moderate	Moderate	Moderate
Gibofsky (2003)	Patient Global Assessment	6	Rofecoxib 25mg versus Placebo	Moderate	Moderate	Moderate
Gibofsky (2003)	Physician Global Assessment	6	Celecoxib 200mg versus Placebo	Moderate	Moderate	Moderate
Gibofsky (2003)	Physician Global	6	Rofecoxib 25mg	Moderate	Moderate	Moderate

	Assessment		versus Placebo			
Gibofsky (2003)	Patient Global Assessment of Response to Treatment	6	Celecoxib 200mg versus Placebo	Moderate	Moderate	Moderate
Gibofsky (2003)	Patient Global Assessment of Response to Treatment	6	Rofecoxib 25mg versus Placebo	Moderate	Moderate	Moderate
Gibofsky (2003)	Patient Global Assessment	6	Celecoxib 200mg versus Rofecoxib 25mg	Moderate	Moderate	Moderate
Gibofsky (2003)	Physician Global Assessment	6	Celecoxib 200mg versus Rofecoxib 25mg	Moderate	Moderate	Moderate
Goregaonkar (2009)	Gastritis	4	Lornoxicam 8mg versus Diclofenac 50mg	Moderate	Moderate	Moderate
Goregaonkar (2009)	Abdominal pain	4	Lornoxicam 8mg versus Diclofenac 50mg	Moderate	Moderate	Moderate
Goregaonkar (2009)	Dizziness	4	Lornoxicam 8mg versus Diclofenac 50mg	Moderate	Moderate	Moderate
Goregaonkar	Drowsiness	4	Lornoxicam 8mg versus Diclofenac	Moderate	Moderate	Moderate

(2009)			50mg			
Goregaonkar (2009)	Headache	4	Lornoxicam 8mg versus Diclofenac 50mg	Moderate	Moderate	Moderate
Goregaonkar (2009)	Nausea/Vomiting	4	Lornoxicam 8mg versus Diclofenac 50mg	Moderate	Moderate	Moderate
Goregaonkar (2009)	Diarrhea	4	Lornoxicam 8mg versus Diclofenac 50mg	Moderate	Moderate	Moderate
Goregaonkar (2009)	GI Events	4	Lornoxicam 8mg versus Diclofenac 50mg	Moderate	Moderate	Moderate
Gottesdiener (2002)	Patient Global Assessment of Disease Status	6	Etoricoxib 60mg versus Etoricoxib 90mg	High	Moderate	High
Gottesdiener (2002)	Patient Global Assessment of Disease Status	6	Etoricoxib 5mg versus Etoricoxib 10mg	High	Moderate	High
Gottesdiener (2002)	Patient Global Assessment of Disease Status	6	Etoricoxib 5mg versus Etoricoxib 30mg	High	Moderate	High
Gottesdiener (2002)	Patient Global Assessment of Disease Status	6	Etoricoxib 5mg versus Etoricoxib 60mg	High	Moderate	High

Gottesdiener (2002)	Patient Global Assessment of Disease Status	6	Etoricoxib 5mg versus Etoricoxib 90mg	High	Moderate	High
Gottesdiener (2002)	Patient Global Assessment of Disease Status	6	Etoricoxib 10mg versus Etoricoxib 30mg	High	Moderate	High
Gottesdiener (2002)	Patient Global Assessment of Disease Status	6	Etoricoxib 10mg versus Etoricoxib 60mg	High	Moderate	High
Gottesdiener (2002)	Patient Global Assessment of Disease Status	6	Etoricoxib 10mg versus Etoricoxib 90mg	High	Moderate	High
Gottesdiener (2002)	Patient Global Assessment of Disease Status	6	Etoricoxib 30mg versus Etoricoxib 60mg	High	Moderate	High
Gottesdiener (2002)	Patient Global Assessment of Disease Status	6	Etoricoxib 30mg versus Etoricoxib 90mg	High	Moderate	High
Gottesdiener (2002)	Patient Global Assessment of Disease Status	6	Etoricoxib 60mg versus Etoricoxib 90mg	High	Moderate	High
Gottesdiener (2002)	Patient Global Assessment of Disease Status	6	Etoricoxib 5mg versus Etoricoxib 10mg	High	Moderate	High
Gottesdiener	Patient Global Assessment of	6	Etoricoxib 5mg versus Etoricoxib	High	Moderate	High

(2002)	Disease Status		30mg			
Gottesdiener (2002)	Patient Global Assessment of Disease Status	6	Etoricoxib 10mg versus Etoricoxib 30mg	High	Moderate	High
Gottesdiener (2002)	Patient Global Assessment of Disease Status	6	Etoricoxib 5mg versus Etoricoxib 60mg	High	Moderate	High
Gottesdiener (2002)	Patient Global Assessment of Disease Status	6	Etoricoxib 10mg versus Etoricoxib 60mg	High	Moderate	High
Gottesdiener (2002)	Patient Global Assessment of Disease Status	6	Etoricoxib 30mg versus Etoricoxib 60mg	High	Moderate	High
Gottesdiener (2002)	Patient Global Assessment of Disease Status	6	Etoricoxib 5mg versus Etoricoxib 90mg	High	Moderate	High
Gottesdiener (2002)	Patient Global Assessment of Disease Status	6	Etoricoxib 10mg versus Etoricoxib 90mg	High	Moderate	High
Gottesdiener (2002)	Patient Global Assessment of Disease Status	6	Etoricoxib 30mg versus Etoricoxib 90mg	High	Moderate	High
Gottesdiener (2002)	Patient Global Assessment of Disease Status	6	Etoricoxib 60mg versus Etoricoxib 90mg	High	Moderate	High

Gottesdiener (2002)	Patient Assessment of Treatment Response	6	Etoricoxib 5mg versus Etoricoxib 10mg	High	Moderate	High
Gottesdiener (2002)	Patient Assessment of Treatment Response	6	Etoricoxib 5mg versus Etoricoxib 30mg	High	Moderate	High
Gottesdiener (2002)	Patient Assessment of Treatment Response	6	Etoricoxib 5mg versus Etoricoxib 60mg	High	Moderate	High
Gottesdiener (2002)	Patient Assessment of Treatment Response	6	Etoricoxib 5mg versus Etoricoxib 90mg	High	Moderate	High
Gottesdiener (2002)	Patient Assessment of Treatment Response	6	Etoricoxib 10mg versus Etoricoxib 30mg	High	Moderate	High
Gottesdiener (2002)	Patient Assessment of Treatment Response	6	Etoricoxib 10mg versus Etoricoxib 60mg	High	Moderate	High
Gottesdiener (2002)	Patient Assessment of Treatment	6	Etoricoxib 10mg versus Etoricoxib 90mg	High	Moderate	High

	Response					
Gottesdiener (2002)	Patient Assessment of Treatment Response	6	Etoricoxib 30mg versus Etoricoxib 60mg	High	Moderate	High
Gottesdiener (2002)	Patient Assessment of Treatment Response	6	Etoricoxib 30mg versus Etoricoxib 90mg	High	Moderate	High
Gottesdiener (2002)	Patient Assessment of Treatment Response	6	Etoricoxib 60mg versus Etoricoxib 90mg	High	Moderate	High
Gottesdiener (2002)	Patient Assessment of Treatment Response	6	Etoricoxib 5mg versus Etoricoxib 10mg	High	Moderate	High
Gottesdiener (2002)	Physician Assessment of Treatment Response	6	Etoricoxib 5mg versus Etoricoxib 30mg	High	Moderate	High
Gottesdiener (2002)	Physician Assessment of Treatment Response	6	Etoricoxib 10mg versus Etoricoxib 30mg	High	Moderate	High
Gottesdiener	Physician Assessment of	6	Etoricoxib 5mg versus Etoricoxib	High	Moderate	High

(2002)	Treatment Response		60mg			
Gottesdiener (2002)	Physician Assessment of Treatment Response	6	Etoricoxib 10mg versus Etoricoxib 60mg	High	Moderate	High
Gottesdiener (2002)	Physician Assessment of Treatment Response	6	Etoricoxib 30mg versus Etoricoxib 60mg	High	Moderate	High
Gottesdiener (2002)	Physician Assessment of Treatment Response	6	Etoricoxib 5mg versus Etoricoxib 90mg	High	Moderate	High
Gottesdiener (2002)	Physician Assessment of Treatment Response	6	Etoricoxib 10mg versus Etoricoxib 90mg	High	Moderate	High
Gottesdiener (2002)	Physician Assessment of Treatment Response	6	Etoricoxib 30mg versus Etoricoxib 90mg	High	Moderate	High
Gottesdiener (2002)	Physician Assessment of Treatment Response	6	Etoricoxib 60mg versus Etoricoxib 90mg	High	Moderate	High

Herrera (2007)	WOMAC Function	4	Diclofenac Cr 100mg versus Diclofenac Ir 50mg	Moderate	Moderate	Moderate
Herrera (2007)	VAS Pain	4	Diclofenac Cr 100mg versus Diclofenac Ir 50mg	Moderate	Moderate	Moderate
Herrera (2007)	WOMAC Pain	4	Diclofenac Cr 100mg versus Diclofenac Ir 50mg	Moderate	Moderate	Moderate
Herrera (2007)	WOMAC Stiffness	4	Diclofenac Cr 100mg versus Diclofenac Ir 50mg	Moderate	Moderate	Moderate
Herrera (2007)	WOMAC Total	4	Diclofenac Cr 100mg versus Diclofenac Ir 50mg	Moderate	Moderate	Moderate
Karbowski (1991)	Time to walk 50ft	6	Etodolac 300mg versus Indomethacin 50mg	Moderate	Moderate	Moderate
Karbowski (1991)	Morning stiffness	6	Etodolac 300mg versus Indomethacin	Moderate	Moderate	Moderate

			50mg			
Kivits (2002)	VAS Pain improvement	6	Valdecoxib versus Placebo	Moderate	Moderate	Moderate
Kivits (2002)	VAS Pain improvement	6	Valdecoxib versus Placebo	Moderate	Moderate	Moderate
Kivits (2002)	VAS Pain improvement	6	Valdecoxib versus Placebo	Moderate	Moderate	Moderate
Kivits (2002)	VAS Pain improvement	12	Valdecoxib versus Placebo	Moderate	Moderate	Moderate
Kivits (2002)	VAS Pain improvement	12	Valdecoxib versus Placebo	Moderate	Moderate	Moderate
Kivits (2002)	VAS Pain improvement	12	Valdecoxib versus Placebo	Moderate	Moderate	Moderate
Kivits (2002)	WOMAC Stiffness	6	Valdecoxib versus Placebo	Moderate	Moderate	Moderate
Kivits (2002)	WOMAC Stiffness	6	Valdecoxib versus Placebo	Moderate	Moderate	Moderate
Kivits (2002)	WOMAC Stiffness	6	Valdecoxib versus Placebo	Moderate	Moderate	Moderate
Kivits (2002)	WOMAC Stiffness	12	Valdecoxib versus Placebo	Moderate	Moderate	Moderate
Kivits (2002)	WOMAC	12	Valdecoxib	Moderate	Moderate	Moderate

	Stiffness		versus Placebo			
Kivits (2002)	WOMAC Stiffness	12	Valdecoxib versus Placebo	Moderate	Moderate	Moderate
Kivits (2002)	WOMAC Total	12	Valdecoxib versus Placebo	Moderate	Moderate	Moderate
Kivits (2002)	WOMAC Total	12	Valdecoxib versus Placebo	Moderate	Moderate	Moderate
Kivits (2002)	WOMAC Total	12	Valdecoxib versus Placebo	Moderate	Moderate	Moderate
Kivits (2002)	WOMAC Total	6	Valdecoxib versus Placebo	Moderate	Moderate	Moderate
Kivits (2002)	WOMAC Total	6	Valdecoxib versus Placebo	Moderate	Moderate	Moderate
Kivits (2002)	WOMAC Total	6	Valdecoxib versus Placebo	Moderate	Moderate	Moderate
Kivits (2002)	Abdominal pain	12	Valdecoxib 20mg versus Naproxen 500mg	Moderate	Moderate	Moderate
Kivits (2002)	Abdominal pain	12	Valdecoxib 10mg versus Naproxen 500mg	Moderate	Moderate	Moderate
Kivits (2002)	Abdominal pain	12	Valdecoxib 5mg versus Naproxen	Moderate	Moderate	Moderate

			500mg			
Kivits (2002)	Accidental injury	12	Valdecoxib 20mg versus Naproxen 500mg	Moderate	Moderate	Moderate
Kivits (2002)	Accidental injury	12	Valdecoxib 10mg versus Naproxen 500mg	Moderate	Moderate	Moderate
Kivits (2002)	Accidental injury	12	Valdecoxib 5mg versus Naproxen 500mg	Moderate	Moderate	Moderate
Kivits (2002)	Constipation	12	Valdecoxib 20mg versus Naproxen 500mg	Moderate	Moderate	Moderate
Kivits (2002)	Constipation	12	Valdecoxib 10mg versus Naproxen 500mg	Moderate	Moderate	Moderate
Kivits (2002)	Constipation	12	Valdecoxib 5mg versus Naproxen 500mg	Moderate	Moderate	Moderate
Kivits (2002)	Diarrhea	12	Valdecoxib 20mg versus Naproxen 500mg	Moderate	Moderate	Moderate
Kivits (2002)	Diarrhea	12	Valdecoxib 10mg versus Naproxen 500mg	Moderate	Moderate	Moderate

Kivits (2002)	Diarrhea	12	Valdecoxib 5mg versus Naproxen 500mg	Moderate	Moderate	Moderate
Kivits (2002)	Dyspepsia	12	Valdecoxib 20mg versus Naproxen 500mg	Moderate	Moderate	Moderate
Kivits (2002)	Dyspepsia	12	Valdecoxib 10mg versus Naproxen 500mg	Moderate	Moderate	Moderate
Kivits (2002)	Dyspepsia	12	Valdecoxib 5mg versus Naproxen 500mg	Moderate	Moderate	Moderate
Kivits (2002)	Flatulence	12	Valdecoxib 20mg versus Naproxen 500mg	Moderate	Moderate	Moderate
Kivits (2002)	Flatulence	12	Valdecoxib 10mg versus Naproxen 500mg	Moderate	Moderate	Moderate
Kivits (2002)	Flatulence	12	Valdecoxib 5mg versus Naproxen 500mg	Moderate	Moderate	Moderate
Kivits (2002)	Headache	12	Valdecoxib 20mg versus Naproxen 500mg	Moderate	Moderate	Moderate
Kivits (2002)	Headache	12	Valdecoxib 10mg versus Naproxen	Moderate	Moderate	Moderate

			500mg			
Kivits (2002)	Headache	12	Valdecoxib 5mg versus Naproxen 500mg	Moderate	Moderate	Moderate
Kivits (2002)	Myalgia	12	Valdecoxib 20mg versus Naproxen 500mg	Moderate	Moderate	Moderate
Kivits (2002)	Myalgia	12	Valdecoxib 10mg versus Naproxen 500mg	Moderate	Moderate	Moderate
Kivits (2002)	Myalgia	12	Valdecoxib 5mg versus Naproxen 500mg	Moderate	Moderate	Moderate
Kivits (2002)	Nausea	12	Valdecoxib 20mg versus Naproxen 500mg	Moderate	Moderate	Moderate
Kivits (2002)	Nausea	12	Valdecoxib 10mg versus Naproxen 500mg	Moderate	Moderate	Moderate
Kivits (2002)	Nausea	12	Valdecoxib 5mg versus Naproxen 500mg	Moderate	Moderate	Moderate
Kivits (2002)	Upper respiratory tract infections	12	Valdecoxib 20mg versus Naproxen 500mg	Moderate	Moderate	Moderate

Kivits (2002)	Upper respiratory tract infections	12	Valdecoxib 10mg versus Naproxen 500mg	Moderate	Moderate	Moderate
Kivits (2002)	Upper respiratory tract infections	12	Valdecoxib 5mg versus Naproxen 500mg	Moderate	Moderate	Moderate
Kivits (2002)	VAS Pain	12	Valdecoxib 5mg versus Naproxen 5mg	Moderate	Moderate	Moderate
Kivits (2002)	VAS Pain	6	Valdecoxib 5mg versus Naproxen 5mg	Moderate	Moderate	Moderate
Kivits (2002)	VAS Pain	12	Valdecoxib 5mg versus Naproxen 5mg	Moderate	Moderate	Moderate
Kivits (2002)	VAS Pain	6	Valdecoxib 5mg versus Naproxen 5mg	Moderate	Moderate	Moderate
Kivits (2002)	VAS Pain	12	Valdecoxib 5mg versus Naproxen 5mg	Moderate	Moderate	Moderate
Kivits (2002)	VAS Pain	6	Valdecoxib 5mg versus Naproxen 5mg	Moderate	Moderate	Moderate
Kivits (2002)	WOMAC	6	Valdecoxib 10mg versus Naproxen	Moderate	Moderate	Moderate

	Stiffness		10mg			
Kivits (2002)	WOMAC Stiffness	12	Valdecoxib 10mg versus Naproxen 10mg	Moderate	Moderate	Moderate
Kivits (2002)	WOMAC Stiffness	12	Valdecoxib 20mg versus Naproxen 20mg	Moderate	Moderate	Moderate
Kivits (2002)	WOMAC Stiffness	6	Valdecoxib 20mg versus Naproxen 20mg	Moderate	Moderate	Moderate
Kivits (2002)	WOMAC Stiffness	12	Valdecoxib 5mg versus Naproxen 5mg	Moderate	Moderate	Moderate
Kivits (2002)	WOMAC Stiffness	6	Valdecoxib 5mg versus Naproxen 5mg	Moderate	Moderate	Moderate
Kivits (2002)	WOMAC Total	12	Valdecoxib 10mg versus Naproxen 10mg	Moderate	Moderate	Moderate
Kivits (2002)	WOMAC Total	6	Valdecoxib 10mg versus Naproxen 10mg	Moderate	Moderate	Moderate
Kivits (2002)	WOMAC Total	6	Valdecoxib 20mg versus Naproxen 20mg	Moderate	Moderate	Moderate

Kivits (2002)	WOMAC Total	12	Valdecoxib 20mg versus Naproxen 20mg	Moderate	Moderate	Moderate
Kivits (2002)	WOMAC Total	12	Valdecoxib 5mg versus Naproxen 5mg	Moderate	Moderate	Moderate
Kivits (2002)	WOMAC Total	6	Valdecoxib 5mg versus Naproxen 5mg	Moderate	Moderate	Moderate
Kivits (2002)	Abdominal pain	12	Valdecoxib 20mg versus Naproxen 500mg	Moderate	Moderate	Moderate
Kivits (2002)	Abdominal pain	12	Valdecoxib 10mg versus Naproxen 500mg	Moderate	Moderate	Moderate
Kivits (2002)	Abdominal pain	12	Valdecoxib 5mg versus Naproxen 500mg	Moderate	Moderate	Moderate
Kivits (2002)	Accidental injury	12	Valdecoxib 20mg versus Naproxen 500mg	Moderate	Moderate	Moderate
Kivits (2002)	Accidental injury	12	Valdecoxib 10mg versus Naproxen 500mg	Moderate	Moderate	Moderate
Kivits (2002)	Accidental injury	12	Valdecoxib 5mg versus Naproxen	Moderate	Moderate	Moderate

			500mg			
Kivits (2002)	Constipation	12	Valdecoxib 20mg versus Naproxen 500mg	Moderate	Moderate	Moderate
Kivits (2002)	Constipation	12	Valdecoxib 10mg versus Naproxen 500mg	Moderate	Moderate	Moderate
Kivits (2002)	Constipation	12	Valdecoxib 5mg versus Naproxen 500mg	Moderate	Moderate	Moderate
Kivits (2002)	Diarrhea	12	Valdecoxib 20mg versus Naproxen 500mg	Moderate	Moderate	Moderate
Kivits (2002)	Diarrhea	12	Valdecoxib 10mg versus Naproxen 500mg	Moderate	Moderate	Moderate
Kivits (2002)	Diarrhea	12	Valdecoxib 5mg versus Naproxen 500mg	Moderate	Moderate	Moderate
Kivits (2002)	Dyspepsia	12	Valdecoxib 20mg versus Naproxen 500mg	Moderate	Moderate	Moderate
Kivits (2002)	Dyspepsia	12	Valdecoxib 10mg versus Naproxen 500mg	Moderate	Moderate	Moderate

Kivits (2002)	Dyspepsia	12	Valdecoxib 5mg versus Naproxen 500mg	Moderate	Moderate	Moderate
Kivits (2002)	Flatulence	12	Valdecoxib 20mg versus Naproxen 500mg	Moderate	Moderate	Moderate
Kivits (2002)	Flatulence	12	Valdecoxib 10mg versus Naproxen 500mg	Moderate	Moderate	Moderate
Kivits (2002)	Flatulence	12	Valdecoxib 5mg versus Naproxen 500mg	Moderate	Moderate	Moderate
Kivits (2002)	Headache	12	Valdecoxib 20mg versus Naproxen 500mg	Moderate	Moderate	Moderate
Kivits (2002)	Headache	12	Valdecoxib 10mg versus Naproxen 500mg	Moderate	Moderate	Moderate
Kivits (2002)	Headache	12	Valdecoxib 5mg versus Naproxen 500mg	Moderate	Moderate	Moderate
Kivits (2002)	Myalgia	12	Valdecoxib 20mg versus Naproxen 500mg	Moderate	Moderate	Moderate
Kivits (2002)	Myalgia	12	Valdecoxib 10mg versus Naproxen	Moderate	Moderate	Moderate

			500mg			
Kivits (2002)	Myalgia	12	Valdecoxib 5mg versus Naproxen 500mg	Moderate	Moderate	Moderate
Kivits (2002)	Nausea	12	Valdecoxib 20mg versus Naproxen 500mg	Moderate	Moderate	Moderate
Kivits (2002)	Nausea	12	Valdecoxib 10mg versus Naproxen 500mg	Moderate	Moderate	Moderate
Kivits (2002)	Nausea	12	Valdecoxib 5mg versus Naproxen 500mg	Moderate	Moderate	Moderate
Kivits (2002)	Upper respiratory tract infections	12	Valdecoxib 20mg versus Naproxen 500mg	Moderate	Moderate	Moderate
Kivits (2002)	Upper respiratory tract infections	12	Valdecoxib 10mg versus Naproxen 500mg	Moderate	Moderate	Moderate
Kivits (2002)	Upper respiratory tract infections	12	Valdecoxib 5mg versus Naproxen 500mg	Moderate	Moderate	Moderate
Kivits (2002)	Abdominal Pain	12	Valdecoxib 20mg versus Naproxen 500mg	Moderate	Moderate	Moderate

Kivits (2002)	Accidental Injury	12	Valdecoxib 20mg versus Naproxen 500mg	Moderate	Moderate	Moderate
Kivits (2002)	Constipation	12	Valdecoxib 20mg versus Naproxen 500mg	Moderate	Moderate	Moderate
Kivits (2002)	Diarrhea	12	Valdecoxib 20mg versus Naproxen 500mg	Moderate	Moderate	Moderate
Kivits (2002)	Dyspepsia	12	Valdecoxib 20mg versus Naproxen 500mg	Moderate	Moderate	Moderate
Kivits (2002)	Flatulence	12	Valdecoxib 20mg versus Naproxen 500mg	Moderate	Moderate	Moderate
Kivits (2002)	Headache	12	Valdecoxib 20mg versus Naproxen 500mg	Moderate	Moderate	Moderate
Kivits (2002)	Myalgia	12	Valdecoxib 20mg versus Naproxen 500mg	Moderate	Moderate	Moderate
Kivits (2002)	Nausea	12	Valdecoxib 20mg versus Naproxen 500mg	Moderate	Moderate	Moderate
Kivits (2002)	Upper respiratory	12	Valdecoxib 20mg versus Naproxen	Moderate	Moderate	Moderate

	tract infections		500mg			
Kivits (2004)	Acid reflux	6	Rofecoxib 12.5mg versus Nabumetone 1000mg	High	Moderate	High
Kivits (2004)	At least one adverse event	6	Rofecoxib 12.5mg versus Naproxen	High	Moderate	High
Kivits (2004)	At least one adverse event	6	Rofecoxib 12.5mg versus Placebo	High	Moderate	High
Kivits (2004)	Dyspepsia	6	Rofecoxib 12.5mg versus Nabumetone 1000mg	High	Moderate	High
Kivits (2004)	Epigastric discomfort	6	Rofecoxib 12.5mg versus Nabumetone 1000mg	High	Moderate	High
Kivits (2004)	GI events	6	Rofecoxib 12.5mg versus Nabumetone 1000mg	High	Moderate	High
Kivits (2004)	Heartburn	6	Rofecoxib 12.5mg versus Nabumetone	High	Moderate	High

			1000mg			
Kivits (2004)	Nausea	6	Rofecoxib 12.5mg versus Nabumetone 1000mg	High	Moderate	High
Kivits (2004)	Vomiting	6	Rofecoxib 12.5mg versus Nabumetone 1000mg	High	Moderate	High
Kivits (2004)	Vomiting	6	Rofecoxib 12.5mg versus Nabumetone 1000mg	Moderate	Moderate	Moderate
Kivits (2004)	At least one adverse event	6	Nabumetone 1000 versus Placebo	High	Moderate	High
Kivits (2004)	Acid reflux	6	Rofecoxib 12.5mg versus Nabumetone 1000mg	High	Moderate	High
Kivits (2004)	At least one adverse event	6	Rofecoxib 12.5mg versus Naproxen	High	Moderate	High
Kivits (2004)	Dyspepsia	6	Rofecoxib 12.5mg versus Nabumetone 1000mg	High	Moderate	High

Kivits (2004)	Epigastric discomfort	6	Rofecoxib 12.5mg versus Nabumetone 1000mg	High	Moderate	High
Kivits (2004)	GI events	6	Rofecoxib 12.5mg versus Nabumetone 1000mg	High	Moderate	High
Kivits (2004)	Heartburn	6	Rofecoxib 12.5mg versus Nabumetone 1000mg	High	Moderate	High
Kivits (2004)	Nausea	6	Rofecoxib 12.5mg versus Nabumetone 1000mg	High	Moderate	High
Kivits (2004)	Vomiting	6	Rofecoxib 12.5mg versus Nabumetone 1000mg	High	Moderate	High
Kivits (2004)	Acid reflux	6	Rofecoxib 12.5mg versus Nabumetone 1000mg	High	Moderate	High
Kivits (2004)	At least one adverse event	6	Rofecoxib 12.5mg versus Naproxen	High	Moderate	High

Kivits (2004)	Dyspepsia	6	Rofecoxib 12.5mg versus Nabumetone 1000mg	High	Moderate	High
Kivits (2004)	Epigastric discomfort	6	Rofecoxib 12.5mg versus Nabumetone 1000mg	High	Moderate	High
Kivits (2004)	GI events	6	Rofecoxib 12.5mg versus Nabumetone 1000mg	High	Moderate	High
Kivits (2004)	Heartburn	6	Rofecoxib 12.5mg versus Nabumetone 1000mg	High	Moderate	High
Kivits (2004)	Nausea	6	Rofecoxib 12.5mg versus Nabumetone 1000mg	High	Moderate	High
Kivits (2004)	Vomiting	6	Rofecoxib 12.5mg versus Nabumetone 1000mg	High	Moderate	High
Kivits (2002)	Physician Global Assessment	6	Valdecoxib 10mg (Cox-2) versus Placebo	Moderate	Moderate	Moderate

Kivits (2002)	Physician Global Assessment	12	Valdecoxib 10mg (Cox-2) versus Placebo	Moderate	Moderate	Moderate
Kivits (2002)	Physician Global Assessment	6	Valdecoxib 20mg (Cox-2) versus Placebo	Moderate	Moderate	Moderate
Kivits (2002)	Physician Global Assessment	12	Valdecoxib 20mg (Cox-2) versus Placebo	Moderate	Moderate	Moderate
Kivits (2002)	Physician Global Assessment	6	Valdecoxib 5mg (Cox-2) versus Placebo	Moderate	Moderate	Moderate
Kivits (2002)	Physician Global Assessment	12	Valdecoxib 5mg (Cox-2) versus Placebo	Moderate	Moderate	Moderate
Kivits (2002)	VAS Pain	12	Naproxen versus Placebo	Moderate	Moderate	Moderate
Kivits (2002)	VAS Pain	6	Naproxen versus Placebo	Moderate	Moderate	Moderate
Kivits (2002)	WOMAC Stiffness	6	Naproxen versus Placebo	Moderate	Moderate	Moderate
Kivits (2002)	WOMAC Stiffness	12	Naproxen versus Placebo	Moderate	Moderate	Moderate
Kivits (2002)	WOMAC Total	6	Naproxen versus	Moderate	Moderate	Moderate

			Placebo			
Kivits (2002)	WOMAC Total	12	Naproxen versus Placebo	Moderate	Moderate	Moderate
Kivits (2002)	Physician Global Assessment	6	Naproxen versus Placebo	Moderate	Moderate	Moderate
Kivits (2002)	Physician Global Assessment	12	Naproxen versus Placebo	Moderate	Moderate	Moderate
Kivits (2002)	physician Global Assessment	6	Valdecoxib 10mg versus Naproxen	Moderate	Moderate	Moderate
Kivits (2002)	Physician Global Assessment	12	Valdecoxib 10mg versus Naproxen	Moderate	Moderate	Moderate
Kivits (2002)	Physician Global Assessment	6	Valdecoxib 20mg versus Naproxen	Moderate	Moderate	Moderate
Kivits (2002)	Physician Global Assessment	12	Valdecoxib 20mg versus Naproxen	Moderate	Moderate	Moderate
Kivits (2002)	Physician Global Assessment	6	Valdecoxib 5mg versus Naproxen	Moderate	Moderate	Moderate
Kivits (2002)	Physician Global Assessment	12	Valdecoxib 5mg versus Naproxen	Moderate	Moderate	Moderate
Kivits (2004)	Patient Global Assessment of Response to Treatment	6	Rofecoxib versus Placebo	High	Moderate	High

Kivits (2004)	Patient Global Assessment of Response to Treatment	6	Nabumetone versus Placebo	High	Moderate	High
Kivits (2004)	Patient Assessment of Treatment Response (good or excellent)	6	Rofecoxib 12.5mg versus Nabumetone	High	Moderate	High
Kogstad (1981)	Sequence A ability to walk (VAS)	4	Piroxicam 20mg versus Naproxen 250mg	Moderate	Moderate	Moderate
Kogstad (1981)	Sequence B ability to walk (VAS)	4	Piroxicam 20mg versus Naproxen 250mg	Moderate	Moderate	Moderate
Kogstad (1981)	Sequence A pain at night (VAS)	4	Piroxicam 20mg versus Naproxen 250mg	Moderate	Moderate	Moderate
Kogstad (1981)	Sequence B pain at night (VAS)	4	Piroxicam 20mg versus Naproxen 250mg	Moderate	Moderate	Moderate
Kogstad (1981)	Sequence A pain on movement (VAS)	4	Piroxicam 20mg versus Naproxen 250mg	Moderate	Moderate	Moderate
Kogstad (1981)	Sequence B pain on movement	4	Piroxicam 20mg versus Naproxen	Moderate	Moderate	Moderate

	(VAS)		250mg			
La Montagna (1998)	Present pain index	12	Piroxicam-Beta-Cyclodextrin 20mg versus Diclofenac 100mg	Moderate	Moderate	Moderate
La Montagna (1998)	Present pain index	24	Piroxicam-Beta-Cyclodextrin 20mg versus Diclofenac 100mg	Moderate	Moderate	Moderate
La Montagna (1998)	Visual analogue scale	12	Piroxicam-Beta-Cyclodextrin 20mg versus Diclofenac 100mg	Moderate	Moderate	Moderate
La Montagna (1998)	Visual analogue scale	24	Piroxicam-Beta-Cyclodextrin 20mg versus Diclofenac 100mg	Moderate	Moderate	Moderate
Lee (1985)	Adverse events	6	High dose diflunisal (NSAID) versus Placebo	Moderate	Moderate	Moderate
Lee (1985)	Adverse events	6	Low dose diflunisal (NSAID) versus Placebo	Moderate	Moderate	Moderate
Lehmann (2005)	Physician Global Assessment of	13	Celecoxib 200mg	Moderate	Moderate	Moderate

	Disease		versus Placebo			
Lehmann (2005)	Physician Global Assessment of Disease	13	Lumiracoxib 100mg versus Placebo	Moderate	Moderate	Moderate
Lehmann (2005)	VAS Pain improvement	13	Lumiracoxib (Cox-2) with loading dose versus Placebo	Moderate	Moderate	Moderate
Lehmann (2005)	WOMAC Pain	13	Lumiracoxib (Cox-2) with loading dose versus Placebo	Moderate	Moderate	Moderate
Lehmann (2005)	VAS Pain improvement	13	Celecoxib versus Placebo	Moderate	Moderate	Moderate
Lehmann (2005)	VAS Pain improvement	13	Lumiracoxib versus Placebo	Moderate	Moderate	Moderate
Lehmann (2005)	WOMAC Pain	13	Celecoxib versus Placebo	Moderate	Moderate	Moderate
Lehmann (2005)	WOMAC Pain	13	Lumiracoxib versus Placebo	Moderate	Moderate	Moderate
Lehmann (2005)	WOMAC Total	13	Lumiracoxib versus Placebo	Moderate	Moderate	Moderate
Lehmann (2005)	WOMAC Total	13	Lumiracoxib versus Placebo	Moderate	Moderate	Moderate

Lehmann (2005)	WOMAC Function improvement	13	Celecoxib 100mg versus Lumiracoxib with loading dose	Moderate	Moderate	Moderate
Lehmann (2005)	WOMAC Function improvement	13	Lumiracoxib 100mg versus Celecoxib	Moderate	Moderate	Moderate
Lehmann (2005)	WOMAC Function improvement	13	Lumiracoxib 100mg versus Lumiracoxib with loading dose	Moderate	Moderate	Moderate
Lehmann (2005)	VAS Pain improvement	13	Celecoxib 100mg versus Lumiracoxib with loading dose	Moderate	Moderate	Moderate
Lehmann (2005)	WOMAC Pain improvement	13	Celecoxib 100mg versus Lumiracoxib with loading dose	Moderate	Moderate	Moderate
Lehmann (2005)	VAS Pain improvement	13	Lumiracoxib 100mg versus Celecoxib	Moderate	Moderate	Moderate
Lehmann (2005)	VAS Pain improvement	13	Lumiracoxib 100mg versus Lumiracoxib with loading dose	Moderate	Moderate	Moderate

Lehmann (2005)	WOMAC Pain improvement	13	Lumiracoxib 100mg versus Celecoxib	Moderate	Moderate	Moderate
Lehmann (2005)	WOMAC Pain improvement	13	Lumiracoxib 100mg versus Lumiracoxib with loading dose	Moderate	Moderate	Moderate
Lehmann (2005)	WOMAC Stiffness improvement	13	Celecoxib 100mg versus Lumiracoxib with loading dose	Moderate	Moderate	Moderate
Lehmann (2005)	WOMAC Stiffness improvement	13	Lumiracoxib 100mg versus Celecoxib	Moderate	Moderate	Moderate
Lehmann (2005)	WOMAC Stiffness improvement	13	Lumiracoxib 100mg versus Lumiracoxib with loading dose	Moderate	Moderate	Moderate
Lehmann (2005)	WOMAC Total	13	Celecoxib 100mg versus Lumiracoxib with loading dose	Moderate	Moderate	Moderate
Lehmann (2005)	WOMAC Total	13	Lumiracoxib 100mg versus Celecoxib	Moderate	Moderate	Moderate
Lehmann (2005)	WOMAC Total	13	Lumiracoxib 100mg versus	Moderate	Moderate	Moderate

			Lumiracoxib with loading dose			
Lehmann (2005)	Physician Global Assessment of Disease	13	Lumiracoxib 100mg versus Celecoxib 200mg	Moderate	Moderate	Moderate
Lehmann (2005)	Patient Global Assessment of Disease	13	Celecoxib versus Placebo	Moderate	Moderate	Moderate
Lehmann (2005)	Patient Global Assessment of Disease	13	Lumiracoxib versus Placebo	Moderate	Moderate	Moderate
Lehmann (2005)	Patient Global Assessment of Disease	13	Lumiracoxib versus Celecoxib	Moderate	Moderate	Moderate
Liang (2003))	Change in Lequesne index	4	Etodolac Sustained-Release 400mg versus Diclofenac 50mg	Moderate	Moderate	Moderate
Lohmander (2005)	Patient Assessment of Treatment Response	6	Naproxcinod versus Naproxen	Low	Moderate	Low
Lohmander (2005)	Patient Global Assessment of Response to Treatment	6	Naproxcinod versus Placebo	Low	Moderate	Low

Lohmander (2005)	Patient Global Assessment of Response to Treatment	6	Naproxen versus Placebo	Low	Moderate	Low
Lohmander (2005)	Adverse events	6	Naproxcinod 750mg versus Piroxicam	Moderate	Moderate	Moderate
Lohmander (2005)	Adverse events	6	Naproxcinod 750mg versus Placebo	Moderate	Moderate	Moderate
Lohmander (2005)	Adverse events	6	Naproxen 500mg versus Placebo	Moderate	Moderate	Moderate
Louthrenoo (2007)	WOMAC Function	4	Diacerein versus Piroxicam	Moderate	Moderate	Moderate
Louthrenoo (2007)	WOMAC Function	8	Diacerein versus Piroxicam	Moderate	Moderate	Moderate
Louthrenoo (2007)	WOMAC Function	12	Diacerein versus Piroxicam	Moderate	Moderate	Moderate
Louthrenoo (2007)	WOMAC Function	16	Diacerein versus Piroxicam	Moderate	Moderate	Moderate
Louthrenoo (2007)	WOMAC Function	20	Diacerein versus Piroxicam	Moderate	Moderate	Moderate
Louthrenoo (2007)	WOMAC Function	24	Diacerein versus Piroxicam	Moderate	Moderate	Moderate

Louthrenoo (2007)	WOMAC Pain	4	Diacerein versus Piroxicam	Moderate	Moderate	Moderate
Louthrenoo (2007)	WOMAC Pain	8	Diacerein versus Piroxicam	Moderate	Moderate	Moderate
Louthrenoo (2007)	WOMAC Pain	12	Diacerein versus Piroxicam	Moderate	Moderate	Moderate
Louthrenoo (2007)	WOMAC Pain	16	Diacerein versus Piroxicam	Moderate	Moderate	Moderate
Louthrenoo (2007)	WOMAC Pain	20	Diacerein versus Piroxicam	Moderate	Moderate	Moderate
Louthrenoo (2007)	WOMAC Pain	24	Diacerein versus Piroxicam	Moderate	Moderate	Moderate
Louthrenoo (2007)	Paracetamol intake pills per day	4	Diacerein versus Piroxicam	Moderate	Moderate	Moderate
Louthrenoo (2007)	Paracetamol intake pills per day	8	Diacerein versus Piroxicam	Moderate	Moderate	Moderate
Louthrenoo (2007)	Paracetamol intake pills per day	12	Diacerein versus Piroxicam	Moderate	Moderate	Moderate
Louthrenoo (2007)	Paracetamol intake pills per day	16	Diacerein versus Piroxicam	Moderate	Moderate	Moderate

Louthrenoo (2007)	Paracetamol intake pills per day	20	Diacerein versus Piroxicam	Moderate	Moderate	Moderate
Louthrenoo (2007)	Paracetamol intake pills per day	24	Diacerein versus Piroxicam	Moderate	Moderate	Moderate
Louthrenoo (2007)	SF-36 sum score	16	Diacerein versus Piroxicam	Moderate	Moderate	Moderate
Louthrenoo (2007)	SF-36 sum score	24	Diacerein versus Piroxicam	Moderate	Moderate	Moderate
Louthrenoo (2007)	WOMAC Stiffness	4	Diacerein versus Piroxicam	Moderate	Moderate	Moderate
Louthrenoo (2007)	WOMAC Stiffness	8	Diacerein versus Piroxicam	Moderate	Moderate	Moderate
Louthrenoo (2007)	WOMAC Stiffness	12	Diacerein versus Piroxicam	Moderate	Moderate	Moderate
Louthrenoo (2007)	WOMAC Stiffness	16	Diacerein versus Piroxicam	Moderate	Moderate	Moderate
Louthrenoo (2007)	WOMAC Stiffness	20	Diacerein versus Piroxicam	Moderate	Moderate	Moderate
Louthrenoo (2007)	WOMAC Stiffness	24	Diacerein versus Piroxicam	Moderate	Moderate	Moderate
Louthrenoo	WOMAC Total	4	Diacerein versus	Moderate	Moderate	Moderate

(2007)			Piroxicam			
Louthrenoo (2007)	WOMAC Total	8	Diacerein versus Piroxicam	Moderate	Moderate	Moderate
Louthrenoo (2007)	WOMAC Total	12	Diacerein versus Piroxicam	Moderate	Moderate	Moderate
Louthrenoo (2007)	WOMAC Total	16	Diacerein versus Piroxicam	Moderate	Moderate	Moderate
Louthrenoo (2007)	WOMAC Total	20	Diacerein versus Piroxicam	Moderate	Moderate	Moderate
Louthrenoo (2007)	WOMAC Total	24	Diacerein versus Piroxicam	Moderate	Moderate	Moderate
Louthrenoo (2007)	Upper respiratory infection	12	Diacerein versus Piroxicam	Moderate	Moderate	Moderate
Louthrenoo (2007)	Dyspepsia	12	Diacerein versus Piroxicam	Moderate	Moderate	Moderate
Louthrenoo (2007)	Diarrhea	12	Diacerein versus Piroxicam	Moderate	Moderate	Moderate
Louthrenoo (2007)	Abdominal pain	12	Diacerein versus Piroxicam	Moderate	Moderate	Moderate
Louthrenoo (2007)	Bowel motility disorders	12	Diacerein versus Piroxicam	Moderate	Moderate	Moderate
Louthrenoo	Constipation	12	Diacerein versus	Moderate	Moderate	Moderate

(2007)			Piroxicam			
Louthrenoo (2007)	Nausea	12	Diacerein versus Piroxicam	Moderate	Moderate	Moderate
Louthrenoo (2007)	Hypertension	12	Diacerein versus Piroxicam	Moderate	Moderate	Moderate
Louthrenoo (2007)	Myalgia	12	Diacerein versus Piroxicam	Moderate	Moderate	Moderate
Louthrenoo (2007)	Arthropathy	12	Diacerein versus Piroxicam	Moderate	Moderate	Moderate
Louthrenoo (2007)	Oedema	12	Diacerein versus Piroxicam	Moderate	Moderate	Moderate
Louthrenoo (2007)	Dizziness	12	Diacerein versus Piroxicam	Moderate	Moderate	Moderate
Louthrenoo (2007)	WOMAC Function	4	Diacerein versus Piroxicam	Moderate	Moderate	Moderate
Louthrenoo (2007)	WOMAC Function	8	Diacerein versus Piroxicam	Moderate	Moderate	Moderate
Louthrenoo (2007)	WOMAC Function	12	Diacerein versus Piroxicam	Moderate	Moderate	Moderate
Luyten (2007)	WOMAC	24	Continuous Celecoxib versus Intermittent Celecoxib	Moderate	Moderate	Moderate

Luyten (2007)	WOMAC Stiffness	24	Continuous Celecoxib versus Intermittent Celecoxib	Moderate	Moderate	Moderate
Luyten (2007)	WOMAC Total	24	Continuous Celecoxib versus Intermittent Celecoxib	Moderate	Moderate	Moderate
Luyten (2007)	WOMAC Pain	24	Continuous Celecoxib versus Intermittent Celecoxib	Moderate	Moderate	Moderate
Luyten (2007)	WOMAC Stiffness	24	Continuous Celecoxib versus Intermittent Celecoxib	Moderate	Moderate	Moderate
Luyten (2007)	WOMAC Total	24	Continuous Celecoxib versus Intermittent Celecoxib	Moderate	Moderate	Moderate
Lücker (1994)	Lequesne functional index	4	Nimesulide 100mg versus Etodolac 300mg	Moderate	Moderate	Moderate
Lücker (1994)	Lequesne functional index	8	Nimesulide 100mg versus Etodolac 300mg	Moderate	Moderate	Moderate

Lücker (1994)	Lequesne Functional index	12	Nimesulide 100mg versus Etodolac 300mg	Moderate	Moderate	Moderate
Lücker (1994)	VAS Pain	4	Nimesulide 100mg versus Etodolac	Moderate	Moderate	Moderate
Lücker (1994)	VAS Pain	8	Nimesulide 100mg versus Etodolac	Moderate	Moderate	Moderate
Lücker (1994)	VAS Pain	12	Nimesulide 100mg versus Etodolac	Moderate	Moderate	Moderate
Lücker (1994)	Lequesne index	4	Nimesulide 100mg versus Etodolac	Moderate	Moderate	Moderate
Lücker (1994)	Lequesne index	8	Nimesulide 100mg versus Etodolac	Moderate	Moderate	Moderate
Lücker (1994)	Lequesne index	12	Nimesulide 100mg versus Etodolac	Moderate	Moderate	Moderate
Lücker (1994)	Lequesne functional index	4	Nimesulide 100mg versus Etodolac 300mg	Moderate	Moderate	Moderate
Lücker (1994)	Lequesne	8	Nimesulide 100mg versus	Moderate	Moderate	Moderate

	Functional index		Etodolac 300mg			
Lücker (1994)	Lequesne Functional index	12	Nimesulide 100mg versus Etodolac 300mg	Moderate	Moderate	Moderate
Lücker (1994)	VAS Pain (10cm)	4	Nimesulide 100mg versus Etodolac 300mg	Moderate	Moderate	Moderate
Lücker (1994)	VAS Pain (10cm)	8	Nimesulide 100mg versus Etodolac 300mg	Moderate	Moderate	Moderate
Lücker (1994)	VAS Pain (10cm)	12	Nimesulide 100mg versus Etodolac 300mg	Moderate	Moderate	Moderate
McKenna (2001)	Alt increased	6	Celecoxib 100mg versus Diclofenac 50mg	Moderate	Moderate	Moderate
McKenna (2001)	Anaemia	6	Celecoxib 100mg versus Diclofenac 50mg	Moderate	Moderate	Moderate
McKenna (2001)	Back pain	6	Celecoxib 100mg versus Diclofenac 50mg	Moderate	Moderate	Moderate
McKenna (2001)	Constipation	6	Celecoxib 100mg versus Diclofenac 50mg	Moderate	Moderate	Moderate

McKenna (2001)	Diarrhea	6	Celecoxib 100mg versus Diclofenac 50mg	Moderate	Moderate	Moderate
McKenna (2001)	Dizziness	6	Celecoxib 100mg versus Diclofenac 50mg	Moderate	Moderate	Moderate
McKenna (2001)	Dyspepsia	6	Celecoxib 100mg versus Diclofenac 50mg	Moderate	Moderate	Moderate
McKenna (2001)	Flatulence	6	Celecoxib 100mg versus Diclofenac 50mg	Moderate	Moderate	Moderate
McKenna (2001)	Headache	6	Celecoxib 100mg versus Diclofenac 50mg	Moderate	Moderate	Moderate
McKenna (2001)	Accidental injury	6	Celecoxib 100mg versus Diclofenac 50mg	Moderate	Moderate	Moderate
McKenna (2001)	Myalgia	6	Celecoxib 100mg versus Diclofenac 50mg	Moderate	Moderate	Moderate
McKenna (2001)	Nausea	6	Celecoxib 100mg versus Diclofenac 50mg	Moderate	Moderate	Moderate
McKenna (2001)	Peripheral	6	Celecoxib 100mg versus Diclofenac	Moderate	Moderate	Moderate

	Oedema		50mg			
McKenna (2001)	Nausea	6	Rofecoxib 25mg versus Naproxcinod 125mg	Moderate	Moderate	Moderate
McKenna (2001)	WOMAC Function	6	Celecoxib versus Placebo	Moderate	Moderate	Moderate
McKenna (2001)	VAS Pain improvement	6	Celecoxib versus Placebo	Moderate	Moderate	Moderate
McKenna (2001)	WOMAC Pain	6	Celecoxib versus Placebo	Moderate	Moderate	Moderate
McKenna (2001)	WOMAC Stiffness	6	Celecoxib versus Placebo	Moderate	Moderate	Moderate
McKenna (2001)	WOMAC Total	6	Celecoxib versus Placebo	Moderate	Moderate	Moderate
McKenna (2001)	Patient Global Assessment	6	Celecoxib versus Placebo	Moderate	Moderate	Moderate
McKenna (2001)	Patient Global Assessment	6	Diclofenac versus Placebo	Moderate	Moderate	Moderate
McKenna (2001)	Patient Global Assessment	6	Celecoxib versus Diclofenac	Moderate	Moderate	Moderate
McKenna (2001)	Physician Global Assessment	6	Celecoxib (Cox-2) versus Placebo	Moderate	Moderate	Moderate

McKenna (2001)	WOMAC Function improvement	6	Diclofenac versus Placebo	Moderate	Moderate	Moderate
McKenna (2001)	VAS Pain	6	Diclofenac versus Placebo	Moderate	Moderate	Moderate
McKenna (2001)	WOMAC Pain	6	Diclofenac versus Placebo	Moderate	Moderate	Moderate
McKenna (2001)	WOMAC Stiffness	6	Diclofenac versus Placebo	Moderate	Moderate	Moderate
McKenna (2001)	WOMAC Total	6	Diclofenac versus Placebo	Moderate	Moderate	Moderate
McKenna (2001)	Physician Global Assessment	6	Diclofenac versus Placebo	Moderate	Moderate	Moderate
McKenna (2001)	WOMAC Function	6	Celecoxib 100mg versus Diclofenac 100mg	Moderate	Moderate	Moderate
McKenna (2001)	WOMAC Pain	6	Celecoxib 100mg versus Diclofenac 100mg	Moderate	Moderate	Moderate
McKenna (2001)	VAS Pain	6	Celecoxib 100mg versus Diclofenac 100mg	Moderate	Moderate	Moderate
McKenna (2001)	WOMAC Stiffness	6	Celecoxib 100mg versus Diclofenac	Moderate	Moderate	Moderate

			100mg			
McKenna (2001)	WOMAC Total	6	Celecoxib 100mg versus Diclofenac 100mg	Moderate	Moderate	Moderate
McKenna (2001)	Physician Global Assessment	6	Celecoxib versus Diclofenac (NSAID)	Moderate	Moderate	Moderate
Micelli (2004)	VAS Pain	6	Acetaminophen versus Placebo	Moderate	Moderate	Moderate
Ottillinger (2001)	VAS Pain	4	Eltenac gel 0.3% versus Eltenac gel 0.1%	Moderate	Moderate	Moderate
Ottillinger (2001)	VAS Pain	5	Eltenac gel 0.3% versus Eltenac gel 0.1%	Moderate	Moderate	Moderate
Ottillinger (2001)	VAS Pain	6	Eltenac gel 0.3% versus Eltenac gel 0.1%	Moderate	Moderate	Moderate
Ottillinger (2001)	VAS Pain	4	Eltenac gel 1% versus Eltenac gel 0.3%	Moderate	Moderate	Moderate
Ottillinger (2001)	VAS Pain	4	Eltenac gel 1% versus Eltenac gel 0.1%	Moderate	Moderate	Moderate

Ottillinger (2001)	VAS Pain	5	Eltenac gel 1% versus Eltenac gel 0.3%	Moderate	Moderate	Moderate
Ottillinger (2001)	VAS Pain	5	Eltenac gel 1% versus Eltenac gel 0.1%	Moderate	Moderate	Moderate
Ottillinger (2001)	VAS Pain	6	Eltenac gel 1% versus Eltenac gel 0.3%	Moderate	Moderate	Moderate
Ottillinger (2001)	VAS Pain	6	Eltenac gel 1% versus Eltenac gel 0.1%	Moderate	Moderate	Moderate
Ottillinger (2001)	VAS Pain	4	Eltenac gel 0.1% versus Placebo gel	Moderate	Moderate	Moderate
Ottillinger (2001)	VAS Pain	5	Eltenac gel 0.1% versus Placebo gel	Moderate	Moderate	Moderate
Ottillinger (2001)	VAS Pain	6	Eltenac gel 0.1% versus Placebo gel	Moderate	Moderate	Moderate
Ottillinger (2001)	VAS Pain	4	Eltenac gel 0.3% versus Placebo gel	Moderate	Moderate	Moderate
Ottillinger (2001)	VAS Pain	5	Eltenac gel 0.3% versus Placebo gel	Moderate	Moderate	Moderate
Ottillinger (2001)	VAS Pain	6	Eltenac gel 0.3% versus Placebo gel	Moderate	Moderate	Moderate

Ottillinger (2001)	VAS Pain	4	Eltenac gel 1% versus Placebo gel	Moderate	Moderate	Moderate
Ottillinger (2001)	VAS Pain	5	Eltenac gel 1% versus Placebo gel	Moderate	Moderate	Moderate
Ottillinger (2001)	VAS Pain	6	Eltenac gel 1% versus Placebo gel	Moderate	Moderate	Moderate
Queiros (1990)	Mean pain at night (1 to 4)	4	Piroxicam 20mg versus Oxaprozin 1200mg	Moderate	Moderate	Moderate
Queiros (1990)	Mean pain on walking in the evening (1 to 21)	4	Piroxicam 20mg versus Oxaprozin 1200mg	Moderate	Moderate	Moderate
Queiros (1990)	Mean pain on walking in the morning (1 to 21)	4	Piroxicam 20mg versus Oxaprozin 1200mg	Moderate	Moderate	Moderate
Roth (2004)	WOMAC Function	12	Topical Diclofenac versus vehicle control	High	Moderate	High
Roth (2004)	WOMAC Pain	12	Topical Diclofenac versus vehicle control	High	Moderate	High
Roth (2004)	WOMAC Pain on walking	12	Topical Diclofenac versus vehicle control	High	Moderate	High

Roth (2004)	WOMAC Stiffness	12	Topical Diclofenac versus vehicle control	High	Moderate	High
Roth (2004)	Patient Global Assessment	12	Topical Diclofenac versus Placebo	High	Moderate	High
Rother (2007)	WOMAC Function	6	Topical Ketoprofen versus Celecoxib	Moderate	Moderate	Moderate
Rother (2007)	WOMAC Function	6	Topical Ketoprofen versus Placebo	Moderate	Moderate	Moderate
Rother (2007)	WOMAC Function	6	Celecoxib versus Placebo	Moderate	Moderate	Moderate
Rother (2007)	WOMAC Pain	6	Topical Ketoprofen versus Celecoxib	Moderate	Moderate	Moderate
Rother (2007)	WOMAC Pain	6	Topical Ketoprofen versus Placebo	Moderate	Moderate	Moderate
Rother (2007)	WOMAC Pain	6	Celecoxib versus Placebo	Moderate	Moderate	Moderate
Schnitzer (2010)	WOMAC Total	12	Naproxen versus Placebo	Moderate	Moderate	Moderate

Schnitzer (1999)	Minimum effective Naproxen dose	8	Tramadol versus Placebo	Moderate	Moderate	Moderate
Schnitzer (2005)	Patient Global Assessment of Disease	6	Rofecoxib 25mg versus Placebo	Moderate	Moderate	Moderate
Schnitzer (2005)	Patient Global Assessment of Response to Treatment	6	Rofecoxib 25mg versus Placebo	Moderate	Moderate	Moderate
Schnitzer (2005)	Patient Assessment of Treatment Response	6	Celecoxib 200mg versus Rofecoxib 12.5mg	Low	Moderate	Low
Schnitzer (2005)	Patient Assessment of Treatment Response	6	Celecoxib 200mg versus Rofecoxib 25mg	Low	Moderate	Low
Schnitzer (2005)	Patient Assessment of Treatment Response	6	Rofecoxib 12.5mg versus Rofecoxib 25mg	Low	Moderate	Low
Schnitzer (2005)	Abdominal pain	6	Acetaminophen 4000mg versus Rofecoxib 12.5mg	Low	Moderate	Low

Schnitzer (2005)	Abdominal pain	6	Acetaminophen 4000mg versus Rofecoxib 25mg	Low	Moderate	Low
Schnitzer (2005)	Abdominal pain		Acetaminophen 4000mg versus Celecoxib 200mg	Low	Moderate	Low
Schnitzer (2005)	Any clinical adverse event, VACT2	6	Rofecoxib 12.5mg versus Rofecoxib 12.5mg	Low	Moderate	Low
Schnitzer (2005)	Any clinical adverse event, VACT2	6	Celecoxib 200mg versus Rofecoxib 25mg	Low	Moderate	Low
Schnitzer (2005)	Any clinical adverse event, VACT2	6	Celecoxib 200mg versus Rofecoxib 25mg	Low	Moderate	Low
Schnitzer (2005)	Diarrhea	6	Acetaminophen 4000mg versus Rofecoxib 12.5mg	Low	Moderate	Low
Schnitzer (2005)	Diarrhea	6	Acetaminophen 4000mg versus Rofecoxib 25mg	Low	Moderate	Low
Schnitzer (2005)	Diarrhea		Acetaminophen 4000mg versus Celecoxib 200mg	Low	Moderate	Low

Schnitzer (2005)	Headache	6	Acetaminophen 4000mg versus Rofecoxib 12.5mg	Low	Moderate	Low
Schnitzer (2005)	Headache	6	Acetaminophen 4000mg versus Rofecoxib 25mg	Low	Moderate	Low
Schnitzer (2005)	Lower extremity edema	6	Acetaminophen 4000mg versus Rofecoxib 12.5mg	Low	Moderate	Low
Schnitzer (2005)	Lower extremity edema	6	Acetaminophen 4000mg versus Rofecoxib 25mg	Low	Moderate	Low
Schnitzer (2005)	Nausea	6	Acetaminophen 4000mg versus Rofecoxib 12.5mg	Low	Moderate	Low
Schnitzer (2005)	Nausea	6	Acetaminophen 4000mg versus Rofecoxib 25mg	Low	Moderate	Low
Schnitzer (2005)	Upper respiratory infection	6	Acetaminophen 4000mg versus Rofecoxib 12.5mg	Low	Moderate	Low
Schnitzer (2005)	Upper respiratory	6	Acetaminophen 4000mg versus	Low	Moderate	Low

	infection		Rofecoxib 25mg			
Schnitzer (2005)	Patient Assessment of Treatment Response	6	Naproxcinod 125mg versus Naproxcinod 375mg	Moderate	Moderate	Moderate
Schnitzer (2005)	Patient Global Assessment of Disease Status	6	Naproxcinod 125mg versus Naproxcinod 750mg	Moderate	Moderate	Moderate
Schnitzer (2005)	Patient Assessment of Treatment Response	6	Naproxcinod 125mg versus Naproxcinod 750mg	Moderate	Moderate	Moderate
Schnitzer (2005)	Patient Global Assessment of Disease Status	6	Naproxcinod 375mg versus Naproxcinod 750mg	Moderate	Moderate	Moderate
Schnitzer (2005)	Patient Assessment of Treatment Response	6	Naproxcinod 375mg versus Naproxcinod 750mg	Moderate	Moderate	Moderate
Schnitzer (2005)	Patient Global Assessment of Disease Status	6	Naproxcinod 125mg versus Naproxen 500mg	Moderate	Moderate	Moderate
Schnitzer (2005)	Patient Assessment of Treatment	6	Naproxcinod 125mg versus	Moderate	Moderate	Moderate

	Response		Naproxen 500mg			
Schnitzer (2005)	Patient Global Assessment of Disease Status	6	Naproxcinod 375mg versus Naproxen 500mg	Moderate	Moderate	Moderate
Schnitzer (2005)	Patient Assessment of Treatment Response	6	Naproxcinod 375mg versus Naproxen 500mg	Moderate	Moderate	Moderate
Schnitzer (2005)	Patient Global Assessment of Disease Status	6	Naproxcinod 750mg versus Naproxen 500mg	Moderate	Moderate	Moderate
Schnitzer (2005)	Patient Assessment of Treatment Response	6	Naproxcinod 750mg versus Naproxen 500mg	Moderate	Moderate	Moderate
Schnitzer (2005)	Patient Global Assessment of Response to Treatment	6	Naproxcinod 125mg versus Placebo	Moderate	Moderate	Moderate
Schnitzer (2005)	Patient Global Assessment of Disease Status	6	Naproxcinod 125mg versus Placebo	Moderate	Moderate	Moderate
Schnitzer (2005)	Patient Global Assessment of Disease Status	6	Naproxcinod 125mg versus Placebo	Moderate	Moderate	Moderate

Schnitzer (2005)	Patient Global Assessment of Response to Treatment	6	Naproxcinod 375mg versus Placebo	Moderate	Moderate	Moderate
Schnitzer (2005)	Patient Global Assessment of Disease Status	6	Naproxcinod 375mg versus Placebo	Moderate	Moderate	Moderate
Schnitzer (2005)	Patient Global Assessment of Response to Treatment	6	Naproxcinod 750mg versus Placebo	Moderate	Moderate	Moderate
Schnitzer (2005)	Patient Global Assessment of Disease Status	6	Naproxcinod 750mg versus Placebo	Moderate	Moderate	Moderate
Schnitzer (2005)	Patient Global Assessment of Response to Treatment	6	Naproxen 500mg versus Placebo	Moderate	Moderate	Moderate
Schnitzer (2005)	Patient Global Assessment of Disease Status	6	Naproxen 500mg versus Placebo	Moderate	Moderate	Moderate
Schnitzer (2005)	Patient Global Assessment of Disease responders	6	Rofecoxib 25mg versus Naproxcinod 125mg	Moderate	Moderate	Moderate
Schnitzer (2005)	Patient Global Assessment of	6	Rofecoxib 25mg versus	Moderate	Moderate	Moderate

	Disease responders		Naproxcinod 375mg			
Schnitzer (2005)	Patient Global Assessment of Disease responders	6	Rofecoxib 25mg versus Naproxcinod 750mg	Moderate	Moderate	Moderate
Schnitzer (2005)	Patient Assessment of Treatment Response (Good or Excellent)	6	Rofecoxib 25mg versus Naproxcinod 125mg	Moderate	Moderate	Moderate
Schnitzer (2005)	Patient Assessment of Treatment Response (Good or Excellent)	6	Rofecoxib 25mg versus Naproxcinod 375mg	Moderate	Moderate	Moderate
Schnitzer (2005)	Patient Assessment of Treatment Response (Good or Excellent)	6	Rofecoxib 25mg versus Naproxcinod 750mg	Moderate	Moderate	Moderate
Schnitzer (2009)	Patient Assessment of Treatment Response	4	Rofecoxib 12.5mg versus Rofecoxib 25mg	Moderate	Moderate	Moderate
Schnitzer (2009)	Physician Assessment of Treatment	4	Rofecoxib 12.5mg versus	Moderate	Moderate	Moderate

	Response		Rofecoxib 25mg			
Schnitzer (2010)	Rescue Acetaminophen	13	Naproxcinod versus Placebo	Moderate	Moderate	Moderate
Schnitzer (2010)	Rescue Acetaminophen	13	Naproxcinod versus Placebo	Moderate	Moderate	Moderate
Schnitzer (2010)	SF-36 MCS improvement	13	Naproxcinod versus Placebo	Moderate	Moderate	Moderate
Schnitzer (2010)	SF-36 MCS improvement	13	Naproxcinod versus Placebo	Moderate	Moderate	Moderate
Schnitzer (2010)	WOMAC Function	13	Naproxcinod versus Placebo	Moderate	Moderate	Moderate
Schnitzer (2010)	VAS Pain at rest improvement	13	Naproxcinod versus Placebo	Moderate	Moderate	Moderate
Schnitzer (2010)	VAS Pain at rest improvement	13	Naproxcinod versus Placebo	Moderate	Moderate	Moderate
Schnitzer (2010)	VAS Pain during walking improvement	13	Naproxcinod versus Placebo	Moderate	Moderate	Moderate
Schnitzer (2010)	VAS Pain during walking improvement	13	Naproxcinod versus Placebo	Moderate	Moderate	Moderate
Schnitzer (2010)	WOMAC Pain	13	Naproxcinod versus Placebo	Moderate	Moderate	Moderate

Schnitzer (2010)	WOMAC Pain	13	Naproxcinod versus Placebo	Moderate	Moderate	Moderate
Schnitzer (2010)	WOMAC Total	13	Naproxcinod versus Placebo	Moderate	Moderate	Moderate
Schnitzer (2010)	WOMAC Total	13	Naproxcinod versus Placebo	Moderate	Moderate	Moderate
Schnitzer (2010)	Rescue Acetaminophen	13	Naproxcinod versus Placebo	Moderate	Moderate	Moderate
Schnitzer (2010)	Rescue Acetaminophen	13	Naproxcinod versus Placebo	Moderate	Moderate	Moderate
Schnitzer (2010)	SF-36 MCS improvement	13	Naproxcinod versus Placebo	Moderate	Moderate	Moderate
Schnitzer (2010)	SF-36 MCS improvement	13	Naproxcinod versus Placebo	Moderate	Moderate	Moderate
Schnitzer (2010)	WOMAC Function	13	Naproxcinod versus Placebo	Moderate	Moderate	Moderate
Schnitzer (2010)	VAS Pain at rest improvement	13	Naproxcinod 375mg versus Placebo	Moderate	Moderate	Moderate
Schnitzer (2010)	VAS Pain at rest improvement	13	Naprocinod 750mg versus Placebo	Moderate	Moderate	Moderate
Schnitzer (2010)	VAS Pain during walking	13	Naproxcinod 375mg versus	Moderate	Moderate	Moderate

	improvement		Placebo			
Schnitzer (2010)	VAS Pain during walking	13	Naprocinod 750mg versus Placebo	Moderate	Moderate	Moderate
Schnitzer (2010)	WOMAC Pain	13	Naproxcinod 375mg versus Placebo	Moderate	Moderate	Moderate
Schnitzer (2010)	WOMAC Pain	13	Naprocinod 750mg versus Placebo	Moderate	Moderate	Moderate
Schnitzer (2009)	WOMAC Function	4	Rofecoxib 12.5mg versus Rofecoxib	Moderate	Moderate	Moderate
Schnitzer (2009)	WOMAC Pain	4	Rofecoxib 12.5mg versus Rofecoxib	Moderate	Moderate	Moderate
Schnitzer (2009)	WOMAC Stiffness	4	Rofecoxib 12.5mg versus Rofecoxib	Moderate	Moderate	Moderate
Schnitzer (2010)	Rescue Acetaminophen	12	Naproxen versus Placebo	Moderate	Moderate	Moderate
Schnitzer (2010)	SF-36 MCS improvement	12	Naproxen versus Placebo	Moderate	Moderate	Moderate
Schnitzer (2010)	WOMAC Function	12	Naproxen versus	Moderate	Moderate	Moderate

	improvement		Placebo			
Schnitzer (2010)	VAS Pain	12	Naproxen versus Placebo	Moderate	Moderate	Moderate
Schnitzer (2010)	VAS Pain during walking improvement	12	Naproxen versus Placebo	Moderate	Moderate	Moderate
Schnitzer (2010)	WOMAC Pain	12	Naproxen versus Placebo	Moderate	Moderate	Moderate
Tannenbaum (2004)	Physician Global Assessment of Disease	13	Celecoxib 200mg versus Placebo	Moderate	Moderate	Moderate
Tannenbaum (2004)	Physician Global Assessment of Disease	13	Lumiracoxib 200mg versus Placebo	Moderate	Moderate	Moderate
Tannenbaum (2004)	Physician Global Assessment of Disease	13	Lumiracoxib 400mg versus Placebo	Moderate	Moderate	Moderate
Tannenbaum (2004)	WOMAC Function	13	Celecoxib versus Placebo	Moderate	Moderate	Moderate
Tannenbaum (2004)	WOMAC Function	13	Lumiracoxib versus Placebo	Moderate	Moderate	Moderate
Tannenbaum (2004)	WOMAC Function	13	Lumiracoxib versus Placebo	Moderate	Moderate	Moderate

Tannenbaum (2004)	VAS Pain improvement	13	Celecoxib versus Placebo	Moderate	Moderate	Moderate
Tannenbaum (2004)	VAS Pain improvement	13	Lumiracoxib versus Placebo	Moderate	Moderate	Moderate
Tannenbaum (2004)	VAS Pain improvement	13	Lumiracoxib versus Placebo	Moderate	Moderate	Moderate
Tannenbaum (2004)	WOMAC Pain	13	Celecoxib versus Placebo	Moderate	Moderate	Moderate
Tannenbaum (2004)	WOMAC Pain	13	Lumiracoxib versus Placebo	Moderate	Moderate	Moderate
Tannenbaum (2004)	WOMAC Pain	13	Lumiracoxib versus Placebo	Moderate	Moderate	Moderate
Tannenbaum (2004)	WOMAC Stiffness	13	Celecoxib versus Placebo	Moderate	Moderate	Moderate
Tannenbaum (2004)	WOMAC Stiffness	13	Lumiracoxib versus Placebo	Moderate	Moderate	Moderate
Tannenbaum (2004)	WOMAC Stiffness	13	Lumiracoxib versus Placebo	Moderate	Moderate	Moderate
Tannenbaum (2004)	WOMAC Total	13	Celecoxib versus Placebo	Moderate	Moderate	Moderate
Tannenbaum (2004)	WOMAC Total	13	Lumiracoxib versus Placebo	Moderate	Moderate	Moderate

Tannenbaum (2004)	WOMAC Total	13	Lumiracoxib versus Placebo	Moderate	Moderate	Moderate
Tannenbaum (2004)	Patient Global Assessment of Disease	13	Celecoxib 200mg versus Placebo	Moderate	Moderate	Moderate
Tannenbaum (2004)	Patient Global Assessment of Disease	13	Lumiracoxib 200mg versus Placebo	Moderate	Moderate	Moderate
Tannenbaum (2004)	Patient Global Assessment of Disease	13	Lumiracoxib 400mg versus Placebo	Moderate	Moderate	Moderate
Tannenbaum (2004)	Adverse events	13	Celecoxib 100mg versus Placebo	Moderate	Moderate	Moderate
Tannenbaum (2004)	Adverse events	13	Lumiracoxib 200mg versus Placebo	Moderate	Moderate	Moderate
Tannenbaum (2004)	Adverse events	13	Lumiracoxib 400mg versus Placebo	Moderate	Moderate	Moderate
Torri (1994)	WOMAC averaged VAS Pain	12	Aceclofenac versus Piroxicam	Moderate	Moderate	Moderate
Tyson (1980)	Linear analogue pain scale	8	Benoxaprofen versus Ibuprofen	Moderate	Moderate	Moderate

Tyson (1980)	Linear analogue pain scale	12	Benoxaprofen versus Ibuprofen	Moderate	Moderate	Moderate
Tyson (1980)	Linear analogue pain scale	16	Benoxaprofen versus Ibuprofen	Moderate	Moderate	Moderate
Williams (2000)	WOMAC Function	6	Celecoxib 200mg QD versus Placebo	Moderate	Moderate	Moderate
Williams (2000)	Lequesne Index	6	Celecoxib 100mg BID versus Placebo	Moderate	Moderate	Moderate
Williams (2000)	Lequesne Index	6	Celecoxib 200mg QD versus Placebo	Moderate	Moderate	Moderate
Williams (2000)	Lequesne Index	6	Celecoxib 200mg versus Celecoxib 100mg bid	Moderate	Moderate	Moderate
Williams (2000)	WOMAC Total	6	Celecoxib 200mg versus Celecoxib	Moderate	Moderate	Moderate
Williams (2000)	Patient Global Assessment	6	Celecoxib 200mg versus Celecoxib 100mg	Moderate	Moderate	Moderate
Williams (2000)	Lequesne Index	6	Celecoxib 100mg BID versus Placebo	Moderate	Moderate	Moderate

Williams (2000)	Lequesne Index	6	Celecoxib 200mg QD versus Placebo	Moderate	Moderate	Moderate
Williams (2000)	Lequesne Index	6	Celecoxib 200mg versus Celecoxib 100mg bid	Moderate	Moderate	Moderate
Williams (2000)	Patient Global Assessment	6	Celecoxib 200mg versus Placebo	Moderate	Moderate	Moderate
Williams (2000)	Patient Global Assessment	6	Celecoxib 100mg versus Placebo	Moderate	Moderate	Moderate
Williams (2000)	Patient Global Assessment	6	Celecoxib 100 versus Celecoxib 200mg	Moderate	Moderate	Moderate
Williams (2001)	Patient Global Assessment	6	Celecoxib 100mg versus Placebo	Moderate	Moderate	Moderate
Williams (2001)	Patient Global Assessment	6	Celecoxib 200mg versus Placebo	Moderate	Moderate	Moderate
Williams (2001)	Lequesne Index	6	Celecoxib versus Placebo	Moderate	Moderate	Moderate
Williams (2001)	Lequesne Index	6	Celecoxib versus Placebo	Moderate	Moderate	Moderate
Williams (2001)	Lequesne Index	6	Celecoxib 100mg BID versus Celecoxib 200mg	Low	Moderate	Low

			qd			
Williams (2001)	Adverse events	6	Celecoxib 100mg versus Celecoxib 200mg	Moderate	Moderate	Moderate
Williams (2001)	Adverse events	6	Celecoxib 100mg versus Placebo	Moderate	Moderate	Moderate
Williams (2001)	Adverse events	6	Celecoxib 200mg versus Placebo	Moderate	Moderate	Moderate
Zheng (2006)	VAS Pain on walking improvement	12	Diacerein versus Diclofenac	Moderate	Moderate	Moderate
Zheng (2006)	VAS Pain on walking		Diacerein versus Diclofenac	Moderate	Moderate	Moderate
Zheng (2006)	WOMAC Total VAS improvement	12	Diacerein versus Diclofenac	Moderate	Moderate	Moderate
Zheng (2006)	WOMAC Total		Diacerein versus Diclofenac	Moderate	Moderate	Moderate
Zheng (2006)	Pain on walking	4	Diacerein versus Diclofenac	Moderate	Moderate	Moderate
Zheng (2006)	Pain on walking	8	Diacerein versus Diclofenac	Moderate	Moderate	Moderate
Zheng (2006)	Pain on walking	12	Diacerein versus	Moderate	Moderate	Moderate

			Diclofenac			
Zheng (2006)	Pain on walking	16	Diacerein versus Diclofenac	Moderate	Moderate	Moderate
Zheng (2006)	WOMAC Total	4	Diacerein versus Diclofenac	Moderate	Moderate	Moderate
Zheng (2006)	WOMAC Total	8	Diacerein versus Diclofenac	Moderate	Moderate	Moderate
Zheng (2006)	WOMAC Total	12	Diacerein versus Diclofenac	Moderate	Moderate	Moderate
Zheng (2006)	WOMAC Total	16	Diacerein versus Diclofenac	Moderate	Moderate	Moderate
Zheng (2006)	Adverse events	16	Diacerein versus Diclofenac	Moderate	Moderate	Moderate
Zheng (2006)	GI adverse events	16	Diacerein versus Diclofenac	Moderate	Moderate	Moderate
Bradley (1991)	HAQ Disability improvement	4	Ibuprofen 300mg versus Ibuprofen 600mg	Moderate	Moderate	Moderate
Bradley (1991)	Health Assessment Questionnaire improvement	4	Ibuprofen 300mg versus Ibuprofen 600	Moderate	Moderate	Moderate
Bradley (1991)	Walk time (sec)	4	Ibuprofen 300mg versus Ibuprofen	Moderate	Moderate	Moderate

	improvement		600mg			
Burch (2007)	Improvement in pain intensity numerical rating scale	12	Tramadol Contramid OAD versus Placebo	Moderate	Moderate	Moderate
Ehrich (1999)	Physician Global Assessment of Disease	6	Rofecoxib 125mg versus Placebo	Moderate	Moderate	Moderate
Ehrich (1999)	Physician Global Assessment of Disease	6	Rofecoxib 25mg versus Placebo	Moderate	Moderate	Moderate
Ehrich (1999)	Physician Global Assessment of Response to Treatment	6	Rofecoxib 125mg versus Placebo	Moderate	Moderate	Moderate
Ehrich (1999)	Physician Global Assessment of Response to Treatment	6	Rofecoxib 25mg versus Placebo	Moderate	Moderate	Moderate
Ehrich (1999)	WOMAC Function	6	Rofecoxib versus Placebo	Moderate	Moderate	Moderate
Ehrich (1999)	WOMAC Pain	6	Rofecoxib versus Placebo	Moderate	Moderate	Moderate
Ehrich (1999)	VAS Pain improvement	6	Rofecoxib versus Placebo	Moderate	Moderate	Moderate

Ehrich (1999)	VAS Pain improvement	6	Rofecoxib versus Placebo	Moderate	Moderate	Moderate
Ehrich (1999)	WOMAC Stiffness	6	Rofecoxib versus Placebo	Moderate	Moderate	Moderate
Ehrich (1999)	Patient Global Assessment of Disease	6	Rofecoxib 125mg versus Placebo	Moderate	Moderate	Moderate
Ehrich (1999)	Patient Global Assessment of Disease	6	Rofecoxib 25mg versus Placebo	Moderate	Moderate	Moderate
Pavelka (2007)	WOMAC Function	8	Diacerein versus Placebo	Moderate	Moderate	Moderate
Pavelka (2007)	WOMAC Function	16	Diacerein versus Placebo	Moderate	Moderate	Moderate
Pavelka (2007)	WOMAC Function	20	Diacerein versus Placebo	Moderate	Moderate	Moderate
Pavelka (2007)	WOMAC Function	24	Diacerein versus Placebo	Moderate	Moderate	Moderate
Pavelka (2007)	WOMAC Pain	8	Diacerein versus Placebo	Moderate	Moderate	Moderate
Pavelka (2007)	WOMAC Pain	12	Diacerein versus Placebo	Moderate	Moderate	Moderate
Pavelka (2007)	WOMAC Pain	16	Diacerein versus	Moderate	Moderate	Moderate

			Placebo			
Pavelka (2007)	WOMAC Pain	20	Diacerein versus Placebo	Moderate	Moderate	Moderate
Pavelka (2007)	WOMAC Pain	24	Diacerein versus Placebo	Moderate	Moderate	Moderate
Pavelka (2007)	WOMAC Stiffness	4	Diacerein versus Placebo	Moderate	Moderate	Moderate
Pavelka (2007)	WOMAC Stiffness	8	Diacerein versus Placebo	Moderate	Moderate	Moderate
Pavelka (2007)	WOMAC Stiffness	16	Diacerein versus Placebo	Moderate	Moderate	Moderate
Pavelka (2007)	WOMAC Stiffness	20	Diacerein versus Placebo	Moderate	Moderate	Moderate
Pavelka (2007)	WOMAC Stiffness	24	Diacerein versus Placebo	Moderate	Moderate	Moderate
Pavelka (2007)	Paracetamol intake pills per day	4	Diacerein versus Placebo	Moderate	Moderate	Moderate
Pavelka (2007)	Paracetamol intake pills per day	8	Diacerein versus Placebo	Moderate	Moderate	Moderate
Pavelka (2007)	Paracetamol intake pills per	12	Diacerein versus Placebo	Moderate	Moderate	Moderate

	day					
Pavelka (2007)	Paracetamol intake pills per day	16	Diacerein versus Placebo	Moderate	Moderate	Moderate
Pavelka (2007)	Paracetamol intake pills per day	20	Diacerein versus Placebo	Moderate	Moderate	Moderate
Pavelka (2007)	Paracetamol intake pills per day	24	Diacerein versus Placebo	Moderate	Moderate	Moderate
Pavelka (2007)	WOMAC Total	4	Diacerein versus Placebo	Moderate	Moderate	Moderate
Pavelka (2007)	WOMAC Total	8	Diacerein versus Placebo	Moderate	Moderate	Moderate
Pavelka (2007)	WOMAC Total	16	Diacerein versus Placebo	Moderate	Moderate	Moderate
Pavelka (2007)	WOMAC Total	20	Diacerein versus Placebo	Moderate	Moderate	Moderate
Pavelka (2007)	WOMAC Total	24	Diacerein versus Placebo	Moderate	Moderate	Moderate
Williams (2001)	Lequesne Index	6	Celecoxib versus Placebo	Moderate	Moderate	Moderate
Williams (2001)	Lequesne Index	6	Celecoxib versus	Moderate	Moderate	Moderate

			Placebo			
Williams (2001)	WOMAC Total	6	Celecoxib versus Placebo	Moderate	Moderate	Moderate
Williams (2001)	WOMAC Total	6	Celecoxib versus Placebo	Moderate	Moderate	Moderate
Williams (2001)	Lequesne Index	6	Celecoxib 100mg BID versus Celecoxib 200mg qd	Moderate	Moderate	Moderate
Williams (2001)	WOMAC Total	6	Celecoxib 100mg BID versus Celecoxib 200mg qd	Moderate	Moderate	Moderate
Williams (2001)	Physician Global Assessment	6	Celecoxib 100mg versus Placebo	Moderate	Moderate	Moderate
Williams (2001)	Physician Global Assessment	6	Celecoxib 200mg versus Placebo	Moderate	Moderate	Moderate
Williams (2001)	physician Global Assessment	6	Celecoxib 100mg versus Celecoxib 200mg	Moderate	Moderate	Moderate

RESULTS

Relevant Tables: Table 145, Table 155-Table165, Figure 47-Figure 80

There were 126 outcomes in which Cox-2 inhibitors were compared to placebo. Cox-2 inhibitors were significantly superior to placebo in 114 outcomes.Of these significant outcomes, 43 were at least possibly clinically important, 38 were of unknown clinical importance, and 33 were not clinically significant.

The critical outcomes were function and stiffness. Nine of 10 functional outcomes were improved in patients who received Cox-2's. One functional outcome was clinically important and eight were possibly clinically important. Nine of 15 stiffness-related outcomes were at least possibly clinically important in favor of Cox-2's. An additional two outcomes were statistically significant but not clinically important.

There was little difference in the efficacies of Cox-2 inhibitors. Out of 88 total outcomes, 24 were statistically significant. However, 23 out of 24 significant outcomes were between high versus lower doses of the same Cox-2's. Only one of 21 critical outcomes was statistically significant in favor of one Cox-2 over another (WOMAC stiffness; Celecoxib over Rofecoxib).

NSAIDs were compared to placebo based on 35 outcomes, of which 31 were statistically significant in favor of the treatment. Seventeen of these outcomes were at least possibly clinically important, and nine were of unknown clinical importance. An additional nine outcomes were statistically significant in favor of NSAIDs but not clinically important.

Pain, function and stiffness were the critical outcomes included in the studies that compared NSAIDs to placebo. All 17 pain outcomes were statistically significant, eight of which were at least possibly clinically important. All three stiffness outcomes were possibly clinically significant in favor of NSAIDs. Three of seven functional outcomes were statistically significant indicating improvement in the treatment group.

There was little difference in the efficacies between various NSAIDs. Thirteen of 91 outcomes were statistically significant endorsing one NSAID over another (table 158)

Thirty-two outcomes compared topical NSAIDs to a placebo/vehicle control solution. Eighteen of 32 were statistically significant indicating improvement in the treatment group. The critical outcomes were pain, function and stiffness. Twelve of 21 pain outcomes were lessened significantly in the treatment group. Three of four stiffness-related outcomes and the single functional outcome significantly favored topical NSAIDs over placebo.

Two studies compared topical NSAIDs to active treatments. Ottillinger et al.[100] found no significant differences in VAS pain scores at 4, 5 and 6 weeks between eltenac .1%, .3% and 1% gels. Rother et al. [101] found insignificant differences in pain and function between Celecoxib and topical Ketoprofen.

NSAIDs and Cox-2 inhibitors appeared to be of similar efficacy. Three of 44 outcomes favored Cox-2s over NSAIDs, and only one outcome favored NSAIDs. Pain, stiffness and function were the included critical outcomes. None were statistically significant between the two drug classifications.

Diacerein (interleukin) was compared to placebo based on 25 outcomes. Sixteen outcomes were significantly superior in the treatment group; 13 were possibly clinically important and three were of unknown clinical importance. Ten of 14 critical outcomes (pain, stiffness, and function) were significantly improved in patients who received Diacerein compared to those who received placebo.

Forty-four outcomes compared interleukins to NSAIDs. The evidence was mixed on whether one treatment was superior to the other. Twenty-seven outcomes were not statistically significant, 12 endorsed interleukins and five favored NSAIDs.

Five studies evaluating 14 outcomes compared Tramadol to placebo. Ten were significantly improved in the treatment group. Five of seven pain outcomes showed Tramadol to be superior over placebo. One of two functional outcomes and one of two stiffness outcomes were statistically significant indicating benefit of Tramadol over placebo.

Fishman et al.[95] compared WOMAC pain scores for 100mg, 200mg and 300mg doses of Tramadol. There were no significant differences by dose.

One study found that VAS pain scores were not significantly different between acetaminophen and placebo.[97] Acetaminophen was compared to NSAIDs based on ten outcomes and Cox-2s based on six. Four outcomes significantly favored NSAIDs over acetaminophen but one was not clinically important. Four of six outcomes were superior in patients who received Cox-2s, and two outcomes were significantly better in the acetaminophen group.

Network Meta Analysis

Network meta-analyses were conducted for the following outcomes: pain, WOMAC function, WOMAC stiffness, WOMAC total, and adverse events. Figures 42 through 46 illustrate conceptual path models of each network meta-analysis that examine direct and indirect treatment comparisons.

Figures 47 through 80 are forest plots summarizing the results of all network meta-analyses separated according to drug comparison and outcome (pain, function, stiffness, WOMAC total, and adverse events). For example, there is a separate plot for the results of Cox-2s versus NSAIDs, Cox-2s versus Cox-2s, NSAIDs versus NSAIDs. Other plots contain comparisons of Cox-2s and NSAIDs to interleukins and Tramadol.

Consistency checks for all network meta-analyses can be found in Appendix XIII. All pairwise effects were statistically compared to indirect treatment effects using the back calculation method described by Dias et al. No indirect effects of any outcome were found to be significantly different than the direct effects in the pairwise meta-analyses.

All Cox-2 inhibitors were significantly more effective than placebo for pain. The NSAIDs Aceclofenac, Diclofenac, Naproxen, Naproxcinod, topical Diclofenac and topical Ketoprofen showed statistically significant benefit for pain. Topical Eltenac, Aceclofenac, Tenidap and Tenoxicam produced lower pain scores than placebo treatment, but they did not reach statistical significance. Patients who received the opioid Tramadol had significantly lower pain scores than those in the placebo group. Diacerein (an interleukin) did not have a statistically significant benefit on pain compared to placebo assignment.

All active treatments showed similar efficacy in terms of pain relief. As can be seen in Figures 48 through 52, there were only two significant treatment comparisons for pain. Patients treated with Rofecoxib reported significantly lower pain scores than Celecoxib and Tenoxicam patients.

Tramadol, Cox-2 inhibitors, and most all NSAIDs produced possibly clinically important improvements in WOMAC function scores relative to placebo. Two of six NSAIDs, Piroxicam and Tenidap, were associated with better function scores than scores based on placebo, but the differences were not statistically significant. Diacerein were not associated with significantly different function scores than placebo.

The active treatments showed similar efficacy for improving WOMAC function scores (see Figures 54 to 58). There were four significant active treatment comparisons. Naproxen produced WOMAC function scores that were significantly higher than all associated with Cox-2 inhibitors and topical Ketoprofen. The differences were possibly clinically important.

Analgesics were less successful in treating stiffness related to knee osteoarthritis than they were for improving pain and function. NSAIDs, interleukins and Tramadol did not produce significantly lower WOMAC stiffness scores than placebo. Two of four Cox-2 inhibitors, Celecoxib and Rofecoxib, had possibly clinically important improvements in stiffness compared to placebo. When each active treatment was compared to one another in the network meta-analysis, there were not any significant differences found in WOMAC stiffness scores.

All WOMAC total scores for Cox-2 inhibitors, NSAIDs, opioids and interleukins were significantly better than all placebo scores. Each drug treatment effect was possibly clinically important since their confidence intervals contained the MCII. There were no statistically significant differences in overall WOMAC scores for any of the active treatments.

Adverse Events

The odds of experiencing adverse events were similar between treatment arms in the network meta-analysis. Pairwise analyses were used to compare specific types of adverse events between analgesics. While the overall occurrence of Gastrointestinal Events are not significantly lower for Cox-2's than for NSAIDs, patients who received Cox-2 inhibitors were significantly less likely to experience abdominal pain, constipation or

dyspepsia (see figure 75). For non gastrointestinal events, there were no significant differences between Cox-2's and NSAIDs (figure 76).

Patients who received Acetaminophen did not have significantly different odds of experiencing any specific adverse event than patients who received Celecoxib (figure 77). Rofecoxib 12.5mg had lesser odds of causing abdominal pain and headaches (figure 78). Compared to Acetaminophen, those who received Rofecoxib 25mg had significantly lesser odds of experiencing diarrhea and abdominal pain, but greater odds of Lower Extremity Edema (figure 79).

Figure 80 presents a comparison of the likelihood of specific adverse events between Acetaminophen (4000mg) and Ibuprofen (1200 and 4000mg). There were no statistically significant differences between the treatments.

Figure 42. Network Meta-Analysis Model: Pain

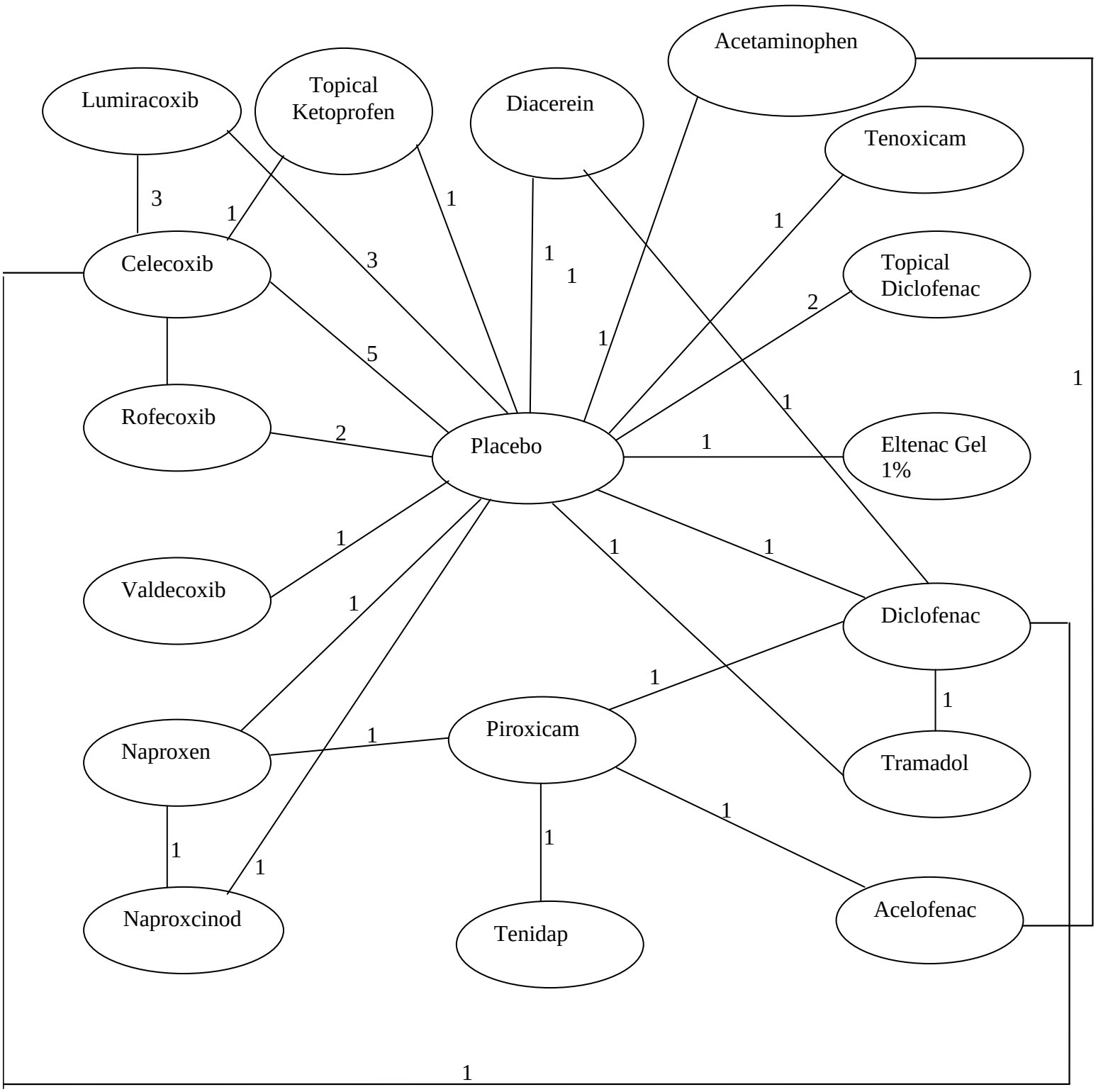


Figure 43. Network Meta-Analysis Model: WOMAC Function

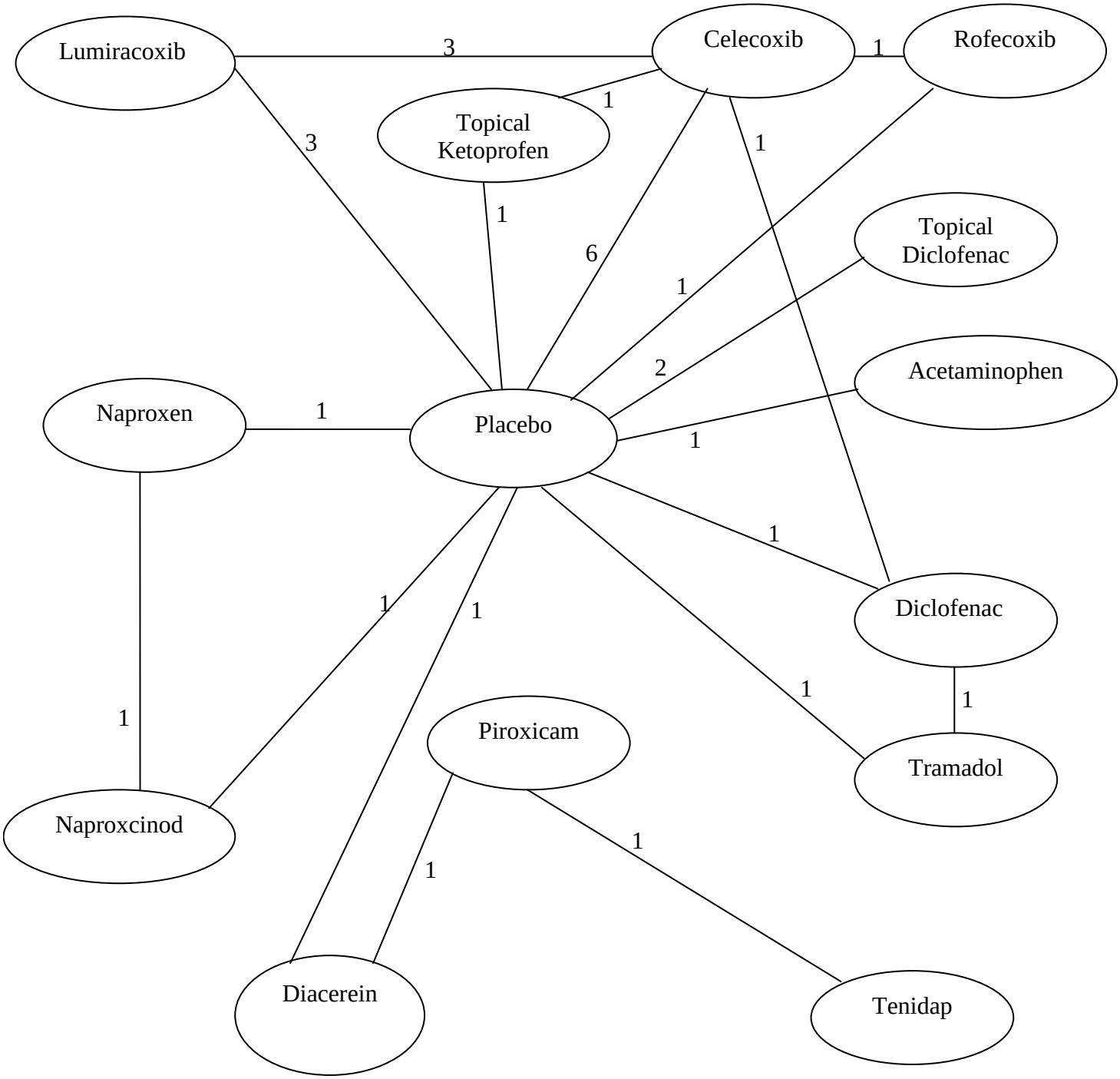


Figure 44. Network Meta-Analysis Model: WOMAC Stiffness

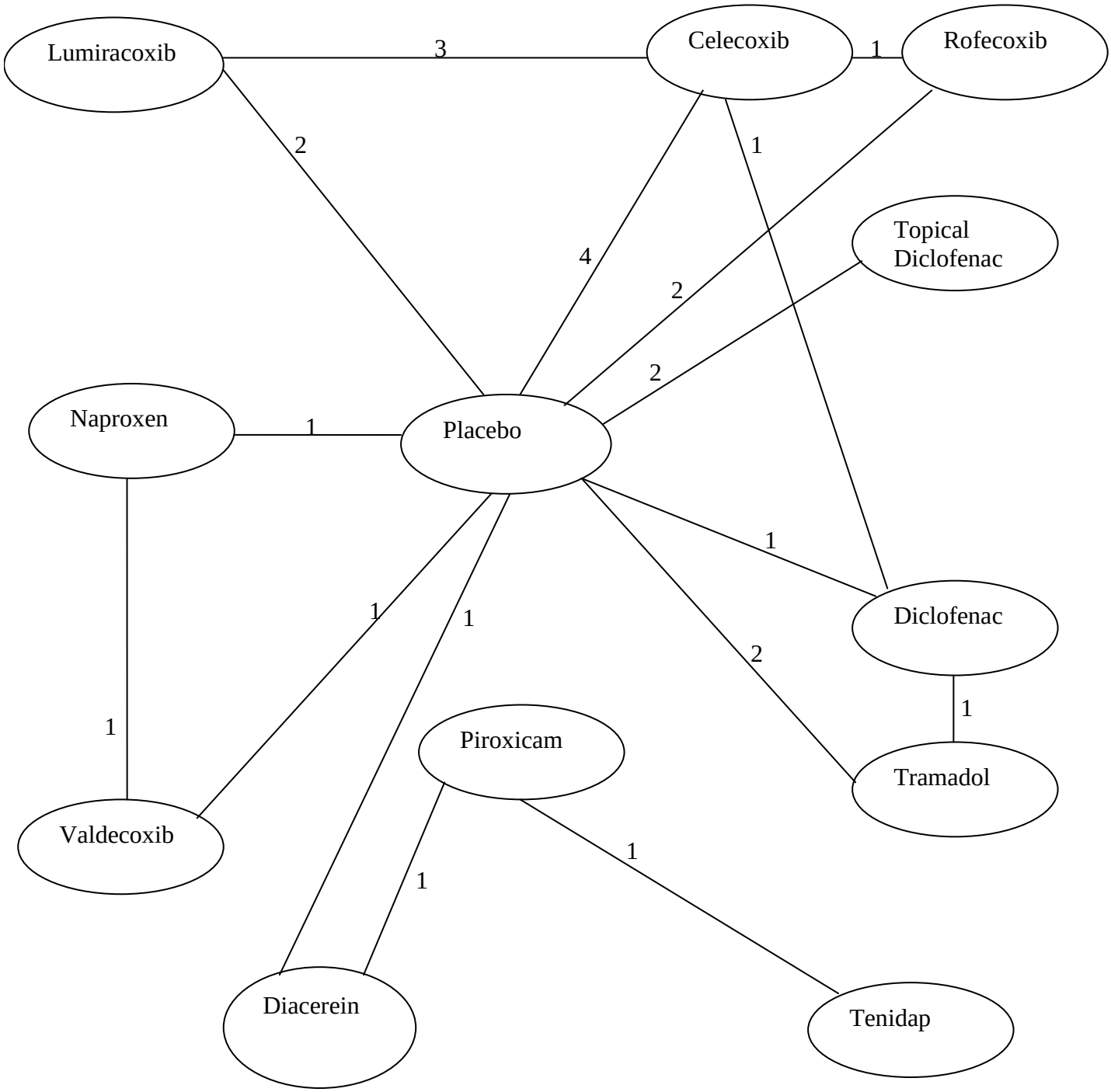
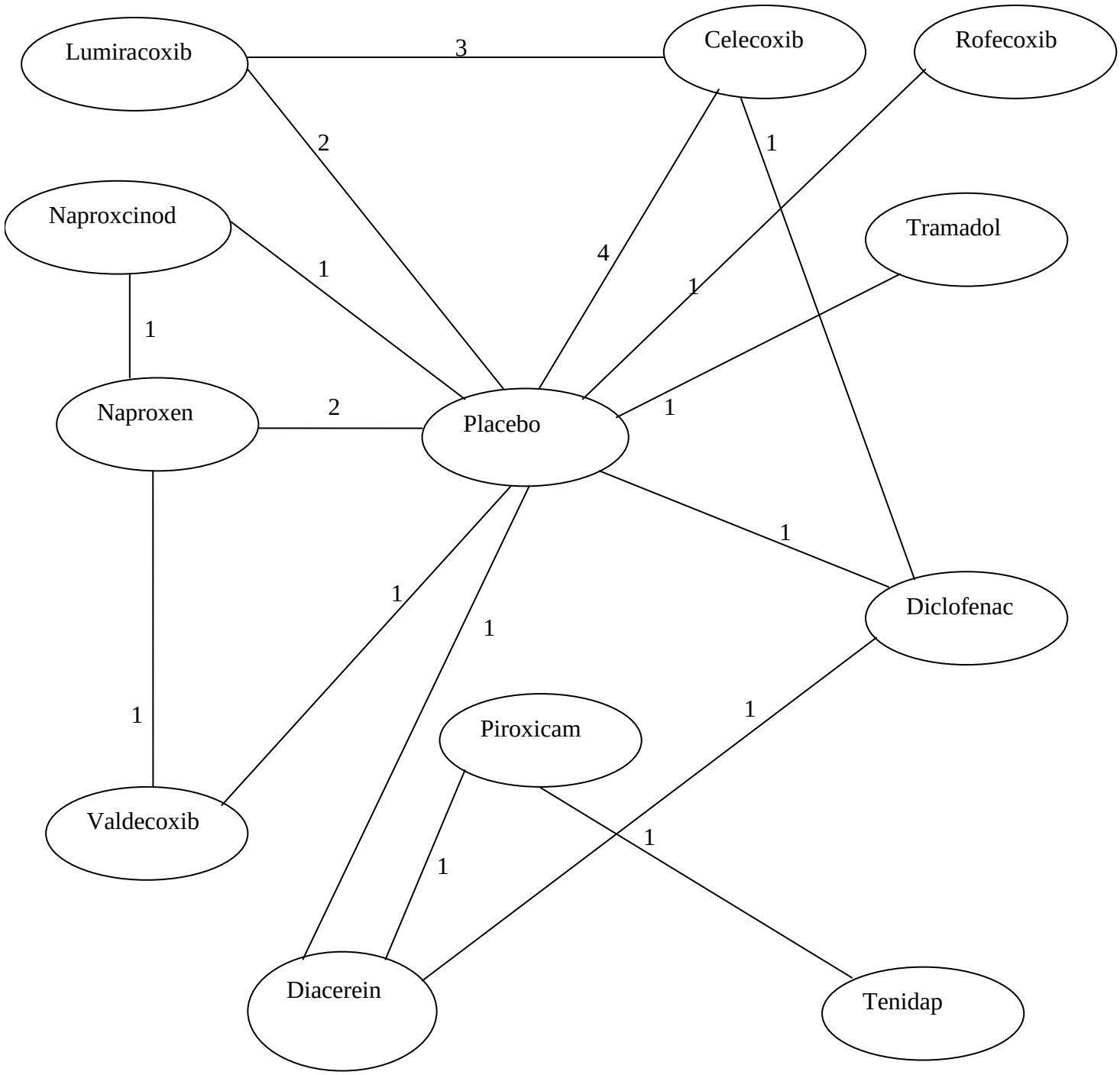


Figure 45. Network Meta-Analysis Model: WOMAC Total



Events Figure 46. Network Meta-Analysis Model: Adverse Events

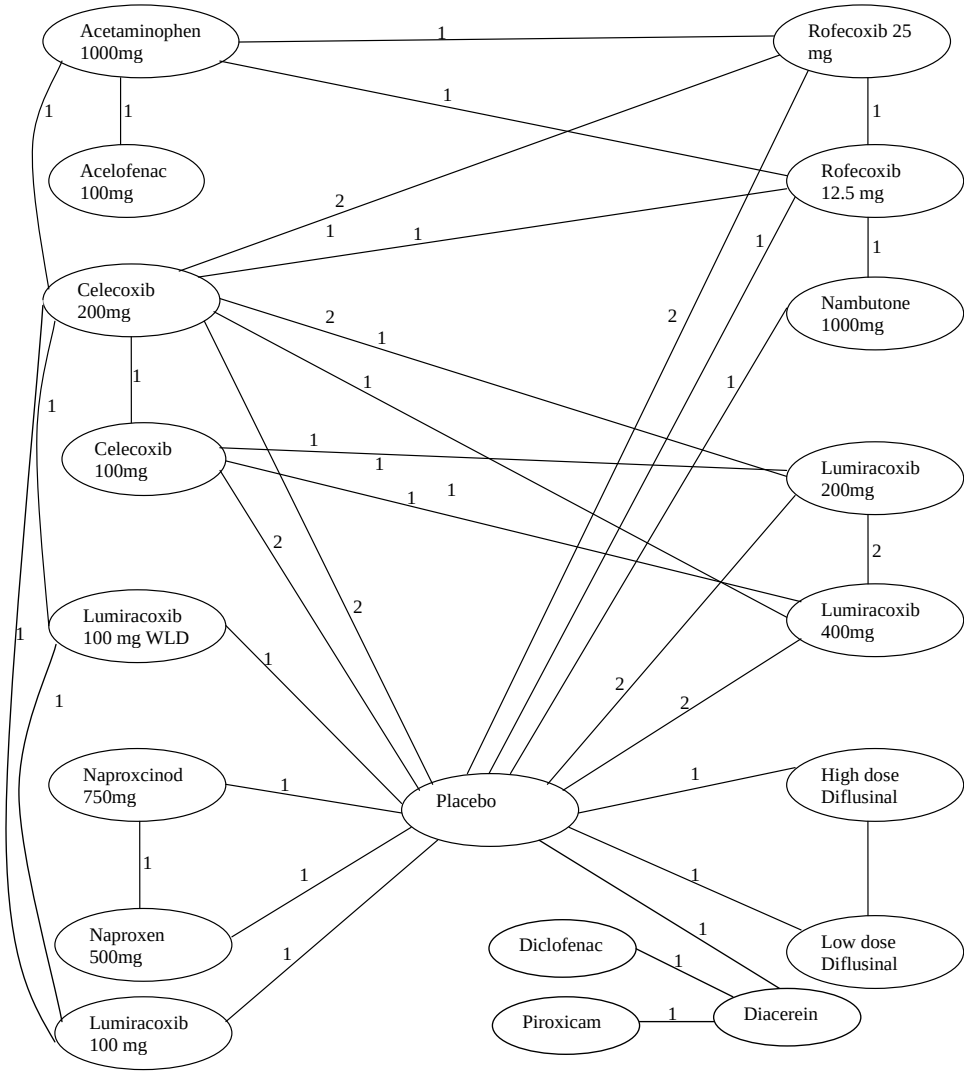


Table 145. Network Meta-Analysis: Statistically Significant Treatment Comparisons

Comparison	Outcome
Rofecoxib over Tenoxicam	Pain
Rofecoxib over Celecoxib	Pain
Naproxen over Lumiracoxib	Function
Naproxen over Celecoxib	Function
Naproxen over Rofecoxib	Function
Naproxen over Topical Ketoprofen	Function

Table 146. Results Summary: Drug Treatments Versus Placebo (Patient and Physician Assessments)

Study	Patient Global Assessment *	Physician Global Assessment	Patient Global Assessment of Disease Status	Physician Global Assessment of Disease Status	Patient Global Assessment of Treatment Response	Physician Global Assessment of Treatment Response
Celecoxib	○○○●●●	●●●●●●	●●	●●		
Lumiracoxib	○○	●●	●●●	●●●		
Rofecoxib	●	○	●●●	●●	●●●	●●
Valdecoxib		●●●●●○				
Diclofenac	○	●				
Topical Diclofenac	○					
Naproxen		●●	●●		●●	
Orgotein					●●	
Naproxcinod			●●○		●●○	

○ Statistically, but not clinically significant (only Patient Global Assessment has an MCII)
● Statistically Significant, but outcome has no MCII
● Possibly clinically significant
● Clinically Significant

Table 147. Statistically Significant Active Treatment Comparisons: Global Assessments

Outcome	Favors	Comparison
Patient Global Assessment	Aceclofenac	Paracetamol (Not Clinically Significant)
Patient Global Assessment	Celecoxib 200mg	Celecoxib 100mg (Clinically Significant)
Patient Global Assessment	Lumiracoxib200mg	Lumiracoxib 400mg(Clinically Significant)
Physician Global Assessment	Aceclofenac	Paracetamol
Physician Global Assessment	Diclofenac (NSAID)	Celecoxib (Cox-2)
Physician Global Assessment	Celecoxib 200mg	Celecoxib 100mg
Patient Global Assessment Of Disease	Etoricoxib 60mg Or 90mg	Etoricoxib 30mg Or Less
Physician Assessment Of Treatment Response	Etoricoxib 60mg Or 90mg	Etoricoxib 30mg Or Less
Patient Assessment Of Treatment Response	Rofecoxib	Acetaminophen
Physician Assessment Of Treatment Response	Rofecoxib	Acetaminophen

EVIDENCE TABLES AND FIGURES

QUALITY AND APPLICABILITY

Table 148. Quality and Applicability: Cox-2

●: Domain free of flaws

○: Domain flaws present

◐: Moderate power

Study	*Outcome*	*Week*	*Comparison*	**Prospective**	**Power**	**Group Assignment**	**Blinding**	**Group Comparability**	**Treatment Integrity**	**Measurement**	**Investigator Bias**	*Quality*	**Participants**	**Intervention and Expertise**	**Compliance and Adherence**	**Analysis**	*Applicability Study*
Ehrich (1999)	Physician Global Assessment of Disease	6	Rofecoxib 125mg versus Placebo	●	●	○	●	●	○	●	○	**Moderate**	○	○	●	●	**Moderate**
Ehrich (1999)	Physician Global Assessment of Disease	6	Rofecoxib 25mg versus Placebo	●	●	○	●	●	○	●	○	**Moderate**	○	○	●	●	**Moderate**
Ehrich (1999)	Physician Global Assessment of Response to Treatment	6	Rofecoxib 125mg versus Placebo	●	●	○	●	●	○	●	○	**Moderate**	○	○	●	●	**Moderate**

●: Domain free of flaws

○: Domain flaws present

◐: Moderate power

Study	*Outcome*	*Week*	*Comparison*	**Prospective**	**Power**	**Group Assignment**	**Blinding**	**Group Comparability**	**Treatment Integrity**	**Measurement**	**Investigator Bias**	*Quality*	**Participants**	**Intervention and Expertise**	**Compliance and Adherence**	**Analysis**	*Applicability Study*
Ehrich (1999)	Physician Global Assessment of Response to Treatment	6	Rofecoxib 25mg versus Placebo	●	●	○	●	●	○	●	○	**Moderate**	○	○	●	●	**Moderate**
Ehrich (1999)	WOMAC Function	6	Rofecoxib versus Placebo	●	○	○	●	●	○	●	○	**Moderate**	○	○	●	●	**Moderate**
Ehrich (1999)	WOMAC Pain	6	Rofecoxib versus Placebo	●	○	○	●	●	○	●	○	**Moderate**	○	○	●	●	**Moderate**
Ehrich (1999)	VAS Pain improvement	6	Rofecoxib versus Placebo	●	●	○	●	●	○	●	○	**Moderate**	○	○	●	●	**Moderate**
Ehrich (1999)	VAS Pain improvement	6	Rofecoxib versus Placebo	●	●	○	●	●	○	●	○	**Moderate**	○	○	●	●	**Moderate**

●: Domain free of flaws

○: Domain flaws present

◐: Moderate power

Study	*Outcome*	*Week*	*Comparison*	**Prospective**	**Power**	**Group Assignment**	**Blinding**	**Group Comparability**	**Treatment Integrity**	**Measurement**	**Investigator Bias**	*Quality*	**Participants**	**Intervention and Expertise**	**Compliance and Adherence**	**Analysis**	*Applicability Study*
Ehrich (1999)	WOMAC Stiffness	6	Rofecoxib versus Placebo	●	○	○	●	●	○	●	○	**Moderate**	○	○	●	●	**Moderate**
Ehrich (1999)	Patient Global Assessment of Response to Treatment	6	Rofecoxib 125mg versus Placebo	●	●	○	●	●	○	●	○	**Moderate**	○	○	●	●	**Moderate**
Ehrich (1999)	Patient Global Assessment of Response to Treatment	6	Rofecoxib 25mg versus Placebo	●	●	○	●	●	○	●	○	**Moderate**	○	○	●	●	**Moderate**
Ehrich (1999)	Patient Global Assessment of Disease	6	Rofecoxib 125mg versus Placebo	●	●	○	●	●	○	●	○	**Moderate**	○	○	●	●	**Moderate**
Ehrich (1999)	Patient Global Assessment of Disease	6	Rofecoxib 25mg versus Placebo	●	●	○	●	●	○	●	○	**Moderate**	○	○	●	●	**Moderate**

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Study	*Outcome*	*Week*	*Comparison*	**Prospective**	**Power**	**Group Assignment**	**Blinding**	**Group Comparability**	**Treatment Integrity**	**Measurement**	**Investigator Bias**	*Quality*	**Participants**	**Intervention and Expertise**	**Compliance and Adherence**	**Analysis**	*Applicability Study*
Fleischmann (2006)	Patient Global Assessment	13	Lumiracoxib 400mg versus Placebo	●	●	○	●	○	○	●	○	**Low**	○	○	●	●	**Moderate**
Fleischmann (2006)	Patient Global Assessment	13	Lumiracoxib 200mg versus Placebo	●	●	○	●	○	○	●	○	**Low**	○	○	●	●	**Moderate**
Fleischmann (2006)	VAS Pain improvement	13	Lumiracoxib versus Placebo	●	●	○	●	○	○	●	○	**Low**	○	○	●	●	**Moderate**
Fleischmann (2006)	VAS Pain improvement	13	Lumiracoxib versus Placebo	●	●	○	●	○	○	●	○	**Low**	○	○	●	●	**Moderate**
Fleischmann (2006)	WOMAC Pain	13	Lumiracoxib versus Placebo	●	●	○	●	○	○	●	○	**Low**	○	○	●	●	**Moderate**

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Study	*Outcome*	*Week*	*Comparison*	**Prospective**	**Power**	**Group Assignment**	**Blinding**	**Group Comparability**	**Treatment Integrity**	**Measurement**	**Investigator Bias**	*Quality*	**Participants**	**Intervention and Expertise**	**Compliance and Adherence**	**Analysis**	*Applicability Study*
Fleischmann (2006)	WOMAC Pain	13	Lumiracoxib versus Placebo	●	●	○	●	○	○	●	○	**Low**	○	○	●	●	**Moderate**
Fleischmann (2006)	Patient Global Assessment	13	Lumiracoxib 200mg versus Celecoxib 200mg	●	●	○	●	○	○	●	○	**Low**	○	○	●	●	**Moderate**
Fleischmann (2006)	Patient Global Assessment	13	Lumiracoxib 400mg versus Celecoxib 200mg	●	●	○	●	○	○	●	○	**Low**	○	○	●	●	**Moderate**
Fleischmann (2006)	Patient Global Assessment	13	Lumiracoxib 200mg versus Lumiracoxib 400mg	●	●	○	●	○	○	●	○	**Low**	○	○	●	●	**Moderate**

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Study	*Outcome*	*Week*	*Comparison*	**Prospective**	**Power**	**Group Assignment**	**Blinding**	**Group Comparability**	**Treatment Integrity**	**Measurement**	**Investigator Bias**	*Quality*	**Participants**	**Intervention and Expertise**	**Compliance and Adherence**	**Analysis**	*Applicability Study*
Fleischmann (2006)	Physician Global Assessment	13	Celecoxib (Cox-2) versus Placebo	●	●	○	●	○	○	●	○	**Low**	○	○	●	●	**Moderate**
Fleischmann (2006)	Physician Global Assessment	13	Lumiracoxib 200mg versus Placebo	●	●	○	●	○	○	●	○	**Low**	○	○	●	●	**Moderate**
Fleischmann (2006)	Physician Global Assessment	13	Lumiracoxib 400mg versus Placebo	●	●	○	●	○	○	●	○	**Low**	○	○	●	●	**Moderate**
Fleischmann (2006)	WOMAC Function	13	Lumiracoxib versus Placebo	●	●	○	●	○	○	●	○	**Low**	○	○	●	●	**Moderate**
Fleischmann (2006)	WOMAC Function	13	Lumiracoxib versus Placebo	●	●	○	●	○	○	●	○	**Low**	○	○	●	●	**Moderate**

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Study	*Outcome*	*Week*	*Comparison*	**Prospective**	**Power**	**Group Assignment**	**Blinding**	**Group Comparability**	**Treatment Integrity**	**Measurement**	**Investigator Bias**	*Quality*	**Participants**	**Intervention and Expertise**	**Compliance and Adherence**	**Analysis**	*Applicability Study*
Fleischmann (2006)	VAS Pain improvement	13	Celecoxib versus Placebo	●	●	○	●	○	○	●	○	**Low**	○	○	●	●	**Moderate**
Fleischmann (2006)	WOMAC Pain	13	Celecoxib versus Placebo	●	●	○	●	○	○	●	○	**Low**	○	○	●	●	**Moderate**
Fleischmann (2006)	WOMAC Stiffness	13	Lumiracoxib versus Placebo	●	●	○	●	○	○	●	○	**Low**	○	○	●	●	**Moderate**
Fleischmann (2006)	WOMAC Stiffness	13	Lumiracoxib versus Placebo	●	●	○	●	○	○	●	○	**Low**	○	○	●	●	**Moderate**
Fleischmann (2006)	WOMAC Total	13	Lumiracoxib versus Placebo	●	●	○	●	○	○	●	○	**Low**	○	○	●	●	**Moderate**
Fleischmann (2006)	WOMAC Total	13	Lumiracoxib versus Placebo	●	●	○	●	○	○	●	○	**Low**	○	○	●	●	**Moderate**

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Study	*Outcome*	*Week*	*Comparison*	**Prospective**	**Power**	**Group Assignment**	**Blinding**	**Group Comparability**	**Treatment Integrity**	**Measurement**	**Investigator Bias**	*Quality*	**Participants**	**Intervention and Expertise**	**Compliance and Adherence**	**Analysis**	*Applicability Study*
Fleischmann (2006)	Physician Global Assessment	13	Lumiracoxib 200mg versus Celecoxib 200mg	●	●	○	●	○	○	●	○	**Low**	○	○	●	●	**Moderate**
Fleischmann (2006)	Physician Global Assessment	13	Lumiracoxib 400mg versus Celecoxib 200mg	●	●	○	●	○	○	●	○	**Low**	○	○	●	●	**Moderate**
Fleischmann (2006)	Physician Global Assessment	13	Lumiracoxib 200mg versus Lumiracoxib 400mg	●	●	○	●	○	○	●	○	**Low**	○	○	●	●	**Moderate**
Gibofsky (2003)	WOMAC Function	6	Celecoxib versus Placebo	●	●	○	●	●	●	●	○	**Moderate**	○	○	●	○	**Moderate**

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Study	*Outcome*	*Week*	*Comparison*	**Prospective**	**Power**	**Group Assignment**	**Blinding**	**Group Comparability**	**Treatment Integrity**	**Measurement**	**Investigator Bias**	*Quality*	**Participants**	**Intervention and Expertise**	**Compliance and Adherence**	**Analysis**	*Applicability Study*
Gibofsky (2003)	WOMAC Function	6	Rofecoxib versus Placebo	●	●	○	●	●	●	●	○	**Moderate**	○	○	●	○	**Moderate**
Gibofsky (2003)	VAS Pain on walking improvement	6	Celecoxib versus Placebo	●	●	○	●	●	●	●	○	**Moderate**	○	○	●	○	**Moderate**
Gibofsky (2003)	VAS Pain on walking improvement	6	Rofecoxib versus Placebo	●	●	○	●	●	●	●	○	**Moderate**	○	○	●	○	**Moderate**
Gibofsky (2003)	WOMAC Pain	6	Rofecoxib versus Placebo	●	●	○	●	●	●	●	○	**Moderate**	○	○	●	○	**Moderate**
Gibofsky (2003)	WOMAC Pain	6	Celecoxib versus Placebo	●	●	○	●	●	●	●	○	**Moderate**	○	○	●	○	**Moderate**
Gibofsky (2003)	WOMAC Stiffness	6	Celecoxib versus Placebo	●	●	○	●	●	●	●	○	**Moderate**	○	○	●	○	**Moderate**

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Study	*Outcome*	*Week*	*Comparison*	**Prospective**	**Power**	**Group Assignment**	**Blinding**	**Group Comparability**	**Treatment Integrity**	**Measurement**	**Investigator Bias**	*Quality*	**Participants**	**Intervention and Expertise**	**Compliance and Adherence**	**Analysis**	*Applicability Study*
Gibofsky (2003)	WOMAC Stiffness	6	Rofecoxib versus Placebo	●	●	○	●	●	●	●	○	**Moderate**	○	○	●	○	**Moderate**
Gibofsky (2003)	WOMAC Function improvement	6	Celecoxib 200mg versus Rofecoxib	●	●	○	●	●	●	●	○	**Moderate**	○	○	●	○	**Moderate**
Gibofsky (2003)	VAS Pain on walking improvement	6	Celecoxib 200mg versus Rofecoxib	●	●	○	●	●	●	●	○	**Moderate**	○	○	●	○	**Moderate**
Gibofsky (2003)	WOMAC Pain improvement	6	Celecoxib 200mg versus Rofecoxib	●	●	○	●	●	●	●	○	**Moderate**	○	○	●	○	**Moderate**

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Study	*Outcome*	*Week*	*Comparison*	**Prospective**	**Power**	**Group Assignment**	**Blinding**	**Group Comparability**	**Treatment Integrity**	**Measurement**	**Investigator Bias**	*Quality*	**Participants**	**Intervention and Expertise**	**Compliance and Adherence**	**Analysis**	*Applicability Study*
Gibofsky (2003)	WOMAC Stiffness improvement	6	Celecoxib 200mg versus Rofecoxib	●	●	○	●	●	●	●	○	**Moderate**	○	○	●	○	**Moderate**
Gibofsky (2003)	Patient Global Assessment	6	Celecoxib 200mg versus Placebo	●	●	○	●	●	●	●	○	**Moderate**	○	○	●	○	**Moderate**
Gibofsky (2003)	Patient Global Assessment	6	Rofecoxib 25mg versus Placebo	●	●	○	●	●	●	●	○	**Moderate**	○	○	●	○	**Moderate**
Gibofsky (2003)	Physician Global Assessment	6	Celecoxib 200mg versus Placebo	●	●	○	●	●	●	●	○	**Moderate**	○	○	●	○	**Moderate**
Gibofsky (2003)	Physician Global Assessment	6	Rofecoxib 25mg versus Placebo	●	◐	○	●	●	●	●	○	**Moderate**	○	○	●	○	**Moderate**

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Study	*Outcome*	*Week*	*Comparison*	**Prospective**	**Power**	**Group Assignment**	**Blinding**	**Group Comparability**	**Treatment Integrity**	**Measurement**	**Investigator Bias**	*Quality*	**Participants**	**Intervention and Expertise**	**Compliance and Adherence**	**Analysis**	*Applicability Study*
Gibofsky (2003)	Patient Global Assessment of Response to Treatment	6	Celecoxib 200mg versus Placebo	●	●	○	●	●	●	●	○	**Moderate**	○	○	●	○	**Moderate**
Gibofsky (2003)	Patient Global Assessment of Response to Treatment	6	Rofecoxib 25mg versus Placebo	●	◐	○	●	●	●	●	○	**Moderate**	○	○	●	○	**Moderate**
Gibofsky (2003)	Patient Global Assessment	6	Celecoxib 200mg versus Rofecoxib 25mg	●	◐	○	●	●	●	●	○	**Moderate**	○	○	●	○	**Moderate**
Gibofsky (2003)	Physician Global Assessment	6	Celecoxib 200mg versus Rofecoxib 25mg	●	◐	○	●	●	●	●	○	**Moderate**	○	○	●	○	**Moderate**

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Study	*Outcome*	*Week*	*Comparison*	**Prospective**	**Power**	**Group Assignment**	**Blinding**	**Group Comparability**	**Treatment Integrity**	**Measurement**	**Investigator Bias**	*Quality*	**Participants**	**Intervention and Expertise**	**Compliance and Adherence**	**Analysis**	*Applicability Study*
Gottesdiener (2002)	Patient Global Assessment of Disease	6	Etoricoxib 60mg versus Etoricoxib 90mg	●	◐	●	●	●	●	●	○	**High**	○	○	●	●	**Moderate**
Gottesdiener (2002)	Patient Global Assessment of Disease	6	Etoricoxib 5mg versus Etoricoxib 10mg	●	◐	●	●	●	●	●	○	**High**	○	○	●	●	**Moderate**
Gottesdiener (2002)	Patient Global Assessment of Disease	6	Etoricoxib 5mg versus Etoricoxib 30mg	●	◐	●	●	●	●	●	○	**High**	○	○	●	●	**Moderate**
Gottesdiener (2002)	Patient Global Assessment of Disease	6	Etoricoxib 5mg versus Etoricoxib 60mg	●	●	●	●	●	●	●	○	**High**	○	○	●	●	**Moderate**

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Study	*Outcome*	*Week*	*Comparison*	**Prospective**	**Power**	**Group Assignment**	**Blinding**	**Group Comparability**	**Treatment Integrity**	**Measurement**	**Investigator Bias**	*Quality*	**Participants**	**Intervention and Expertise**	**Compliance and Adherence**	**Analysis**	*Applicability Study*
Gottesdiener (2002)	Patient Global Assessment of Disease	6	Etoricoxib 5mg versus Etoricoxib 90mg	●	●	●	●	●	●	●	○	**High**	○	○	●	●	**Moderate**
Gottesdiener (2002)	Patient Global Assessment of Disease	6	Etoricoxib 10mg versus Etoricoxib 30mg	●	◐	●	●	●	●	●	○	**High**	○	○	●	●	**Moderate**
Gottesdiener (2002)	Patient Global Assessment of Disease	6	Etoricoxib 10mg versus Etoricoxib 60mg	●	●	●	●	●	●	●	○	**High**	○	○	●	●	**Moderate**
Gottesdiener (2002)	Patient Global Assessment of Disease	6	Etoricoxib 10mg versus Etoricoxib 90mg	●	●	●	●	●	●	●	○	**High**	○	○	●	●	**Moderate**

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Study	*Outcome*	*Week*	*Comparison*	**Prospective**	**Power**	**Group Assignment**	**Blinding**	**Group Comparability**	**Treatment Integrity**	**Measurement**	**Investigator Bias**	*Quality*	**Participants**	**Intervention and Expertise**	**Compliance and Adherence**	**Analysis**	*Applicability Study*
Gottesdiener (2002)	Patient Global Assessment of Disease	6	Etoricoxib 30mg versus Etoricoxib 60mg	●	●	●	●	●	●	●	○	**High**	○	○	●	●	**Moderate**
Gottesdiener (2002)	Patient Global Assessment of Disease	6	Etoricoxib 30mg versus Etoricoxib 90mg	●	◐	●	●	●	●	●	○	**High**	○	○	●	●	**Moderate**
Gottesdiener (2002)	Patient Global Assessment of Disease	6	Etoricoxib 60mg versus Etoricoxib 90mg	●	◐	●	●	●	●	●	○	**High**	○	○	●	●	**Moderate**
Gottesdiener (2002)	Physician Global Assessment of Disease	6	Etoricoxib 5mg versus Etoricoxib 10mg	●	◐	●	●	●	●	●	○	**High**	○	○	●	●	**Moderate**

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Study	*Outcome*	*Week*	*Comparison*	**Prospective**	**Power**	**Group Assignment**	**Blinding**	**Group Comparability**	**Treatment Integrity**	**Measurement**	**Investigator Bias**	*Quality*	**Participants**	**Intervention and Expertise**	**Compliance and Adherence**	**Analysis**	*Applicability Study*
Gottesdiener (2002)	Physician Global Assessment of Disease	6	Etoricoxib 5mg versus Etoricoxib 30mg	●	◐	●	●	●	●	●	○	**High**	○	○	●	●	**Moderate**
Gottesdiener (2002)	Physician Global Assessment of Disease	6	Etoricoxib 10mg versus Etoricoxib 30mg	●	◐	●	●	●	●	●	○	**High**	○	○	●	●	**Moderate**
Gottesdiener (2002)	Physician Global Assessment of Disease	6	Etoricoxib 5mg versus Etoricoxib 60mg	●	●	●	●	●	●	●	○	**High**	○	○	●	●	**Moderate**
Gottesdiener (2002)	Physician Global Assessment of Disease	6	Etoricoxib 10mg versus Etoricoxib 60mg	●	●	●	●	●	●	●	○	**High**	○	○	●	●	**Moderate**

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Study	*Outcome*	*Week*	*Comparison*	**Prospective**	**Power**	**Group Assignment**	**Blinding**	**Group Comparability**	**Treatment Integrity**	**Measurement**	**Investigator Bias**	*Quality*	**Participants**	**Intervention and Expertise**	**Compliance and Adherence**	**Analysis**	*Applicability Study*
Gottesdiener (2002)	Physician Global Assessment of Disease	6	Etoricoxib 30mg versus Etoricoxib 60mg	●	●	●	●	●	●	●	○	**High**	○	○	●	●	**Moderate**
Gottesdiener (2002)	Physician Global Assessment of Disease	6	Etoricoxib 5mg versus Etoricoxib 90mg	●	●	●	●	●	●	●	○	**High**	○	○	●	●	**Moderate**
Gottesdiener (2002)	Physician Global Assessment of Disease	6	Etoricoxib 10mg versus Etoricoxib 90mg	●	●	●	●	●	●	●	○	**High**	○	○	●	●	**Moderate**
Gottesdiener (2002)	Physician Global Assessment of Disease	6	Etoricoxib 30mg versus Etoricoxib 90mg	●	◐	●	●	●	●	●	○	**High**	○	○	●	●	**Moderate**

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Study	*Outcome*	*Week*	*Comparison*	**Prospective**	**Power**	**Group Assignment**	**Blinding**	**Group Comparability**	**Treatment Integrity**	**Measurement**	**Investigator Bias**	*Quality*	**Participants**	**Intervention and Expertise**	**Compliance and Adherence**	**Analysis**	*Applicability Study*
Gottesdiener (2002)	Physician Global Assessment of Disease	6	Etoricoxib 60mg versus Etoricoxib 90mg	●	◐	●	●	●	●	●	○	**High**	○	○	●	●	**Moderate**
Gottesdiener (2002)	Patient Assessment of Treatment Response	6	Etoricoxib 5mg versus Etoricoxib 10mg	●	◐	●	●	●	●	●	○	**High**	○	○	●	●	**Moderate**
Gottesdiener (2002)	Patient Assessment of Treatment Response	6	Etoricoxib 5mg versus Etoricoxib 30mg	●	◐	●	●	●	●	●	○	**High**	○	○	●	●	**Moderate**
Gottesdiener (2002)	Patient Assessment of Treatment Response	6	Etoricoxib 5mg versus Etoricoxib 60mg	●	●	●	●	●	●	●	○	**High**	○	○	●	●	**Moderate**

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Study	*Outcome*	*Week*	*Comparison*	**Prospective**	**Power**	**Group Assignment**	**Blinding**	**Group Comparability**	**Treatment Integrity**	**Measurement**	**Investigator Bias**	*Quality*	**Participants**	**Intervention and Expertise**	**Compliance and Adherence**	**Analysis**	*Applicability Study*
Gottesdiener (2002)	Patient Assessment of Treatment Response	6	Etoricoxib 5mg versus Etoricoxib 90mg	●	●	●	●	●	●	●	○	**High**	○	○	●	●	**Moderate**
Gottesdiener (2002)	Patient Assessment of Treatment Response	6	Etoricoxib 10mg versus Etoricoxib 30mg	●	◐	●	●	●	●	●	○	**High**	○	○	●	●	**Moderate**
Gottesdiener (2002)	Patient Assessment of Treatment Response	6	Etoricoxib 10mg versus Etoricoxib 60mg	●	●	●	●	●	●	●	○	**High**	○	○	●	●	**Moderate**
Gottesdiener (2002)	Patient Assessment of Treatment Response	6	Etoricoxib 10mg versus Etoricoxib 90mg	●	●	●	●	●	●	●	○	**High**	○	○	●	●	**Moderate**

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Study	*Outcome*	*Week*	*Comparison*	**Prospective**	**Power**	**Group Assignment**	**Blinding**	**Group Comparability**	**Treatment Integrity**	**Measurement**	**Investigator Bias**	*Quality*	**Participants**	**Intervention and Expertise**	**Compliance and Adherence**	**Analysis**	*Applicability Study*
Gottesdiener (2002)	Patient Assessment of Treatment Response	6	Etoricoxib 30mg versus Etoricoxib 60mg	●	●	●	●	●	●	●	○	**High**	○	○	●	●	**Moderate**
Gottesdiener (2002)	Patient Assessment of Treatment Response	6	Etoricoxib 30mg versus Etoricoxib 90mg	●	◐	●	●	●	●	●	○	**High**	○	○	●	●	**Moderate**
Gottesdiener (2002)	Patient Assessment of Treatment Response	6	Etoricoxib 60mg versus Etoricoxib 90mg	●	◐	●	●	●	●	●	○	**High**	○	○	●	●	**Moderate**
Gottesdiener (2002)	Patient Assessment of Treatment Response	6	Etoricoxib 5mg versus Etoricoxib 10mg	●	◐	●	●	●	●	●	○	**High**	○	○	●	●	**Moderate**

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Study	*Outcome*	*Week*	*Comparison*	**Prospective**	**Power**	**Group Assignment**	**Blinding**	**Group Comparability**	**Treatment Integrity**	**Measurement**	**Investigator Bias**	*Quality*	**Participants**	**Intervention and Expertise**	**Compliance and Adherence**	**Analysis**	*Applicability Study*
Gottesdiener (2002)	Physician Assessment of Treatment Response	6	Etoricoxib 5mg versus Etoricoxib 30mg	●	◐	●	●	●	●	●	○	**High**	○	○	●	●	**Moderate**
Gottesdiener (2002)	Physician Assessment of Treatment Response	6	Etoricoxib 10mg versus Etoricoxib 30mg	●	◐	●	●	●	●	●	○	**High**	○	○	●	●	**Moderate**
Gottesdiener (2002)	Physician Assessment of Treatment Response	6	Etoricoxib 5mg versus Etoricoxib 60mg	●	●	●	●	●	●	●	○	**High**	○	○	●	●	**Moderate**
Gottesdiener (2002)	Physician Assessment of Treatment Response	6	Etoricoxib 10mg versus Etoricoxib 60mg	●	●	●	●	●	●	●	○	**High**	○	○	●	●	**Moderate**

●: Domain free of flaws

○: Domain flaws present

◐: Moderate power

Study	*Outcome*	*Week*	*Comparison*	**Prospective**	**Power**	**Group Assignment**	**Blinding**	**Group Comparability**	**Treatment Integrity**	**Measurement**	**Investigator Bias**	*Quality*	**Participants**	**Intervention and Expertise**	**Compliance and Adherence**	**Analysis**	*Applicability Study*
Gottesdiener (2002)	Physician Assessment of Treatment Response	6	Etoricoxib 30mg versus Etoricoxib 60mg	●	●	●	●	●	●	●	○	**High**	○	○	●	●	**Moderate**
Gottesdiener (2002)	Physician Assessment of Treatment Response	6	Etoricoxib 5mg versus Etoricoxib 90mg	●	●	●	●	●	●	●	○	**High**	○	○	●	●	**Moderate**
Gottesdiener (2002)	Physician Assessment of Treatment Response	6	Etoricoxib 10mg versus Etoricoxib 90mg	●	●	●	●	●	●	●	○	**High**	○	○	●	●	**Moderate**
Gottesdiener (2002)	Physician Assessment of Treatment Response	6	Etoricoxib 30mg versus Etoricoxib 90mg	●	◐	●	●	●	●	●	○	**High**	○	○	●	●	**Moderate**

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Study	*Outcome*	*Week*	*Comparison*	**Prospective**	**Power**	**Group Assignment**	**Blinding**	**Group Comparability**	**Treatment Integrity**	**Measurement**	**Investigator Bias**	*Quality*	**Participants**	**Intervention and Expertise**	**Compliance and Adherence**	**Analysis**	*Applicability Study*
Gottesdiener (2002)	Physician Assessment of Treatment Response	6	Etoricoxib 60mg versus Etoricoxib 90mg	●	◐	●	●	●	●	●	○	**High**	○	○	●	●	**Moderate**
Kivits (2002)	VAS Pain improvement	6	Valdecoxib versus Placebo	●	●	○	●	●	●	●	○	**Moderate**	○	○	●	●	**Moderate**
Kivits (2002)	VAS Pain improvement	6	Valdecoxib versus Placebo	●	●	○	●	●	●	●	○	**Moderate**	○	○	●	●	**Moderate**
Kivits (2002)	VAS Pain improvement	6	Valdecoxib versus Placebo	●	●	○	●	●	●	●	○	**Moderate**	○	○	●	●	**Moderate**
Kivits (2002)	VAS Pain improvement	12	Valdecoxib versus Placebo	●	●	○	●	●	●	●	○	**Moderate**	○	○	●	●	**Moderate**

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Study	*Outcome*	*Week*	*Comparison*	**Prospective**	**Power**	**Group Assignment**	**Blinding**	**Group Comparability**	**Treatment Integrity**	**Measurement**	**Investigator Bias**	*Quality*	**Participants**	**Intervention and Expertise**	**Compliance and Adherence**	**Analysis**	*Applicability Study*
Kivits (2002)	VAS Pain improvement	12	Valdecoxib versus Placebo	●	●	○	●	●	●	●	○	**Moderate**	○	○	●	●	**Moderate**
Kivits (2002)	VAS Pain improvement	12	Valdecoxib versus Placebo	●	●	○	●	●	●	●	○	**Moderate**	○	○	●	●	**Moderate**
Kivits (2002)	WOMAC Stiffness	6	Valdecoxib versus Placebo	●	●	○	●	●	●	●	○	**Moderate**	○	○	●	●	**Moderate**
Kivits (2002)	WOMAC Stiffness	6	Valdecoxib versus Placebo	●	●	○	●	●	●	●	○	**Moderate**	○	○	●	●	**Moderate**
Kivits (2002)	WOMAC Stiffness	6	Valdecoxib versus Placebo	●	●	○	●	●	●	●	○	**Moderate**	○	○	●	●	**Moderate**
Kivits (2002)	WOMAC Stiffness	12	Valdecoxib versus Placebo	●	●	○	●	●	●	●	○	**Moderate**	○	○	●	●	**Moderate**

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Study	*Outcome*	*Week*	*Comparison*	Prospective	Power	Group Assignment	Blinding	Group Comparability	Treatment Integrity	Measurement	Investigator Bias	*Quality*	Participants	Intervention and Expertise	Compliance and Adherence	Analysis	*Applicability Study*
Kivits (2002)	WOMAC Stiffness	12	Valdecoxib versus Placebo	●	●	○	●	●	●	●	○	**Moderate**	○	○	●	●	**Moderate**
Kivits (2002)	WOMAC Stiffness	12	Valdecoxib versus Placebo	●	●	○	●	●	●	●	○	**Moderate**	○	○	●	●	**Moderate**
Kivits (2002)	WOMAC Total	12	Valdecoxib versus Placebo	●	●	○	●	●	●	●	○	**Moderate**	○	○	●	●	**Moderate**
Kivits (2002)	WOMAC Total	12	Valdecoxib versus Placebo	●	●	○	●	●	●	●	○	**Moderate**	○	○	●	●	**Moderate**
Kivits (2002)	WOMAC Total	12	Valdecoxib versus Placebo	●	●	○	●	●	●	●	○	**Moderate**	○	○	●	●	**Moderate**
Kivits (2002)	WOMAC Total	6	Valdecoxib versus Placebo	●	●	○	●	●	●	●	○	**Moderate**	○	○	●	●	**Moderate**

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Study	*Outcome*	*Week*	*Comparison*	**Prospective**	**Power**	**Group Assignment**	**Blinding**	**Group Comparability**	**Treatment Integrity**	**Measurement**	**Investigator Bias**	*Quality*	**Participants**	**Intervention and Expertise**	**Compliance and Adherence**	**Analysis**	*Applicability Study*
Kivits (2002)	WOMAC Total	6	Valdecoxib versus Placebo	●	●	○	●	●	●	●	○	**Moderate**	○	○	●	●	**Moderate**
Kivits (2002)	WOMAC Total	6	Valdecoxib versus Placebo	●	●	○	●	●	●	●	○	**Moderate**	○	○	●	●	**Moderate**
Kivits (2002)	Physician Global Assessment	6	Valdecoxib 10mg (Cox-2) versus Placebo	●	●	○	●	●	●	●	○	**Moderate**	○	○	●	●	**Moderate**
Kivits (2002)	Physician Global Assessment	12	Valdecoxib 10mg (Cox-2) versus Placebo	●	●	○	●	●	●	●	○	**Moderate**	○	○	●	●	**Moderate**
Kivits (2002)	Physician Global Assessment	6	Valdecoxib 20mg (Cox-2) versus Placebo	●	◐	○	●	●	●	●	○	**Moderate**	○	○	●	●	**Moderate**

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Study	*Outcome*	*Week*	*Comparison*	**Prospective**	**Power**	**Group Assignment**	**Blinding**	**Group Comparability**	**Treatment Integrity**	**Measurement**	**Investigator Bias**	*Quality*	**Participants**	**Intervention and Expertise**	**Compliance and Adherence**	**Analysis**	*Applicability Study*
Kivits (2002)	Physician Global Assessment	12	Valdecoxib 20mg (Cox-2) versus Placebo	●	●	○	●	●	●	●	○	**Moderate**	○	○	●	●	**Moderate**
Kivits (2002)	Physician Global Assessment	6	Valdecoxib 5mg (Cox-2) versus Placebo	●	●	○	●	●	●	●	○	**Moderate**	○	○	●	●	**Moderate**
Kivits (2002)	Physician Global Assessment	12	Valdecoxib 5mg (Cox-2) versus Placebo	●	●	○	●	●	●	●	○	**Moderate**	○	○	●	●	**Moderate**
Kivitz (2004)	Patient Global Assessment of Response to Treatment	6	Rofecoxib versus Placebo	●	●	●	●	●	●	●	○	**High**	●	○	●	●	**Moderate**

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Study	*Outcome*	*Week*	*Comparison*	**Prospective**	**Power**	**Group Assignment**	**Blinding**	**Group Comparability**	**Treatment Integrity**	**Measurement**	**Investigator Bias**	*Quality*	**Participants**	**Intervention and Expertise**	**Compliance and Adherence**	**Analysis**	*Applicability Study*
Lehmann (2005)	Physician Global Assessment of Disease	13	Celecoxib 200mg versus Placebo	●	●	○	●	○	●	●	○	**Moderate**	○	○	●	●	**Moderate**
Lehmann (2005)	Physician Global Assessment of Disease	13	Lumiracoxib 100mg versus Placebo	●	●	○	●	○	●	●	○	**Moderate**	○	○	●	●	**Moderate**
Lehmann (2005)	VAS Pain improvement	13	Lumiracoxib (Cox-2) with loading dose versus Placebo	●	●	○	●	○	●	●	○	**Moderate**	○	○	●	●	**Moderate**
Lehmann (2005)	WOMAC Pain	13	Lumiracoxib (Cox-2) with loading dose versus Placebo	●	●	○	●	○	●	●	○	**Moderate**	○	○	●	●	**Moderate**

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Study	*Outcome*	*Week*	*Comparison*	**Prospective**	**Power**	**Group Assignment**	**Blinding**	**Group Comparability**	**Treatment Integrity**	**Measurement**	**Investigator Bias**	*Quality*	**Participants**	**Intervention and Expertise**	**Compliance and Adherence**	**Analysis**	*Applicability Study*
Lehmann (2005)	VAS Pain improvement	13	Celecoxib versus Placebo	●	●	○	●	○	●	●	○	**Moderate**	○	○	●	●	**Moderate**
Lehmann (2005)	VAS Pain improvement	13	Lumiracoxib versus Placebo	●	●	○	●	○	●	●	○	**Moderate**	○	○	●	●	**Moderate**
Lehmann (2005)	WOMAC Pain	13	Celecoxib versus Placebo	●	●	○	●	○	●	●	○	**Moderate**	○	○	●	●	**Moderate**
Lehmann (2005)	WOMAC Pain	13	Lumiracoxib versus Placebo	●	●	○	●	○	●	●	○	**Moderate**	○	○	●	●	**Moderate**
Lehmann (2005)	WOMAC Total	13	Lumiracoxib versus Placebo	●	●	○	●	○	●	●	○	**Moderate**	○	○	●	●	**Moderate**
Lehmann (2005)	WOMAC Total	13	Lumiracoxib versus Placebo	●	●	○	●	○	●	●	○	**Moderate**	○	○	●	●	**Moderate**

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Study	*Outcome*	*Week*	*Comparison*	**Prospective**	**Power**	**Group Assignment**	**Blinding**	**Group Comparability**	**Treatment Integrity**	**Measurement**	**Investigator Bias**	*Quality*	**Participants**	**Intervention and Expertise**	**Compliance and Adherence**	**Analysis**	*Applicability Study*
Lehmann (2005)	WOMAC Function improvement	13	Celecoxib 100mg versus Lumiracoxib with loading dose	●	●	○	●	○	●	●	○	**Moderate**	○	○	●	●	**Moderate**
Lehmann (2005)	WOMAC Function improvement	13	Lumiracoxib 100mg versus Celecoxib	●	●	○	●	○	●	●	○	**Moderate**	○	○	●	●	**Moderate**
Lehmann (2005)	WOMAC Function improvement	13	Lumiracoxib 100mg versus Lumiracoxib with loading dose	●	●	○	●	○	●	●	○	**Moderate**	○	○	●	●	**Moderate**

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Study	*Outcome*	*Week*	*Comparison*	**Prospective**	**Power**	**Group Assignment**	**Blinding**	**Group Comparability**	**Treatment Integrity**	**Measurement**	**Investigator Bias**	*Quality*	**Participants**	**Intervention and Expertise**	**Compliance and Adherence**	**Analysis**	*Applicability Study*
Lehmann (2005)	VAS Pain improvement	13	Celecoxib 100mg versus Lumiracoxib with loading dose	●	●	○	●	○	●	●	○	**Moderate**	○	○	●	●	**Moderate**
Lehmann (2005)	WOMAC Pain improvement	13	Celecoxib 100mg versus Lumiracoxib with loading dose	●	●	○	●	○	●	●	○	**Moderate**	○	○	●	●	**Moderate**
Lehmann (2005)	VAS Pain improvement	13	Lumiracoxib 100mg versus Celecoxib	●	●	○	●	○	●	●	○	**Moderate**	○	○	●	●	**Moderate**

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Study	*Outcome*	*Week*	*Comparison*	**Prospective**	**Power**	**Group Assignment**	**Blinding**	**Group Comparability**	**Treatment Integrity**	**Measurement**	**Investigator Bias**	*Quality*	**Participants**	**Intervention and Expertise**	**Compliance and Adherence**	**Analysis**	*Applicability Study*
Lehmann (2005)	VAS Pain improvement	13	Lumiracoxib 100mg versus Lumiracoxib with loading dose	●	●	○	●	○	●	●	○	**Moderate**	○	○	●	●	**Moderate**
Lehmann (2005)	WOMAC Pain improvement	13	Lumiracoxib 100mg versus Celecoxib	●	●	○	●	○	●	●	○	**Moderate**	○	○	●	●	**Moderate**
Lehmann (2005)	WOMAC Pain improvement	13	Lumiracoxib 100mg versus Lumiracoxib with loading dose	●	●	○	●	○	●	●	○	**Moderate**	○	○	●	●	**Moderate**

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Study	*Outcome*	*Week*	*Comparison*	**Prospective**	**Power**	**Group Assignment**	**Blinding**	**Group Comparability**	**Treatment Integrity**	**Measurement**	**Investigator Bias**	*Quality*	**Participants**	**Intervention and Expertise**	**Compliance and Adherence**	**Analysis**	*Applicability Study*
Lehmann (2005)	WOMAC Stiffness improvement	13	Celecoxib 100mg versus Lumiracoxib with loading dose	●	●	○	●	○	●	●	○	**Moderate**	○	○	●	●	**Moderate**
Lehmann (2005)	WOMAC Stiffness improvement	13	Lumiracoxib 100mg versus Celecoxib	●	●	○	●	○	●	●	○	**Moderate**	○	○	●	●	**Moderate**
Lehmann (2005)	WOMAC Stiffness improvement	13	Lumiracoxib 100mg versus Lumiracoxib with loading dose	●	●	○	●	○	●	●	○	**Moderate**	○	○	●	●	**Moderate**

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Study	*Outcome*	*Week*	*Comparison*	**Prospective**	**Power**	**Group Assignment**	**Blinding**	**Group Comparability**	**Treatment Integrity**	**Measurement**	**Investigator Bias**	*Quality*	**Participants**	**Intervention and Expertise**	**Compliance and Adherence**	**Analysis**	*Applicability Study*
Lehmann (2005)	WOMAC Total	13	Celecoxib 100mg versus Lumiracoxib with loading dose	●	●	○	●	○	●	●	○	**Moderate**	○	○	●	●	**Moderate**
Lehmann (2005)	WOMAC Total	13	Lumiracoxib 100mg versus Celecoxib	●	●	○	●	○	●	●	○	**Moderate**	○	○	●	●	**Moderate**
Lehmann (2005)	WOMAC Total	13	Lumiracoxib 100mg versus Lumiracoxib with loading dose	●	●	○	●	○	●	●	○	**Moderate**	○	○	●	●	**Moderate**

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Study	*Outcome*	*Week*	*Comparison*	**Prospective**	**Power**	**Group Assignment**	**Blinding**	**Group Comparability**	**Treatment Integrity**	**Measurement**	**Investigator Bias**	*Quality*	**Participants**	**Intervention and Expertise**	**Compliance and Adherence**	**Analysis**	*Applicability Study*
Lehmann (2005)	Physician Global Assessment of Disease	13	Lumiracoxib 100mg versus Celecoxib 200mg	●	◐	○	●	○	●	●	○	**Moderate**	○	○	●	●	**Moderate**
Lehmann (2005)	Patient Global Assessment of Disease	13	Celecoxib versus Placebo	●	●	○	●	○	●	●	○	**Moderate**	○	○	●	●	**Moderate**
Lehmann (2005)	Patient Global Assessment of Disease	13	Lumiracoxib versus Placebo	●	●	○	●	○	●	●	○	**Moderate**	○	○	●	●	**Moderate**
Lehmann (2005)	Patient Global Assessment of Disease	13	Lumiracoxib versus Celecoxib	●	●	○	●	○	●	●	○	**Moderate**	○	○	●	●	**Moderate**

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Study	*Outcome*	*Week*	*Comparison*	**Prospective**	**Power**	**Group Assignment**	**Blinding**	**Group Comparability**	**Treatment Integrity**	**Measurement**	**Investigator Bias**	*Quality*	**Participants**	**Intervention and Expertise**	**Compliance and Adherence**	**Analysis**	*Applicability Study*
Luyten (2007)	WOMAC	24	Continuous Celecoxib versus Intermittent Celecoxib	●	◐	○	●	●	○	●	○	**Moderate**	○	○	●	●	**Moderate**
Luyten (2007)	WOMAC Stiffness	24	Continuous Celecoxib versus Intermittent Celecoxib	●	◐	○	●	●	○	●	○	**Moderate**	○	○	●	●	**Moderate**
Luyten (2007)	WOMAC Total	24	Continuous Celecoxib versus Intermittent Celecoxib	●	◐	○	●	●	○	●	○	**Moderate**	○	○	●	●	**Moderate**
Mckenna (2001)	WOMAC Function	6	Celecoxib versus Placebo	●	●	○	●	●	●	●	○	**Moderate**	○	○	●	●	**Moderate**

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Study	*Outcome*	*Week*	*Comparison*	**Prospective**	**Power**	**Group Assignment**	**Blinding**	**Group Comparability**	**Treatment Integrity**	**Measurement**	**Investigator Bias**	*Quality*	**Participants**	**Intervention and Expertise**	**Compliance and Adherence**	**Analysis**	*Applicability Study*
Mckenna (2001)	VAS Pain improvement	6	Celecoxib versus Placebo	●	●	○	●	●	●	●	○	**Moderate**	○	○	●	●	**Moderate**
Mckenna (2001)	WOMAC Pain	6	Celecoxib versus Placebo	●	●	○	●	●	●	●	○	**Moderate**	○	○	●	●	**Moderate**
Mckenna (2001)	WOMAC Stiffness	6	Celecoxib versus Placebo	●	●	○	●	●	●	●	○	**Moderate**	○	○	●	●	**Moderate**
Mckenna (2001)	WOMAC Total	6	Celecoxib versus Placebo	●	●	○	●	●	●	●	○	**Moderate**	○	○	●	●	**Moderate**
Mckenna (2001)	Patient Global Assessment	6	Celecoxib versus Placebo	●	●	○	●	●	●	●	○	**Moderate**	○	○	●	●	**Moderate**

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Study	*Outcome*	*Week*	*Comparison*	**Prospective**	**Power**	**Group Assignment**	**Blinding**	**Group Comparability**	**Treatment Integrity**	**Measurement**	**Investigator Bias**	*Quality*	**Participants**	**Intervention and Expertise**	**Compliance and Adherence**	**Analysis**	*Applicability Study*
Mckenna (2001)	Physician Global Assessment	6	Celecoxib (Cox-2) versus Placebo	●	●	○	●	●	●	●	○	**Moderate**	○	○	●	●	**Moderate**
Schnitzer (2005)	Patient Global Assessment of Disease	6	Rofecoxib 25mg versus Placebo	●	●	○	●	○	●	●	○	**Moderate**	○	○	○	●	**Moderate**
Schnitzer (2005)	Patient Global Assessment of Response to Treatment	6	Rofecoxib 25mg versus Placebo	●	●	○	●	○	●	●	○	**Moderate**	○	○	○	●	**Moderate**
Schnitzer (2005)	Patient Assessment of Treatment Response	6	Celecoxib 200mg versus Rofecoxib 12.5mg	○	◐	○	○	○	●	●	○	**Low**	○	○	●	●	**Moderate**

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Study	*Outcome*	*Week*	*Comparison*	**Prospective**	**Power**	**Group Assignment**	**Blinding**	**Group Comparability**	**Treatment Integrity**	**Measurement**	**Investigator Bias**	*Quality*	**Participants**	**Intervention and Expertise**	**Compliance and Adherence**	**Analysis**	*Applicability Study*
Schnitzer (2005)	Patient Assessment of Treatment Response	6	Celecoxib 200mg versus Rofecoxib 25mg	○	◐	○	○	○	●	●	○	**Low**	○	○	●	●	**Moderate**
Schnitzer (2005)	Patient Assessment of Treatment Response	6	Rofecoxib 12.5mg versus Rofecoxib 25mg	○	◐	○	○	○	●	●	○	**Low**	○	○	●	●	**Moderate**
Schnitzer (2009)	Patient Assessment of Treatment Response	4	Rofecoxib 12.5mg versus Rofecoxib 25mg	●	◐	○	●	○	●	●	○	**Moderate**	○	○	●	●	**Moderate**

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Study	*Outcome*	*Week*	*Comparison*	**Prospective**	**Power**	**Group Assignment**	**Blinding**	**Group Comparability**	**Treatment Integrity**	**Measurement**	**Investigator Bias**	*Quality*	**Participants**	**Intervention and Expertise**	**Compliance and Adherence**	**Analysis**	*Applicability Study*
Schnitzer (2009)	Physician Assessment of Treatment Response	4	Rofecoxib 12.5mg versus Rofecoxib 25mg	●	◐	○	●	○	●	●	○	**Moderate**	○	○	●	●	**Moderate**
Schnitzer (2010)	Rescue Acetaminophen	13	Naproxcinod versus Placebo	●	◐	○	●	●	●	●	○	**Moderate**	○	○	●	●	**Moderate**
Schnitzer (2010)	Rescue Acetaminophen	13	Naproxcinod versus Placebo	●	◐	○	●	●	●	●	○	**Moderate**	○	○	●	●	**Moderate**
Schnitzer (2010)	SF-36 MCS improvement	13	Naproxcinod versus Placebo	●	◐	○	●	●	●	●	○	**Moderate**	○	○	●	●	**Moderate**
Schnitzer (2010)	SF-36 MCS improvement	13	Naproxcinod versus Placebo	●	◐	○	●	●	●	●	○	**Moderate**	○	○	●	●	**Moderate**

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Study	*Outcome*	*Week*	*Comparison*	**Prospective**	**Power**	**Group Assignment**	**Blinding**	**Group Comparability**	**Treatment Integrity**	**Measurement**	**Investigator Bias**	*Quality*	**Participants**	**Intervention and Expertise**	**Compliance and Adherence**	**Analysis**	*Applicability Study*
Schnitzer (2010)	WOMAC Function	13	Naproxcinod versus Placebo	●	○	○	●	●	●	●	○	**Moderate**	○	○	●	●	**Moderate**
Schnitzer (2010)	VAS Pain at rest improvement	13	Naproxcinod versus Placebo	●	●	○	●	●	●	●	○	**Moderate**	○	○	●	●	**Moderate**
Schnitzer (2010)	VAS Pain at rest improvement	13	Naproxcinod versus Placebo	●	●	○	●	●	●	●	○	**Moderate**	○	○	●	●	**Moderate**
Schnitzer (2010)	VAS Pain during walking improvement	13	Naproxcinod versus Placebo	●	●	○	●	●	●	●	○	**Moderate**	○	○	●	●	**Moderate**
Schnitzer (2010)	VAS Pain during walking improvement	13	Naproxcinod versus Placebo	●	●	○	●	●	●	●	○	**Moderate**	○	○	●	●	**Moderate**

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Study	*Outcome*	*Week*	*Comparison*	**Prospective**	**Power**	**Group Assigment**	**Blinding**	**Group Comparability**	**Treatment Integrity**	**Measurement**	**Investigator Bias**	*Quality*	**Participants**	**Intervention and Expertise**	**Compliance and Adherence**	**Analysis**	*Applicability Study*
Schnitzer (2010)	WOMAC Pain	13	Naproxcinod versus Placebo	●	●	○	●	●	●	●	○	**Moderate**	○	○	●	●	**Moderate**
Schnitzer (2010)	WOMAC Pain	13	Naproxcinod versus Placebo	●	●	○	●	●	●	●	○	**Moderate**	○	○	●	●	**Moderate**
Schnitzer (2010)	WOMAC Total	13	Naproxcinod versus Placebo	●	●	○	●	●	●	●	○	**Moderate**	○	○	●	●	**Moderate**
Schnitzer (2010)	WOMAC Total	13	Naproxcinod versus Placebo	●	●	○	●	●	●	●	○	**Moderate**	○	○	●	●	**Moderate**
Schnitzer (2009)	WOMAC Function	4	Rofecoxib 12.5mg versus Rofecoxib	●	○	○	●	○	●	●	○	**Moderate**	○	○	●	●	**Moderate**

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Study	*Outcome*	*Week*	*Comparison*	**Prospective**	**Power**	**Group Assignment**	**Blinding**	**Group Comparability**	**Treatment Integrity**	**Measurement**	**Investigator Bias**	*Quality*	**Participants**	**Intervention and Expertise**	**Compliance and Adherence**	**Analysis**	*Applicability Study*
Schnitzer (2009)	WOMAC Pain	4	Rofecoxib 12.5mg versus Rofecoxib	●	●	○	●	○	●	●	○	**Moderate**	○	○	●	●	**Moderate**
Schnitzer (2009)	WOMAC Stiffness	4	Rofecoxib 12.5mg versus Rofecoxib	●	○	○	●	○	●	●	○	**Moderate**	○	○	●	●	**Moderate**
Tannenbaum (2004)	Physician Global Assessment of Disease	13	Celecoxib 200mg versus Placebo	●	●	○	●	●	●	●	○	**Moderate**	○	○	●	●	**Moderate**
Tannenbaum (2004)	Physician Global Assessment of Disease	13	Lumiracoxib 200mg versus Placebo	●	●	○	●	●	●	●	○	**Moderate**	○	○	●	●	**Moderate**

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Study	*Outcome*	*Week*	*Comparison*	**Prospective**	**Power**	**Group Assignment**	**Blinding**	**Group Comparability**	**Treatment Integrity**	**Measurement**	**Investigator Bias**	*Quality*	**Participants**	**Intervention and Expertise**	**Compliance and Adherence**	**Analysis**	*Applicability Study*
Tannenbaum (2004)	Physician Global Assessment of Disease	13	Lumiracoxib 400mg versus Placebo	●	●	○	●	●	●	●	○	**Moderate**	○	○	●	●	**Moderate**
Tannenbaum (2004)	WOMAC Function	13	Celecoxib versus Placebo	●	●	○	●	●	●	●	○	**Moderate**	○	○	●	●	**Moderate**
Tannenbaum (2004)	WOMAC Function	13	Lumiracoxib versus Placebo	●	●	○	●	●	●	●	○	**Moderate**	○	○	●	●	**Moderate**
Tannenbaum (2004)	WOMAC Function	13	Lumiracoxib versus Placebo	●	●	○	●	●	●	●	○	**Moderate**	○	○	●	●	**Moderate**
Tannenbaum (2004)	VAS Pain improvement	13	Celecoxib versus Placebo	●	●	○	●	●	●	●	○	**Moderate**	○	○	●	●	**Moderate**

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Study	*Outcome*	*Week*	*Comparison*	**Prospective**	**Power**	**Group Assignment**	**Blinding**	**Group Comparability**	**Treatment Integrity**	**Measurement**	**Investigator Bias**	*Quality*	**Participants**	**Intervention and Expertise**	**Compliance and Adherence**	**Analysis**	*Applicability Study*
Tannenbaum (2004)	VAS Pain improvement	13	Lumiracoxib versus Placebo	●	●	○	●	●	●	●	○	**Moderate**	○	○	●	●	**Moderate**
Tannenbaum (2004)	VAS Pain improvement	13	Lumiracoxib versus Placebo	●	●	○	●	●	●	●	○	**Moderate**	○	○	●	●	**Moderate**
Tannenbaum (2004)	WOMAC Pain	13	Celecoxib versus Placebo	●	●	○	●	●	●	●	○	**Moderate**	○	○	●	●	**Moderate**
Tannenbaum (2004)	WOMAC Pain	13	Lumiracoxib versus Placebo	●	●	○	●	●	●	●	○	**Moderate**	○	○	●	●	**Moderate**
Tannenbaum (2004)	WOMAC Pain	13	Lumiracoxib versus Placebo	●	●	○	●	●	●	●	○	**Moderate**	○	○	●	●	**Moderate**
Tannenbaum (2004)	WOMAC Stiffness	13	Celecoxib versus Placebo	●	●	○	●	●	●	●	○	**Moderate**	○	○	●	●	**Moderate**

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Study	*Outcome*	*Week*	*Comparison*	**Prospective**	**Power**	**Group Assignment**	**Blinding**	**Group Comparability**	**Treatment Integrity**	**Measurement**	**Investigator Bias**	*Quality*	**Participants**	**Intervention and Expertise**	**Compliance and Adherence**	**Analysis**	*Applicability Study*
Tannenbaum (2004)	WOMAC Stiffness	13	Lumiracoxib versus Placebo	●	●	○	●	●	●	●	○	**Moderate**	○	○	●	●	**Moderate**
Tannenbaum (2004)	WOMAC Stiffness	13	Lumiracoxib versus Placebo	●	●	○	●	●	●	●	○	**Moderate**	○	○	●	●	**Moderate**
Tannenbaum (2004)	WOMAC Total	13	Celecoxib versus Placebo	●	●	○	●	●	●	●	○	**Moderate**	○	○	●	●	**Moderate**
Tannenbaum (2004)	WOMAC Total	13	Lumiracoxib versus Placebo	●	●	○	●	●	●	●	○	**Moderate**	○	○	●	●	**Moderate**
Tannenbaum (2004)	WOMAC Total	13	Lumiracoxib versus Placebo	●	●	○	●	●	●	●	○	**Moderate**	○	○	●	●	**Moderate**

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Study	*Outcome*	*Week*	*Comparison*	**Prospective**	**Power**	**Group Assignment**	**Blinding**	**Group Comparability**	**Treatment Integrity**	**Measurement**	**Investigator Bias**	*Quality*	**Participants**	**Intervention and Expertise**	**Compliance and Adherence**	**Analysis**	*Applicability Study*
Tannenbaum (2004)	Patient Global Assessment of Disease	13	Celecoxib 200mg versus Placebo	●	●	○	●	●	●	●	○	**Moderate**	○	○	●	●	**Moderate**
Tannenbaum (2004)	Patient Global Assessment of Disease	13	Lumiracoxib 200mg versus Placebo	●	●	○	●	●	●	●	○	**Moderate**	○	○	●	●	**Moderate**
Tannenbaum (2004)	Patient Global Assessment of Disease	13	Lumiracoxib 400mg versus Placebo	●	●	○	●	●	●	●	○	**Moderate**	○	○	●	●	**Moderate**
Williams (2000)	WOMAC Function	6	Celecoxib 200mg QD versus Placebo	●	○	○	●	●	●	●	○	**Moderate**	○	○	●	●	**Moderate**

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Study	*Outcome*	*Week*	*Comparison*	**Prospective**	**Power**	**Group Assignment**	**Blinding**	**Group Comparability**	**Treatment Integrity**	**Measurement**	**Investigator Bias**	*Quality*	**Participants**	**Intervention and Expertise**	**Compliance and Adherence**	**Analysis**	*Applicability Study*
Williams (2000)	Lequesne index	6	Celecoxib 100mg BID versus Placebo	●	◐	○	●	●	●	●	○	**Moderate**	○	○	●	●	**Moderate**
Williams (2000)	Lequesne index	6	Celecoxib 200mg QD versus Placebo	●	◐	○	●	●	●	●	○	**Moderate**	○	○	●	●	**Moderate**
Williams (2000)	Lequesne index	6	Celecoxib 200mg versus Celecoxib 100mg bid	●	◐	○	●	●	●	●	○	**Moderate**	○	○	●	●	**Moderate**
Williams (2000)	WOMAC Total	6	Celecoxib 200mg versus Celecoxib	●	●	○	●	●	●	●	○	**Moderate**	○	○	●	●	**Moderate**

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Study	*Outcome*	*Week*	*Comparison*	**Prospective**	**Power**	**Group Assignment**	**Blinding**	**Group Comparability**	**Treatment Integrity**	**Measurement**	**Investigator Bias**	*Quality*	**Participants**	**Intervention and Expertise**	**Compliance and Adherence**	**Analysis**	*Applicability Study*
Williams (2000)	Patient Global Assessment	6	Celecoxib 200mg versus Celecoxib 100mg	●	◐	○	●	●	●	●	○	**Moderate**	○	○	●	●	**Moderate**
Williams (2001)	Lequesne index	6	Celecoxib versus Placebo	●	◐	○	●	●	●	●	○	**Moderate**	○	○	●	●	**Moderate**
Williams (2001)	Lequesne index	6	Celecoxib versus Placebo	●	◐	○	●	●	●	●	○	**Moderate**	○	○	●	●	**Moderate**
Williams (2001)	WOMAC Total	6	Celecoxib versus Placebo	●	●	○	●	●	●	●	○	**Moderate**	○	○	●	●	**Moderate**
Williams (2001)	WOMAC Total	6	Celecoxib versus Placebo	●	●	○	●	●	●	●	○	**Moderate**	○	○	●	●	**Moderate**

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Williams (2001)	Lequesne index	6	Celecoxib 100mg BID versus Celecoxib 200mg qd	●	◐	○	●	●	●	●	○	**Moderate**	○	○	●	●	**Moderate**
Williams (2001)	WOMAC Total	6	Celecoxib 100mg BID versus Celecoxib 200mg qd	●	●	○	●	●	●	●	○	**Moderate**	○	○	●	●	**Moderate**
Williams (2000)	Patient Global Assessment	6	Celecoxib 200mg versus Placebo	●	●	○	●	●	●	●	○	**Moderate**	○	○	●	●	**Moderate**
Williams (2000)	Patient Global Assessment	6	Celecoxib 100mg versus Placebo	●	●	○	●	●	●	●	○	**Moderate**	○	○	●	●	**Moderate**

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Study	*Outcome*	*Week*	*Comparison*	**Prospective**	**Power**	**Group Assignment**	**Blinding**	**Group Comparability**	**Treatment Integrity**	**Measurement**	**Investigator Bias**	*Quality*	**Participants**	**Intervention and Expertise**	**Compliance and Adherence**	**Analysis**	*Applicability Study*
Williams (2000)	Patient Global Assessment	6	Celecoxib 100 versus Celecoxib 200mg	●	●	○	●	●	●	●	○	**Moderate**	○	○	●	●	**Moderate**
Williams (2001)	Patient Global Assessment	6	Celecoxib 100mg versus Placebo	●	●	○	●	●	●	●	○	**Moderate**	○	○	●	●	**Moderate**
Williams (2001)	Patient Global Assessment	6	Celecoxib 200mg versus Placebo	●	●	○	●	●	●	●	○	**Moderate**	○	○	●	●	**Moderate**
Williams (2001)	Physician Global Assessment	6	Celecoxib 100mg versus Placebo	●	●	○	●	●	●	●	○	**Moderate**	○	○	●	●	**Moderate**

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Study	*Outcome*	*Week*	*Comparison*	**Prospective**	**Power**	**Group Assignment**	**Blinding**	**Group Comparability**	**Treatment Integrity**	**Measurement**	**Investigator Bias**	*Quality*	**Participants**	**Intervention and Expertise**	**Compliance and Adherence**	**Analysis**	*Applicability Study*
Williams (2001)	Physician Global Assessment	6	Celecoxib 200mg versus Placebo	●	●	○	●	●	●	●	○	**Moderate**	○	○	●	●	**Moderate**
Williams (2001)	Physician Global Assessment	6	Celecoxib 100mg versus Celecoxib 200mg	●	●	○	●	●	●	●	○	**Moderate**	○	○	●	●	**Moderate**
Ehrich (1999)	WOMAC Function	6	Rofecoxib versus Placebo	●	○	○	●	●	○	●	○	**Moderate**	○	○	●	●	**Moderate**
Fleischmann (2006)	Adverse events	13	Lumiracoxib 200mg versus Celecoxib 200mg	●	●	○	●	○	○	●	○	**Moderate**	○	○	●	●	**Moderate**

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Study	*Outcome*	*Week*	*Comparison*	**Prospective**	**Power**	**Group Assignment**	**Blinding**	**Group Comparability**	**Treatment Integrity**	**Measurement**	**Investigator Bias**	*Quality*	**Participants**	**Intervention and Expertise**	**Compliance and Adherence**	**Analysis**	*Applicability Study*
Fleischmann (2006)	Adverse events	13	Lumiracoxib 400mg versus Celecoxib 200mg	●	●	○	●	○	○	●	○	**Moderate**	○	○	●	●	**Moderate**
Fleischmann (2006)	Adverse events	13	Lumiracoxib 200mg versus Lumiracoxib 400mg	●	●	○	●	○	○	●	○	**Moderate**	○	○	●	●	**Moderate**
Fleischmann (2006)	Adverse events	13	Lumiracoxib 200mg versus Placebo	●	◐	○	●	○	○	●	○	**Moderate**	○	○	●	●	**Moderate**
Fleischmann (2006)	Adverse events	13	Lumiracoxib 400mg versus Placebo	●	◐	○	●	○	○	●	○	**Moderate**	○	○	●	●	**Moderate**

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Gibofsky (2003)	Adverse events	6	Celecoxib 200mg versus Placebo	●	◐	○	●	●	●	●	○	**Moderate**	○	○	●	●	**Moderate**
Gibofsky (2003)	Adverse events	6	Rofecoxib 25mg versus Placebo	●	◐	○	●	●	●	●	○	**Moderate**	○	○	●	●	**Moderate**
Gibofsky (2003)	Adverse events	6	Celecoxib 200mg versus Aceclofenac	●	◐	○	●	●	●	●	○	**Moderate**	○	○	●	●	**Moderate**
Gibofsky (2003)	Any adverse event	6	Rofecoxib 25mg versus Placebo	●	◐	○	●	●	●	●	○	**Moderate**	○	○	●	●	**Moderate**
Kivits (2002)	Abdominal pain	12	Valdecoxib 20mg versus Naproxen 500mg	●	◐	○	●	●	●	●	○	**Moderate**	○	○	●	●	**Moderate**

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Study	*Outcome*	*Week*	*Comparison*	**Prospective**	**Power**	**Group Assignment**	**Blinding**	**Group Comparability**	**Treatment Integrity**	**Measurement**	**Investigator Bias**	*Quality*	**Participants**	**Intervention and Expertise**	**Compliance and Adherence**	**Analysis**	*Applicability Study*
Kivits (2002)	Abdominal pain	12	Valdecoxib 10mg versus Naproxen 500mg	●	◐	○	●	●	●	●	○	**Moderate**	○	○	●	●	**Moderate**
Kivits (2002)	Abdominal pain	12	Valdecoxib 5mg versus Naproxen 500mg	●	◐	○	●	●	●	●	○	**Moderate**	○	○	●	●	**Moderate**
Kivits (2002)	Accidental injury	12	Valdecoxib 20mg versus Naproxen 500mg	●	◐	○	●	●	●	●	○	**Moderate**	○	○	●	●	**Moderate**
Kivits (2002)	Accidental injury	12	Valdecoxib 10mg versus Naproxen 500mg	●	◐	○	●	●	●	●	○	**Moderate**	○	○	●	●	**Moderate**

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Study	*Outcome*	*Week*	*Comparison*	**Prospective**	**Power**	**Group Assignment**	**Blinding**	**Group Comparability**	**Treatment Integrity**	**Measurement**	**Investigator Bias**	*Quality*	**Participants**	**Intervention and Expertise**	**Compliance and Adherence**	**Analysis**	*Applicability Study*
Kivits (2002)	Accidental injury	12	Valdecoxib 5mg versus Naproxen 500mg	●	◐	○	●	●	●	●	○	**Moderate**	○	○	●	●	**Moderate**
Kivits (2002)	Constipation	12	Valdecoxib 20mg versus Naproxen 500mg	●	◐	○	●	●	●	●	○	**Moderate**	○	○	●	●	**Moderate**
Kivits (2002)	Constipation	12	Valdecoxib 10mg versus Naproxen 500mg	●	◐	○	●	●	●	●	○	**Moderate**	○	○	●	●	**Moderate**
Kivits (2002)	Constipation	12	Valdecoxib 5mg versus Naproxen 500mg	●	◐	○	●	●	●	●	○	**Moderate**	○	○	●	●	**Moderate**

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Kivits (2002)	Diarrhea	12	Valdecoxib 20mg versus Naproxen 500mg	●	◐	○	●	●	●	●	○	**Moderate**	○	○	●	●	**Moderate**
Kivits (2002)	Diarrhea	12	Valdecoxib 10mg versus Naproxen 500mg	●	◐	○	●	●	●	●	○	**Moderate**	○	○	●	●	**Moderate**
Kivits (2002)	Diarrhea	12	Valdecoxib 5mg versus Naproxen 500mg	●	◐	○	●	●	●	●	○	**Moderate**	○	○	●	●	**Moderate**
Kivits (2002)	Dyspepsia	12	Valdecoxib 20mg versus Naproxen 500mg	●	◐	○	●	●	●	●	○	**Moderate**	○	○	●	●	**Moderate**

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Study	*Outcome*	*Week*	*Comparison*	**Prospective**	**Power**	**Group Assignment**	**Blinding**	**Group Comparability**	**Treatment Integrity**	**Measurement**	**Investigator Bias**	*Quality*	**Participants**	**Intervention and Expertise**	**Compliance and Adherence**	**Analysis**	*Applicability Study*
Kivits (2002)	Dyspepsia	12	Valdecoxib 10mg versus Naproxen 500mg	●	◐	○	●	●	●	●	○	**Moderate**	○	○	●	●	**Moderate**
Kivits (2002)	Dyspepsia	12	Valdecoxib 5mg versus Naproxen 500mg	●	◐	○	●	●	●	●	○	**Moderate**	○	○	●	●	**Moderate**
Kivits (2002)	Flatulence	12	Valdecoxib 20mg versus Naproxen 500mg	●	◐	○	●	●	●	●	○	**Moderate**	○	○	●	●	**Moderate**
Kivits (2002)	Flatulence	12	Valdecoxib 10mg versus Naproxen 500mg	●	◐	○	●	●	●	●	○	**Moderate**	○	○	●	●	**Moderate**

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Study	*Outcome*	*Week*	*Comparison*	**Prospective**	**Power**	**Group Assignment**	**Blinding**	**Group Comparability**	**Treatment Integrity**	**Measurement**	**Investigator Bias**	*Quality*	**Participants**	**Intervention and Expertise**	**Compliance and Adherence**	**Analysis**	*Applicability Study*
Kivits (2002)	Flatulence	12	Valdecoxib 5mg versus Naproxen 500mg	●	◐	○	●	●	●	●	○	**Moderate**	○	○	●	●	**Moderate**
Kivits (2002)	Headache	12	Valdecoxib 20mg versus Naproxen 500mg	●	◐	○	●	●	●	●	○	**Moderate**	○	○	●	●	**Moderate**
Kivits (2002)	Headache	12	Valdecoxib 10mg versus Naproxen 500mg	●	◐	○	●	●	●	●	○	**Moderate**	○	○	●	●	**Moderate**
Kivits (2002)	Headache	12	Valdecoxib 5mg versus Naproxen 500mg	●	◐	○	●	●	●	●	○	**Moderate**	○	○	●	●	**Moderate**

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Study	*Outcome*	*Week*	*Comparison*	**Prospective**	**Power**	**Group Assignment**	**Blinding**	**Group Comparability**	**Treatment Integrity**	**Measurement**	**Investigator Bias**	*Quality*	**Participants**	**Intervention and Expertise**	**Compliance and Adherence**	**Analysis**	*Applicability Study*
Kivits (2002)	Myalgia	12	Valdecoxib 20mg versus Naproxen 500mg	●	◐	○	●	●	●	●	○	**Moderate**	○	○	●	●	**Moderate**
Kivits (2002)	Myalgia	12	Valdecoxib 10mg versus Naproxen 500mg	●	◐	○	●	●	●	●	○	**Moderate**	○	○	●	●	**Moderate**
Kivits (2002)	Myalgia	12	Valdecoxib 5mg versus Naproxen 500mg	●	◐	○	●	●	●	●	○	**Moderate**	○	○	●	●	**Moderate**
Kivits (2002)	Nausea	12	Valdecoxib 20mg versus Naproxen 500mg	●	◐	○	●	●	●	●	○	**Moderate**	○	○	●	●	**Moderate**

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Study	*Outcome*	*Week*	*Comparison*	Prospective	Power	Group Assignment	Blinding	Group Comparability	Treatment Integrity	Measurement	Investigator Bias	*Quality*	Participants	Intervention and Expertise	Compliance and Adherence	Analysis	*Applicability Study*
Kivits (2002)	Nausea	12	Valdecoxib 10mg versus Naproxen 500mg	●	◐	○	●	●	●	●	○	**Moderate**	○	○	●	●	**Moderate**
Kivits (2002)	Nausea	12	Valdecoxib 5mg versus Naproxen 500mg	●	◐	○	●	●	●	●	○	**Moderate**	○	○	●	●	**Moderate**
Kivits (2002)	Upper respiratory tract infections	12	Valdecoxib 20mg versus Naproxen 500mg	●	◐	○	●	●	●	●	○	**Moderate**	○	○	●	●	**Moderate**
Kivits (2002)	Upper respiratory tract infections	12	Valdecoxib 10mg versus Naproxen 500mg	●	◐	○	●	●	●	●	○	**Moderate**	○	○	●	●	**Moderate**

●: Domain free of flaws

○: Domain flaws present

◐: Moderate power

Study	*Outcome*	*Week*	*Comparison*	**Prospective**	**Power**	**Group Assignment**	**Blinding**	**Group Comparability**	**Treatment Integrity**	**Measurement**	**Investigator Bias**	*Quality*	**Participants**	**Intervention and Expertise**	**Compliance and Adherence**	**Analysis**	*Applicability Study*
Kivits (2002)	Upper respiratory tract infections	12	Valdecoxib 5mg versus Naproxen 500mg	●	◐	○	●	●	●	●	○	**Moderate**	○	○	●	●	**Moderate**
Kivits (2004)	Acid reflux	6	Rofecoxib 12.5mg versus Nabumetone 1000mg	●	●	●	●	●	●	●	○	**High**	●	○	●	●	**Moderate**
Kivits (2004)	At least one adverse event	6	Rofecoxib 12.5mg versus Naproxen	●	●	●	●	●	●	●	○	**High**	●	○	●	●	**Moderate**
Kivits (2004)	At least one adverse event	6	Rofecoxib 12.5mg versus Placebo	●	◐	●	●	●	●	●	○	**High**	●	○	●	●	**Moderate**

●: Domain free of flaws

○: Domain flaws present

◐: Moderate power

Study	*Outcome*	*Week*	*Comparison*	**Prospective**	**Power**	**Group Assignment**	**Blinding**	**Group Comparability**	**Treatment Integrity**	**Measurement**	**Investigator Bias**	*Quality*	**Participants**	**Intervention and Expertise**	**Compliance and Adherence**	**Analysis**	*Applicability Study*
Kivits (2004)	Dyspepsia	6	Rofecoxib 12.5mg versus Nabumetone 1000mg	●	●	●	●	●	●	●	○	**High**	●	○	●	●	**Moderate**
Kivits (2004)	Epigastric discomfort	6	Rofecoxib 12.5mg versus Nabumetone 1000mg	●	●	●	●	●	●	●	○	**High**	●	○	●	●	**Moderate**
Kivits (2004)	GI events	6	Rofecoxib 12.5mg versus Nabumetone 1000mg	●	●	●	●	●	●	●	○	**High**	●	○	●	●	**Moderate**

●: Domain free of flaws

○: Domain flaws present

◐: Moderate power

Study	*Outcome*	*Week*	*Comparison*	**Prospective**	**Power**	**Group Assignment**	**Blinding**	**Group Comparability**	**Treatment Integrity**	**Measurement**	**Investigator Bias**	*Quality*	**Participants**	**Intervention and Expertise**	**Compliance and Adherence**	**Analysis**	*Applicability Study*
Kivits (2004)	Heartburn	6	Rofecoxib 12.5mg versus Nabumetone 1000mg	●	●	●	●	●	●	●	○	**High**	●	○	●	●	**Moderate**
Kivits (2004)	Nausea	6	Rofecoxib 12.5mg versus Nabumetone 1000mg	●	●	●	●	●	●	●	○	**High**	●	○	●	●	**Moderate**
Kivits (2004)	Vomiting	6	Rofecoxib 12.5mg versus Nabumetone 1000mg	●	●	●	●	●	●	●	○	**High**	●	○	●	●	**Moderate**

●: Domain free of flaws

○: Domain flaws present

◐: Moderate power

Study	*Outcome*	*Week*	*Comparison*	**Prospective**	**Power**	**Group Assignment**	**Blinding**	**Group Comparability**	**Treatment Integrity**	**Measurement**	**Investigator Bias**	*Quality*	**Participants**	**Intervention and Expertise**	**Compliance and Adherence**	**Analysis**	*Applicability Study*
Schnitzer (2005)	Abdominal pain	6	Acetaminophen 4000mg versus Rofecoxib 12.5mg	○	◐	○	○	○	●	●	○	**Low**	○	○	●	●	**Moderate**
Schnitzer (2005)	Abdominal pain	6	Acetaminophen 4000mg versus Rofecoxib 25mg	○	◐	○	○	○	●	●	○	**Low**	○	○	●	●	**Moderate**
Schnitzer (2005)	Abdominal pain		Acetaminophen 4000mg versus Celecoxib 200mg	○	◐	○	○	○	●	●	○	**Low**	○	○	●	●	**Moderate**

●: Domain free of flaws

○: Domain flaws present

◐: Moderate power

Study	*Outcome*	*Week*	*Comparison*	**Prospective**	**Power**	**Group Assignment**	**Blinding**	**Group Comparability**	**Treatment Integrity**	**Measurement**	**Investigator Bias**	*Quality*	**Participants**	**Intervention and Expertise**	**Compliance and Adherence**	**Analysis**	*Applicability Study*
Schnitzer (2005)	Any clinical adverse event, VACT2	6	Rofecoxib 12.5mg versus Rofecoxib 12.5mg	○	●	○	○	○	●	●	○	**Low**	○	○	●	●	**Moderate**
Schnitzer (2005)	Any clinical adverse event, VACT2	6	Celecoxib 200mg versus Rofecoxib 25mg	○	◐	○	○	○	●	●	○	**Low**	○	○	●	●	**Moderate**
Schnitzer (2005)	Any clinical adverse event, VACT2	6	Celecoxib 200mg versus Rofecoxib 25mg	○	●	○	○	○	●	●	○	**Low**	○	○	●	●	**Moderate**

●: Domain free of flaws

○: Domain flaws present

◐: Moderate power

Study	*Outcome*	*Week*	*Comparison*	**Prospective**	**Power**	**Group Assignment**	**Blinding**	**Group Comparability**	**Treatment Integrity**	**Measurement**	**Investigator Bias**	*Quality*	**Participants**	**Intervention and Expertise**	**Compliance and Adherence**	**Analysis**	*Applicability Study*
Schnitzer (2005)	Diarrhea	6	Acetaminophen 4000mg versus Rofecoxib 12.5mg	○	◐	○	○	○	●	●	○	**Low**	○	○	●	●	**Moderate**
Schnitzer (2005)	Diarrhea	6	Acetaminophen 4000mg versus Rofecoxib 25mg	○	◐	○	○	○	●	●	○	**Low**	○	○	●	●	**Moderate**
Schnitzer (2005)	Diarrhea		Acetaminophen 4000mg versus Celecoxib 200mg	○	◐	○	○	○	●	●	○	**Low**	○	○	●	●	**Moderate**

●: Domain free of flaws

○: Domain flaws present

◐: Moderate power

Study	*Outcome*	*Week*	*Comparison*	**Prospective**	**Power**	**Group Assignment**	**Blinding**	**Group Comparability**	**Treatment Integrity**	**Measurement**	**Investigator Bias**	*Quality*	**Participants**	**Intervention and Expertise**	**Compliance and Adherence**	**Analysis**	*Applicability Study*
Schnitzer (2005)	Headache	6	Acetaminophen 4000mg versus Rofecoxib 12.5mg	○	◐	○	○	○	●	●	○	**Low**	○	○	●	●	**Moderate**
Schnitzer (2005)	Headache	6	Acetaminophen 4000mg versus Rofecoxib 25mg	○	◐	○	○	○	●	●	○	**Low**	○	○	●	●	**Moderate**
Schnitzer (2005)	Lower extremity edema	6	Acetaminophen 4000mg versus Rofecoxib 12.5mg	○	◐	○	○	○	●	●	○	**Low**	○	○	●	●	**Moderate**

●: Domain free of flaws

○: Domain flaws present

◐: Moderate power

Study	*Outcome*	*Week*	*Comparison*	**Prospective**	**Power**	**Group Assignment**	**Blinding**	**Group Comparability**	**Treatment Integrity**	**Measurement**	**Investigator Bias**	*Quality*	**Participants**	**Intervention and Expertise**	**Compliance and Adherence**	**Analysis**	*Applicability Study*
Schnitzer (2005)	Lower extremity edema	6	Acetaminophen 4000mg versus Rofecoxib 25mg	○	◐	○	○	○	●	●	○	**Low**	○	○	●	●	**Moderate**
Schnitzer (2005)	Nausea	6	Acetaminophen 4000mg versus Rofecoxib 12.5mg	○	◐	○	○	○	●	●	○	**Low**	○	○	●	●	**Moderate**
Schnitzer (2005)	Nausea	6	Acetaminophen 4000mg versus Rofecoxib 25mg	○	◐	○	○	○	●	●	○	**Low**	○	○	●	●	**Moderate**

●: Domain free of flaws

○: Domain flaws present

◐: Moderate power

Study	*Outcome*	*Week*	*Comparison*	**Prospective**	**Power**	**Group Assignment**	**Blinding**	**Group Comparability**	**Treatment Integrity**	**Measurement**	**Investigator Bias**	*Quality*	**Participants**	**Intervention and Expertise**	**Compliance and Adherence**	**Analysis**	*Applicability Study*
Schnitzer (2005)	Upper respiratory infection	6	Acetaminophen 4000mg versus Rofecoxib 12.5mg	○	◐	○	○	○	●	●	○	**Low**	○	○	●	●	**Moderate**
Schnitzer (2005)	Upper respiratory infection	6	Acetaminophen 4000mg versus Rofecoxib 25mg	○	◐	○	○	○	●	●	○	**Low**	○	○	●	●	**Moderate**
Tannenbaum (2004)	Adverse events	13	Celecoxib 100mg versus Placebo	●	◐	○	●	●	●	●	○	**Moderate**	○	○	●	●	**Moderate**
Tannenbaum (2004)	Adverse events	13	Lumiracoxib 200mg versus Placebo	●	◐	○	●	●	●	●	○	**Moderate**	○	○	●	●	**Moderate**

●: Domain free of flaws

○: Domain flaws present

◐: Moderate power

Study	*Outcome*	*Week*	*Comparison*	**Prospective**	**Power**	**Group Assignment**	**Blinding**	**Group Comparability**	**Treatment Integrity**	**Measurement**	**Investigator Bias**	*Quality*	**Participants**	**Intervention and Expertise**	**Compliance and Adherence**	**Analysis**	*Applicability Study*
Tannenbaum (2004)	Adverse events	13	Lumiracoxib 400mg versus Placebo	●	◐	○	●	●	●	●	○	**Moderate**	○	○	●	●	**Moderate**
Williams (2000)	Lequesne index	6	Celecoxib 100mg BID versus Placebo	●	◐	○	●	●	●	●	○	**Moderate**	○	○	●	●	**Moderate**
Williams (2000)	Lequesne index	6	Celecoxib 200mg QD versus Placebo	●	◐	○	●	●	●	●	○	**Moderate**	○	○	●	●	**Moderate**
Williams (2000)	Lequesne index	6	Celecoxib 200mg versus Celecoxib 100mg bid	●	◐	○	●	●	●	●	○	**Moderate**	○	○	●	●	**Moderate**

●: Domain free of flaws

○: Domain flaws present

◐: Moderate power

Study	*Outcome*	*Week*	*Comparison*	**Prospective**	**Power**	**Group Assignment**	**Blinding**	**Group Comparability**	**Treatment Integrity**	**Measurement**	**Investigator Bias**	*Quality*	**Participants**	**Intervention and Expertise**	**Compliance and Adherence**	**Analysis**	*Applicability Study*
Williams (2001)	Lequesne index	6	Celecoxib versus Placebo	●	◐	○	●	●	●	●	○	**Moderate**	○	○	●	●	**Moderate**
Williams (2001)	Lequesne index	6	Celecoxib versus Placebo	●	◐	○	●	●	●	●	○	**Moderate**	○	○	●	●	**Moderate**
Williams (2001)	Lequesne index	6	Celecoxib 100mg BID versus Celecoxib 200mg qd	●	◐	○	●	○	○	●	○	**Low**	○	○	●	●	**Moderate**
Williams (2001)	Adverse events	6	Celecoxib 100mg versus Celecoxib 200mg	●	◐	○	●	●	●	●	○	**Moderate**	○	○	●	●	**Moderate**

●: Domain free of flaws

○: Domain flaws present

◐: Moderate power

Study	*Outcome*	*Week*	*Comparison*	**Prospective**	**Power**	**Group Assignment**	**Blinding**	**Group Comparability**	**Treatment Integrity**	**Measurement**	**Investigator Bias**	*Quality*	**Participants**	**Intervention and Expertise**	**Compliance and Adherence**	**Analysis**	*Applicability Study*
Williams (2001)	Adverse events	6	Celecoxib 100mg versus Placebo	●	◐	○	●	●	●	●	○	**Moderate**	○	○	●	●	**Moderate**
Williams (2001)	Adverse events	6	Celecoxib 200mg versus Placebo	●	◐	○	●	●	●	●	○	**Moderate**	○	○	●	●	**Moderate**

Table 149. Quality and Applicability: NSAIDs Versus Control

●: Domain free of flaws

○: Domain flaws present

◐: Moderate power

Study	*Outcome*	*Week*	*Comparison*	Prospective	Power	Group Assignment	Blinding	Group Comparability	Treatment Integrity	Measurement	Investigator Bias	*Quality*	Participants	Intervention and Expertise	Compliance and Adherence	Analysis	*Applicability Study*
Astorga (1991)	Time to walk 50ft	4	Etodolac 300mg versus Piroxicam 20mg	●	◐	○	●	○	●	●	○	**Moderate**	○	○	●	●	**Moderate**
Astorga (1991)	Time to walk 50ft	6	Etodolac 300mg versus Piroxicam 20mg	●	◐	○	●	○	●	●	○	**Moderate**	○	○	●	●	**Moderate**
Astorga (1991)	Time to walk 50ft	8	Etodolac 300mg versus Piroxicam 20mg	●	◐	○	●	○	●	●	○	**Moderate**	○	○	●	●	**Moderate**

●: Domain free of flaws

○: Domain flaws present

◐: Moderate power

Study	*Outcome*	*Week*	*Comparison*	Prospective	Power	Group Assignment	Blinding	Group Comparability	Treatment Integrity	Measurement	Investigator Bias	*Quality*	Participants	Intervention and Expertise	Compliance and Adherence	Analysis	*Applicability Study*
Astorga (1991)	Morning stiffness	4	Etodolac 300mg versus Piroxicam 20mg	●	◐	○	●	○	●	●	○	**Moderate**	○	○	●	●	**Moderate**
Astorga (1991)	Morning stiffness	6	Etodolac 300mg versus Piroxicam 20mg	●	◐	○	●	○	●	●	○	**Moderate**	○	○	●	●	**Moderate**
Astorga (1991)	Morning stiffness	8	Etodolac 300mg versus Piroxicam 20mg	●	◐	○	●	○	●	●	○	**Moderate**	○	○	●	●	**Moderate**
Astorga (1991)	Morning stiffness	Final follow up	Etodolac 300mg versus Piroxicam 20mg	●	◐	○	●	○	●	●	○	**Moderate**	○	○	●	●	**Moderate**

●: Domain free of flaws

○: Domain flaws present

◐: Moderate power

Study	*Outcome*	*Week*	*Comparison*	Prospective	Power	Group Assignment	Blinding	Group Comparability	Treatment Integrity	Measurement	Investigator Bias	*Quality*	Participants	Intervention and Expertise	Compliance and Adherence	Analysis	*Applicability Study*
Goregaonkar (2009)	Gastritis	4	Lornoxicam 8mg versus Diclofenac 50mg	●	◐	○	●	●	●	●	○	**Moderate**	●	○	●	●	**Moderate**
Goregaonkar (2009)	Abdominal pain	4	Lornoxicam 8mg versus Diclofenac 50mg	●	◐	○	●	●	●	●	○	**Moderate**	●	○	●	●	**Moderate**
Goregaonkar (2009)	Dizziness	4	Lornoxicam 8mg versus Diclofenac 50mg	●	◐	○	●	●	●	●	○	**Moderate**	●	○	●	●	**Moderate**
Goregaonkar (2009)	Drowsiness	4	Lornoxicam 8mg versus Diclofenac 50mg	●	◐	○	●	●	●	●	○	**Moderate**	●	○	●	●	**Moderate**

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○: Domain flaws present

◐: Moderate power

Study	*Outcome*	*Week*	*Comparison*	**Prospective**	**Power**	**Group Assignment**	**Blinding**	**Group Comparability**	**Treatment Integrity**	**Measurement**	**Investigator Bias**	*Quality*	**Participants**	**Intervention and Expertise**	**Compliance and Adherence**	**Analysis**	*Applicability Study*
Goregaonkar (2009)	Headache	4	Lornoxicam 8mg versus Diclofenac 50mg	●	◐	○	●	●	●	●	○	**Moderate**	●	○	●	●	**Moderate**
Goregaonkar (2009)	Nausea/ Vomiting	4	Lornoxicam 8mg versus Diclofenac 50mg	●	◐	○	●	●	●	●	○	**Moderate**	●	○	●	●	**Moderate**
Goregaonkar (2009)	Diarrhea	4	Lornoxicam 8mg versus Diclofenac 50mg	●	◐	○	●	●	●	●	○	**Moderate**	●	○	●	●	**Moderate**
Goregaonkar (2009)	GI events	4	Lornoxicam 8mg versus Diclofenac 50mg	●	◐	○	●	●	●	●	○	**Moderate**	●	○	●	●	**Moderate**

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○: Domain flaws present

◐: Moderate power

Study	*Outcome*	*Week*	*Comparison*	**Prospective**	**Power**	**Group Assignment**	**Blinding**	**Group Comparability**	**Treatment Integrity**	**Measurement**	**Investigator Bias**	*Quality*	**Participants**	**Intervention and Expertise**	**Compliance and Adherence**	**Analysis**	*Applicability Study*
Ayral (2003)	Change in WOMAC averaged VAS Function	52	Tenidap 120mg versus Piroxicam 20mg	●	○	○	●	○	●	●	○	**Moderate**	○	○	●	●	**Moderate**
Ayral (2003)	Change in WOMAC averaged VAS Pain	52	Tenidap 40mg versus Tenidap 120mg	●	●	○	●	○	●	●	○	**Moderate**	○	○	●	●	**Moderate**
Ayral (2003)	Change in WOMAC averaged VAS Pain	52	Tenidap 40mg versus Piroxicam 20mg	●	●	○	●	○	●	●	○	**Moderate**	○	○	●	●	**Moderate**
Ayral (2003)	Change in WOMAC averaged VAS Pain	52	Tenidap 120mg versus Piroxicam 20mg	●	●	○	●	○	●	●	○	**Moderate**	○	○	●	●	**Moderate**

●: Domain free of flaws

○: Domain flaws present

◐: Moderate power

Study	*Outcome*	*Week*	*Comparison*	Prospective	Power	Group Assignment	Blinding	Group Comparability	Treatment Integrity	Measurement	Investigator Bias	*Quality*	Participants	Intervention and Expertise	Compliance and Adherence	Analysis	*Applicability Study*
Ayral (2003)	Change in WOMAC averaged VAS Stiffness	52	Tenidap 40mg versus Tenidap 120mg	●	●	○	●	○	●	●	○	**Moderate**	○	○	●	●	**Moderate**
Ayral (2003)	Change in WOMAC averaged VAS Stiffness	52	Tenidap 40mg versus Piroxicam 20	●	●	○	●	○	●	●	○	**Moderate**	○	○	●	●	**Moderate**
Ayral (2003)	Change in WOMAC averaged VAS Stiffness	52	Tenidap 120mg versus Piroxicam 20	●	●	○	●	○	●	●	○	**Moderate**	○	○	●	●	**Moderate**

●: Domain free of flaws

○: Domain flaws present

◐: Moderate power

Study	*Outcome*	*Week*	*Comparison*	**Prospective**	**Power**	**Group Assignment**	**Blinding**	**Group Comparability**	**Treatment Integrity**	**Measurement**	**Investigator Bias**	*Quality*	**Participants**	**Intervention and Expertise**	**Compliance and Adherence**	**Analysis**	*Applicability Study*
Ayral (2003)	Change in WOMAC averaged VAS Total	52	Tenidap 40mg versus Tenidap 120mg	●	●	○	●	○	●	●	○	**Moderate**	○	○	●	●	**Moderate**
Ayral (2003)	Change in WOMAC averaged VAS Total	52	Tenidap 40mg versus Piroxicam 20	●	●	○	●	○	●	●	○	**Moderate**	○	○	●	●	**Moderate**
Ayral (2003)	Change in WOMAC averaged VAS Total	52	Tenidap 120mg versus Piroxicam 20	●	●	○	●	○	●	●	○	**Moderate**	○	○	●	●	**Moderate**
Bellamy (1993)	WOMAC Function	12	Tenoxicam versus Diclofenac	●	◐	○	●	○	●	●	○	**Moderate**	○	○	●	●	**Moderate**
Bellamy (1993)	WOMAC Pain	12	Tenoxicam versus Diclofenac	●	◐	○	●	○	●	●	○	**Moderate**	○	○	●	●	**Moderate**

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○: Domain flaws present

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Study	*Outcome*	*Week*	*Comparison*	Prospective	Power	Group Assignment	Blinding	Group Comparability	Treatment Integrity	Measurement	Investigator Bias	*Quality*	Participants	Intervention and Expertise	Compliance and Adherence	Analysis	*Applicability Study*
Bellamy (1993)	WOMAC Stiffness	12	Tenoxicam versus Diclofenac	●	◐	○	●	○	●	●	○	**Moderate**	○	○	●	●	**Moderate**
Bradley (1991)	HAQ Disability improvement	4	Ibuprofen 300 versus Ibuprofen 600mg	●	◐	○	●	○	●	●	●	**Moderate**	○	○	●	●	**Moderate**
Bradley (1991)	Health Assessment Questionnaire improvement	4	Ibuprofen 300mg versus Ibuprofen 600	●	◐	○	●	○	●	●	●	**Moderate**	○	○	●	●	**Moderate**
Bradley (1991)	Walk time (sec) improvement	4	Ibuprofen 300mg versus Ibuprofen 600	●	◐	○	●	○	●	●	●	**Moderate**	○	○	●	●	**Moderate**

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○: Domain flaws present

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Study	*Outcome*	*Week*	*Comparison*	Prospective	Power	Group Assignment	Blinding	Group Comparability	Treatment Integrity	Measurement	Investigator Bias	*Quality*	Participants	Intervention and Expertise	Compliance and Adherence	Analysis	*Applicability Study*
Chubick (1987)	Improvement in morning weight-bearing pain	4	Sulindac 300-400mg Qd versus Sulindac 300-400mg Bid	●	◐	○	●	○	●	●	○	**Moderate**	○	○	●	●	**Moderate**
Chubick (1987)	Improvement in afternoon weight-bearing pain	4	Sulindac 300-400mg Qd versus Sulindac 300-400mg Bid	●	◐	○	●	○	●	●	○	**Moderate**	○	○	●	●	**Moderate**
Chubick (1987)	Improvement in night pain	4	Sulindac 300-400mg Qd versus Sulindac 300-400mg Bid	●	◐	○	●	○	●	●	○	**Moderate**	○	○	●	●	**Moderate**

●: Domain free of flaws

○: Domain flaws present

◐: Moderate power

Study	*Outcome*	*Week*	*Comparison*	Prospective	Power	Group Assignment	Blinding	Group Comparability	Treatment Integrity	Measurement	Investigator Bias	*Quality*	Participants	Intervention and Expertise	Compliance and Adherence	Analysis	*Applicability Study*
Chubick (1987)	Improvement in tenderness	4	Sulindac 300-400mg Qd versus Sulindac 300-400mg Bid	●	◐	○	●	○	●	●	○	**Moderate**	○	○	●	●	**Moderate**
Dick (1992)	Time to walk 50ft	6	Etodolac 300mgx2 versus Piroxicam 20mg	●	◐	○	●	○	●	●	○	**Moderate**	○	○	●	●	**Moderate**
Dick (1992)	Morning stiffness	6	Etodolac 300mgx2 versus Piroxicam 20mg	●	◐	○	●	○	●	●	○	**Moderate**	○	○	●	●	**Moderate**

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○: Domain flaws present

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Study	*Outcome*	*Week*	*Comparison*	Prospective	Power	Group Assignment	Blinding	Group Comparability	Treatment Integrity	Measurement	Investigator Bias	*Quality*	Participants	Intervention and Expertise	Compliance and Adherence	Analysis	*Applicability Study*
Evcik (2003)	Health Assessment Questionnaire	26	Tenoxicam versus Placebo	●	◐	○	○	○	●	●	○	**Low**	●	○	●	○	**Moderate**
Evcik (2003)	Lequesne index	26	Tenoxicam versus Placebo	●	◐	○	○	○	●	●	○	**Low**	●	○	●	○	**Moderate**
Evcik (2003)	VAS Ascending stairs	26	Tenoxicam versus Placebo	●	●	○	○	○	●	●	○	**Low**	●	○	●	○	**Moderate**
Evcik (2003)	VAS Descending stairs	26	Tenoxicam versus Placebo	●	●	○	○	○	●	●	○	**Low**	●	○	●	○	**Moderate**
Evcik (2003)	VAS Walking	26	Tenoxicam versus Placebo	●	●	○	○	○	●	●	○	**Low**	●	○	●	○	**Moderate**

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Study	*Outcome*	*Week*	*Comparison*	Prospective	Power	Group Assignment	Blinding	Group Comparability	Treatment Integrity	Measurement	Investigator Bias	*Quality*	Participants	Intervention and Expertise	Compliance and Adherence	Analysis	*Applicability Study*
Evcik (2003)	VAS at rest	26	Tenoxicam versus Placebo	●	●	○	○	○	●	●	○	*Low*	◐	○	●	○	*Moderate*
Herrera (2007)	WOMAC Function	4	Diclofenac Cr 100mg versus Diclofenac Ir 50mg	●	◐	○	●	○	●	●	○	**Moderate**	○	○	●	●	**Moderate**
Herrera (2007)	VAS	4	Diclofenac Cr 100mg versus Diclofenac Ir 50mg	●	◐	○	●	○	●	●	○	**Moderate**	○	○	●	●	**Moderate**
Herrera (2007)	WOMAC Pain	4	Diclofenac Cr 100mg versus Diclofenac Ir 50mg	●	◐	○	●	○	●	●	○	**Moderate**	○	○	●	●	**Moderate**

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Study	*Outcome*	*Week*	*Comparison*	**Prospective**	**Power**	**Group Assignment**	**Blinding**	**Group Comparability**	**Treatment Integrity**	**Measurement**	**Investigator Bias**	*Quality*	**Participants**	**Intervention and Expertise**	**Compliance and Adherence**	**Analysis**	*Applicability Study*
Herrera (2007)	WOMAC Stiffness	4	Diclofenac Cr 100mg versus Diclofenac Ir 50mg	●	◐	○	●	○	●	●	○	**Moderate**	○	○	●	●	**Moderate**
Herrera (2007)	WOMAC Total	4	Diclofenac Cr 100mg versus Diclofenac Ir 50mg	●	◐	○	●	○	●	●	○	**Moderate**	○	○	●	●	**Moderate**
Karbowski (1991)	Time to walk 50ft	6	Etodolac 300mg versus Indomethacin 50mg	●	◐	○	●	○	●	●	○	**Moderate**	○	○	●	●	**Moderate**
Karbowski (1991)	Morning stiffness	6	Etodolac 300mg versus Indomethacin 50mg	●	◐	○	●	○	●	●	○	**Moderate**	○	○	●	●	**Moderate**

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Study	*Outcome*	*Week*	*Comparison*	Prospective	Power	Group Assignment	Blinding	Group Comparability	Treatment Integrity	Measurement	Investigator Bias	*Quality*	Participants	Intervention and Expertise	Compliance and Adherence	Analysis	*Applicability Study*
Kivits (2002)	VAS Pain	12	Naproxen versus Placebo	●	●	○	●	●	●	●	○	**Moderate**	○	○	●	●	**Moderate**
Kivits (2002)	VAS Pain	6	Naproxen versus Placebo	●	●	○	●	●	●	●	○	**Moderate**	○	○	●	●	**Moderate**
Kivits (2002)	WOMAC Stiffness	6	Naproxen versus Placebo	●	●	○	●	●	●	●	○	**Moderate**	○	○	●	●	**Moderate**
Kivits (2002)	WOMAC Stiffness	12	Naproxen versus Placebo	●	●	○	●	●	●	●	○	**Moderate**	○	○	●	●	**Moderate**
Kivits (2002)	WOMAC Total	6	Naproxen versus Placebo	●	●	○	●	●	●	●	○	**Moderate**	○	○	●	●	**Moderate**
Kivits (2002)	WOMAC Total	12	Naproxen versus Placebo	●	●	○	●	●	●	●	○	**Moderate**	○	○	●	●	**Moderate**

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Study	*Outcome*	*Week*	*Comparison*	**Prospective**	**Power**	**Group Assignment**	**Blinding**	**Group Comparability**	**Treatment Integrity**	**Measurement**	**Investigator Bias**	*Quality*	**Participants**	**Intervention and Expertise**	**Compliance and Adherence**	**Analysis**	*Applicability Study*
Kogstad (1981)	Sequence A ability to walk (VAS)	4	Piroxicam 20mg versus Naproxen 250mg	●	●	○	●	○	●	●	○	**Moderate**	○	○	●	●	**Moderate**
Kogstad (1981)	Sequence B ability to walk (VAS)	4	Piroxicam 20mg versus Naproxen 250mg	●	●	○	●	○	●	●	○	**Moderate**	○	○	●	●	**Moderate**
Kogstad (1981)	Sequence A pain at night (VAS)	4	Piroxicam 20mg versus Naproxen 250mg	●	●	○	●	○	●	●	○	**Moderate**	○	○	●	●	**Moderate**
Kogstad (1981)	Sequence B pain at night (VAS)	4	Piroxicam 20mg versus Naproxen 250mg	●	●	○	●	○	●	●	○	**Moderate**	○	○	●	●	**Moderate**

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Study	*Outcome*	*Week*	*Comparison*	**Prospective**	**Power**	**Group Assignment**	**Blinding**	**Group Comparability**	**Treatment Integrity**	**Measurement**	**Investigator Bias**	*Quality*	**Participants**	**Intervention and Expertise**	**Compliance and Adherence**	**Analysis**	*Applicability Study*
Kogstad (1981)	Sequence A pain on movement (VAS)	4	Piroxicam 20mg versus Naproxen 250mg	●	●	○	●	○	●	●	○	**Moderate**	○	○	●	●	**Moderate**
Kogstad (1981)	Sequence B pain on movement (VAS)	4	Piroxicam 20mg versus Naproxen 250mg	●	●	○	●	○	●	●	○	**Moderate**	○	○	●	●	**Moderate**
La Montagna (1998)	Present Pain index	12	Piroxicam-Beta-Cyclodextrin 20mg versus Diclofenac 100mg	●	◐	○	●	○	●	●	○	**Moderate**	○	○	●	●	**Moderate**

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Study	*Outcome*	*Week*	*Comparison*	Prospective	Power	Group Assignment	Blinding	Group Comparability	Treatment Integrity	Measurement	Investigator Bias	*Quality*	Participants	Intervention and Expertise	Compliance and Adherence	Analysis	*Applicability Study*
La Montagna (1998)	Present Pain index	24	Piroxicam-Beta-Cyclodextrin 20mg versus Diclofenac 100mg	●	◐	○	●	○	●	●	○	**Moderate**	○	○	●	●	**Moderate**
La Montagna (1998)	Adverse events	12	Piroxicam-Beta-Cyclodextrin 20mg versus Diclofenac 100mg	●	◐	○	●	○	●	●	○	**Moderate**	○	○	●	●	**Moderate**
La Montagna (1998)	VAS	24	Piroxicam-Beta-Cyclodextrin 20mg versus Diclofenac 100mg	●	◐	○	●	○	●	●	○	**Moderate**	○	○	●	●	**Moderate**

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Study	*Outcome*	*Week*	*Comparison*	**Prospective**	**Power**	**Group Assignment**	**Blinding**	**Group Comparability**	**Treatment Integrity**	**Measurement**	**Investigator Bias**	*Quality*	**Participants**	**Intervention and Expertise**	**Compliance and Adherence**	**Analysis**	*Applicability Study*
Liang (2003)	Change in Lequesne index	4	Etodolac Sustained-Release400mg versus Diclofenac 50mg	●	◐	○	●	○	●	●	○	**Moderate**	○	○	●	●	**Moderate**
Lücker (1994)	Lequesne Functional index	4	Nimesulide 100mg versus Etodolac 300mg	●	◐	○	●	●	●	●	○	**Moderate**	○	○	●	●	**Moderate**
Lücker (1994)	Lequesne Functional index	8	Nimesulide 100mg versus Etodolac 300mg	●	◐	○	●	●	●	●	○	**Moderate**	○	○	●	●	**Moderate**

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Study	*Outcome*	*Week*	*Comparison*	Prospective	Power	Group Assignment	Blinding	Group Comparability	Treatment Integrity	Measurement	Investigator Bias	*Quality*	Participants	Intervention and Expertise	Compliance and Adherence	Analysis	*Applicability Study*
Lücker (1994)	Lequesne Functional index	12	Nimesulide 100mg versus Etodolac 300mg	●	◐	○	●	●	●	●	○	**Moderate**	○	○	●	●	**Moderate**
Lücker (1994)	Lequesne Functional index	4	Nimesulide 100mg versus Etodolac 300mg	●	◐	○	●	●	●	●	○	**Moderate**	○	○	●	●	**Moderate**
Lücker (1994)	Lequesne Functional index	8	Nimesulide 100mg versus Etodolac 300mg	●	◐	○	●	●	●	●	○	**Moderate**	○	○	●	●	**Moderate**

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Study	*Outcome*	*Week*	*Comparison*	Prospective	Power	Group Assignment	Blinding	Group Comparability	Treatment Integrity	Measurement	Investigator Bias	*Quality*	Participants	Intervention and Expertise	Compliance and Adherence	Analysis	*Applicability Study*
Lücker (1994)	Lequesne Functional index	12	Nimesulide 100mg versus Etodolac 300mg	●	◐	○	●	●	●	●	○	**Moderate**	○	○	●	●	**Moderate**
Lücker (1994)	VAS Pain 10cm	4	Nimesulide 100mg versus Etodolac 300mg	●	●	○	●	●	●	●	○	**Moderate**	○	○	●	●	**Moderate**
Lücker (1994)	VAS Pain 10cm	8	Nimesulide 100mg versus Etodolac 300mg	●	●	○	●	●	●	●	○	**Moderate**	○	○	●	●	**Moderate**

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Study	*Outcome*	*Week*	*Comparison*	Prospective	Power	Group Assignment	Blinding	Group Comparability	Treatment Integrity	Measurement	Investigator Bias	*Quality*	Participants	Intervention and Expertise	Compliance and Adherence	Analysis	*Applicability Study*
Lücker (1994)	VAS Pain 10cm	12	Nimesulide 100mg versus Etodolac 300mg Continuous	●	●	○	●	●	●	●	○	**Moderate**	○	○	●	●	**Moderate**
Luyten (2007)	WOMAC Pain	24	Celecoxib versus Intermittent Celecoxib	●	◐	○	●	●	○	●	○	**Moderate**	○	○	●	●	**Moderate**
Luyten (2007)	WOMAC Stiffness	24	Continuous Celecoxib versus Intermittent Celecoxib	●	◐	○	●	●	○	●	○	**Moderate**	○	○	●	●	**Moderate**

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Luyten (2007)	WOMAC Total	24	Continuous Celecoxib versus Intermittent Celecoxib	●	◐	○	●	●	○	●	○	**Moderate**	○	○	●	●	**Moderate**
Mckenna (2001)	WOMAC Function improvement	6	Diclofenac versus Placebo	●	●	○	●	●	●	●	○	**Moderate**	○	○	●	●	**Moderate**
Mckenna (2001)	VAS Pain	6	Diclofenac versus Placebo	●	●	○	●	●	●	●	○	**Moderate**	○	○	●	●	**Moderate**
Mckenna (2001)	WOMAC Pain	6	Diclofenac versus Placebo	●	●	○	●	●	●	●	○	**Moderate**	○	○	●	●	**Moderate**
Mckenna (2001)	WOMAC Stiffness	6	Diclofenac versus Placebo	●	●	○	●	●	●	●	○	**Moderate**	○	○	●	●	**Moderate**

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Study	*Outcome*	*Week*	*Comparison*	**Prospective**	**Power**	**Group Assignment**	**Blinding**	**Group Comparability**	**Treatment Integrity**	**Measurement**	**Investigator Bias**	*Quality*	**Participants**	**Intervention and Expertise**	**Compliance and Adherence**	**Analysis**	*Applicability Study*
Mckenna (2001)	WOMAC Total	6	Diclofenac versus Placebo	●	●	○	●	●	●	●	○	**Moderate**	○	○	●	●	**Moderate**
Queiros (1990)	Mean pain at night (1 to 4)	4	Piroxicam 20mg versus Oxaprozin 1200mg	●	◐	○	●	○	●	●	○	**Moderate**	○	○	●	○	**Moderate**
Queiros (1990)	Mean pain on walking in the evening (1 to 21)	4	Piroxicam 20mg versus Oxaprozin 1200mg	●	◐	○	●	○	●	●	○	**Moderate**	○	○	●	○	**Moderate**
Queiros (1990)	Mean pain on walking in the morning (1 to 21)	4	Piroxicam 20mg versus Oxaprozin 1200mg	●	◐	○	●	○	●	●	○	**Moderate**	○	○	●	○	**Moderate**
Schnitzer	WOMAC Total	12	Naproxen versus Placebo	●	●	○	●	○	●	●	○	**Moderate**	○	○	●	○	**Moderate**

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Study	*Outcome*	*Week*	*Comparison*	Prospective	Power	Group Assignment	Blinding	Group Comparability	Treatment Integrity	Measurement	Investigator Bias	*Quality*	Participants	Intervention and Expertise	Compliance and Adherence	Analysis	*Applicability Study*
Schnitzer (2010)	Rescue Acetaminophen	13	Naproxcinod versus Placebo	●	◐	○	●	●	●	●	○	**Moderate**	○	○	●	●	**Moderate**
Schnitzer (2010)	Rescue Acetaminophen	13	Naproxcinod versus Placebo	●	◐	○	●	●	●	●	○	**Moderate**	○	○	●	●	**Moderate**
Schnitzer (2010)	SF-36 MCS improvement	13	Naproxcinod versus Placebo	●	◐	○	●	●	●	●	○	**Moderate**	○	○	●	●	**Moderate**
Schnitzer (2010)	SF-36 MCS improvement	13	Naproxcinod versus Placebo	●	◐	○	●	●	●	●	○	**Moderate**	○	○	●	●	**Moderate**
Schnitzer (2010)	WOMAC Function	13	Naproxcinod versus Placebo	●	○	○	●	●	●	●	○	**Moderate**	○	○	●	●	**Moderate**
Schnitzer (2010)	VAS Pain at rest improvement	13	Naproxcinod 375mg versus Placebo	●	●	○	●	●	●	●	○	**Moderate**	○	○	●	●	**Moderate**

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Study	*Outcome*	*Week*	*Comparison*	**Prospective**	**Power**	**Group Assignment**	**Blinding**	**Group Comparability**	**Treatment Integrity**	**Measurement**	**Investigator Bias**	*Quality*	**Participants**	**Intervention and Expertise**	**Compliance and Adherence**	**Analysis**	*Applicability Study*
Schnitzer (2010)	VAS Pain at rest improvement	13	Naprocinod 750mg versus Placebo	●	●	○	●	●	●	●	○	**Moderate**	○	○	●	●	**Moderate**
Schnitzer (2010)	VAS Pain during walking improvement	13	Naproxcinod 375mg versus Placebo	●	●	○	●	●	●	●	○	**Moderate**	○	○	●	●	**Moderate**
Schnitzer (2010)	VAS Pain during walking	13	Naprocinod 750mg versus Placebo	●	●	○	●	●	●	●	○	**Moderate**	○	○	●	●	**Moderate**
Schnitzer (2010)	WOMAC Pain	13	Naproxcinod 375mg versus Placebo	●	●	○	●	●	●	●	○	**Moderate**	○	○	●	●	**Moderate**
Schnitzer (2010)	WOMAC Pain	13	Naprocinod 750mg versus Placebo	●	●	○	●	●	●	●	○	**Moderate**	○	○	●	●	**Moderate**

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Study	*Outcome*	*Week*	*Comparison*	**Prospective**	**Power**	**Group Assignment**	**Blinding**	**Group Comparability**	**Treatment Integrity**	**Measurement**	**Investigator Bias**	*Quality*	**Participants**	**Intervention and Expertise**	**Compliance and Adherence**	**Analysis**	*Applicability Study*
Schnitzer (2010)	Rescue Acetaminophen	12	Naproxen versus Placebo	●	◐	○	●	●	●	●	○	**Moderate**	○	○	●	●	**Moderate**
Schnitzer (2010)	SF-36 MCS improvement	12	Naproxen versus Placebo	●	◐	○	●	●	●	●	○	**Moderate**	○	○	●	●	**Moderate**
Schnitzer (2010)	WOMAC Function improvement	12	Naproxen versus Placebo	●	●	○	●	●	●	●	○	**Moderate**	○	○	●	●	**Moderate**
Schnitzer (2010)	VAS Pain	12	Naproxen versus Placebo	●	●	○	●	●	●	●	○	**Moderate**	○	○	●	●	**Moderate**
Schnitzer (2010)	VAS Pain during walking improvement	12	Naproxen versus Placebo	●	●	○	●	●	●	●	○	**Moderate**	○	○	●	●	**Moderate**

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Schnitzer (2010)	WOMAC Pain	12	Naproxen versus Placebo	●	●	○	●	●	●	●	○	**Moderate**	○	○	●	●	**Moderate**
Tyson (1980)	Linear analogue pain scale	8	Benoxaprofen versus Ibuprofen	●	◐	○	●	○	●	●	○	**Moderate**	●	○	●	●	**Moderate**
Tyson (1980)	Linear analogue pain scale	12	Benoxaprofen versus Ibuprofen	●	◐	○	●	○	●	●	○	**Moderate**	●	○	●	●	**Moderate**
Tyson (1980)	Linear analogue pain scale	16	Benoxaprofen versus Ibuprofen	●	◐	○	●	○	●	●	○	**Moderate**	●	○	●	●	**Moderate**
Bookman (2004)	Mean WOMAC Stiffness (Likert)	4	Topical Diclofenac versus Placebo	●	○	●	●	●	●	●	○	**High**	○	○	●	●	**Moderate**

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Bookman (2004)	Mean WOMAC Pain (Likert)	4	Topical Diclofenac versus Placebo gel	●	○	●	●	●	●	●	○	**High**	○	○	●	●	**Moderate**
Bookman (2004)	Mean WOMAC Function (Likert)	4	Topical Diclofenac versus vehicle control	●	○	●	●	●	●	●	○	**High**	○	○	●	●	**Moderate**
Bookman (2004)	Acetaminophen consumption	4	Topical Diclofenac versus vehicle control	●	◐	●	●	●	●	●	○	**High**	○	○	●	●	**Moderate**
Bookman (2004)	Acetaminophen consumption	4	Topical Diclofenac versus Placebo	●	◐	●	●	●	●	●	○	**High**	○	○	●	●	**Moderate**

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Study	*Outcome*	*Week*	*Comparison*	Prospective	Power	Group Assignment	Blinding	Group Comparability	Treatment Integrity	Measurement	Investigator Bias	*Quality*	Participants	Intervention and Expertise	Compliance and Adherence	Analysis	*Applicability Study*
Barthel (2009)	Weeks with no rescue drug	12	Diclofenac sodium 1% gel in DMSO versus DMSO vehicle	●	●	○	●	○	●	●	○	**Moderate**	○	○	○	●	**Moderate**
Bookman (2004)	Acetaminophen consumption	4	Topical Diclofenac versus vehicle control	●	◐	○	●	○	●	●	○	**Moderate**	○	○	○	●	**Moderate**
Bookman (2004)	Acetaminophen consumption	4	Topical Diclofenac versus Placebo	●	◐	○	●	○	●	●	○	**Moderate**	○	○	○	●	**Moderate**

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Study	*Outcome*	*Week*	*Comparison*	**Prospective**	**Power**	**Group Assignment**	**Blinding**	**Group Comparability**	**Treatment Integrity**	**Measurement**	**Investigator Bias**	*Quality*	**Participants**	**Intervention and Expertise**	**Compliance and Adherence**	**Analysis**	*Applicability Study*
Barthel (2009)	Weeks with no rescue drug	12	Diclofenac sodium 1% gel in DMSO versus DMSO vehicle	●	●	○	●	○	●	●	○	**Moderate**	○	○	○	●	**Moderate**
Roth (2004)	WOMAC Function	12	Topical Diclofenac versus vehicle control	●	●	●	●	●	●	●	○	**High**	○	○	●	●	**Moderate**

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Study	*Outcome*	*Week*	*Comparison*	**Prospective**	**Power**	**Group Assignment**	**Blinding**	**Group Comparability**	**Treatment Integrity**	**Measurement**	**Investigator Bias**	*Quality*	**Participants**	**Intervention and Expertise**	**Compliance and Adherence**	**Analysis**	*Applicability Study*
Baer (2005)	WOMAC Function	6	Pennsaid (topical Diclofenac solution) versus vehicle control solution	●	●	●	●	●	●	●	○	**High**	○	○	●	●	**Moderate**
Bookman (2004)	WOMAC Function	4	Topical Diclofenac versus Placebo	●	●	●	●	●	●	●	○	**High**	○	○	●	●	**Moderate**
Bookman (2004)	WOMAC Function	4	Topical Diclofenac versus vehicle control	●	●	●	●	●	●	●	○	**High**	○	○	●	●	**Moderate**

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Study	*Outcome*	*Week*	*Comparison*	**Prospective**	**Power**	**Group Assignment**	**Blinding**	**Group Comparability**	**Treatment Integrity**	**Measurement**	**Investigator Bias**	*Quality*	**Participants**	**Intervention and Expertise**	**Compliance and Adherence**	**Analysis**	*Applicability Study*
Rother (2007)	WOMAC Function	6	topical Ketoprofen versus Celecoxib	●	●	○	●	○	●	●	○	**Moderate**	○	○	●	●	**Moderate**
Rother (2007)	WOMAC Function	6	topical Ketoprofen versus Placebo	●	●	○	●	○	●	●	○	**Moderate**	○	○	●	●	**Moderate**
Rother (2007)	WOMAC Function	6	Celecoxib versus Placebo	●	●	○	●	○	●	●	○	**Moderate**	○	○	●	●	**Moderate**
Bookman (2004)	WOMAC Function	4	Topical Diclofenac versus Placebo	●	●	●	●	●	●	●	○	**High**	○	○	●	●	**Moderate**

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Study	*Outcome*	*Week*	*Comparison*	Prospective	Power	Group Assignment	Blinding	Group Comparability	Treatment Integrity	Measurement	Investigator Bias	*Quality*	Participants	Intervention and Expertise	Compliance and Adherence	Analysis	*Applicability Study*
Bookman (2004)	WOMAC Function	4	Topical Diclofenac versus vehicle control	●	●	●	●	●	●	●	○	**High**	○	○	●	●	**Moderate**
Roth (2004)	WOMAC Pain	12	Topical Diclofenac versus vehicle control	●	●	●	●	●	●	●	○	**High**	○	○	●	●	**Moderate**
Roth (2004)	WOMAC Pain on walking	12	Topical Diclofenac versus vehicle control	●	●	●	●	●	●	●	○	**High**	○	○	●	●	**Moderate**

●: Domain free of flaws

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◐: Moderate power

Study	*Outcome*	*Week*	*Comparison*	**Prospective**	**Power**	**Group Assignment**	**Blinding**	**Group Comparability**	**Treatment Integrity**	**Measurement**	**Investigator Bias**	*Quality*	**Participants**	**Intervention and Expertise**	**Compliance and Adherence**	**Analysis**	*Applicability Study*
Baer (2005)	WOMAC Pain	6	Pennsaid (topical Diclofenac solution) versus vehicle control solution	●	●	●	●	●	●	●	○	**High**	○	○	●	●	**Moderate**
Baer (2005)	WOMAC Pain on walking	6	Pennsaid (topical Diclofenac solution) versus vehicle control solution	●	●	●	●	●	●	●	○	**High**	○	○	●	●	**Moderate**

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Study	*Outcome*	*Week*	*Comparison*	**Prospective**	**Power**	**Group Assignment**	**Blinding**	**Group Comparability**	**Treatment Integrity**	**Measurement**	**Investigator Bias**	*Quality*	**Participants**	**Intervention and Expertise**	**Compliance and Adherence**	**Analysis**	*Applicability Study*
Ottillinger (2001)	VAS Pain	4	Eltenac gel 0.3% versus Eltenac gel 0.1%	●	●	○	●	●	●	●	○	**Moderate**	○	○	●	●	**Moderate**
Ottillinger (2001)	VAS Pain	5	Eltenac gel 0.3% versus Eltenac gel 0.1%	●	●	○	●	●	●	●	○	**Moderate**	○	○	●	●	**Moderate**
Ottillinger (2001)	VAS Pain	6	Eltenac gel 0.3% versus Eltenac gel 0.1%	●	●	○	●	●	●	●	○	**Moderate**	○	○	●	●	**Moderate**
Ottillinger (2001)	VAS Pain	4	Eltenac gel 1% versus Eltenac gel 0.3%	●	●	○	●	●	●	●	○	**Moderate**	○	○	●	●	**Moderate**

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Study	*Outcome*	*Week*	*Comparison*	Prospective	Power	Group Assignment	Blinding	Group Comparability	Treatment Integrity	Measurement	Investigator Bias	*Quality*	Participants	Intervention and Expertise	Compliance and Adherence	Analysis	*Applicability Study*
Ottillinger (2001)	VAS Pain	4	Eltenac gel 1% versus Eltenac gel 0.1%	●	●	○	●	●	●	●	○	**Moderate**	○	○	●	●	**Moderate**
Ottillinger (2001)	VAS Pain	5	Eltenac gel 1% versus Eltenac gel 0.3%	●	●	○	●	●	●	●	○	**Moderate**	○	○	●	●	**Moderate**
Ottillinger (2001)	VAS Pain	5	Eltenac gel 1% versus Eltenac gel 0.1%	●	●	○	●	●	●	●	○	**Moderate**	○	○	●	●	**Moderate**
Ottillinger (2001)	VAS Pain	6	Eltenac gel 1% versus Eltenac gel 0.3%	●	●	○	●	●	●	●	○	**Moderate**	○	○	●	●	**Moderate**

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Study	*Outcome*	*Week*	*Comparison*	**Prospective**	**Power**	**Group Assignment**	**Blinding**	**Group Comparability**	**Treatment Integrity**	**Measurement**	**Investigator Bias**	*Quality*	**Participants**	**Intervention and Expertise**	**Compliance and Adherence**	**Analysis**	*Applicability Study*
Ottillinger (2001)	VAS Pain	6	Eltenac gel 1% versus Eltenac gel 0.1%	●	●	○	●	●	●	●	○	**Moderate**	○	○	●	●	**Moderate**
Ottillinger (2001)	VAS Pain	4	Eltenac gel 0.1% versus Placebo gel	●	●	○	●	●	●	●	○	**Moderate**	○	○	●	●	**Moderate**
Ottillinger (2001)	VAS Pain	5	Eltenac gel 0.1% versus Placebo gel	●	●	○	●	●	●	●	○	**Moderate**	○	○	●	●	**Moderate**
Ottillinger (2001)	VAS Pain	6	Eltenac gel 0.1% versus Placebo gel	●	●	○	●	●	●	●	○	**Moderate**	○	○	●	●	**Moderate**
Ottillinger (2001)	VAS Pain	4	Eltenac gel 0.3% versus Placebo gel	●	●	○	●	●	●	●	○	**Moderate**	○	○	●	●	**Moderate**

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Study	*Outcome*	*Week*	*Comparison*	Prospective	Power	Group Assignment	Blinding	Group Comparability	Treatment Integrity	Measurement	Investigator Bias	*Quality*	Participants	Intervention and Expertise	Compliance and Adherence	Analysis	*Applicability Study*
Ottillinger (2001)	VAS Pain	5	Eltenac gel 0.3% versus Placebo gel	●	●	○	●	●	●	●	○	**Moderate**	○	○	●	●	**Moderate**
Ottillinger (2001)	VAS Pain	6	Eltenac gel 0.3% versus Placebo gel	●	●	○	●	●	●	●	○	**Moderate**	○	○	●	●	**Moderate**
Ottillinger (2001)	VAS Pain	4	Eltenac gel 1% versus Placebo gel	●	●	○	●	●	●	●	○	**Moderate**	○	○	●	●	**Moderate**
Ottillinger (2001)	VAS Pain	5	Eltenac gel 1% versus Placebo gel	●	●	○	●	●	●	●	○	**Moderate**	○	○	●	●	**Moderate**
Ottillinger (2001)	VAS Pain	6	Eltenac gel 1% versus Placebo gel	●	●	○	●	●	●	●	○	**Moderate**	○	○	●	●	**Moderate**

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Study	*Outcome*	*Week*	*Comparison*	Prospective	Power	Group Assignment	Blinding	Group Comparability	Treatment Integrity	Measurement	Investigator Bias	*Quality*	Participants	Intervention and Expertise	Compliance and Adherence	Analysis	*Applicability Study*
Bookman (2004)	WOMAC Pain	4	Topical Diclofenac versus vehicle control	●	●	●	●	●	●	●	○	**High**	○	○	●	●	**Moderate**
Bookman (2004)	WOMAC Pain	4	Topical Diclofenac versus Placebo	●	●	●	●	●	●	●	○	**High**	○	○	●	●	**Moderate**
Bookman (2004)	WOMAC Pain on walking	4	Topical Diclofenac versus vehicle control	●	●	●	●	●	●	●	○	**High**	○	○	●	●	**Moderate**
Bookman (2004)	WOMAC Pain on walking	4	Topical Diclofenac versus Placebo	●	●	●	●	●	●	●	○	**High**	○	○	●	●	**Moderate**

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Study	*Outcome*	*Week*	*Comparison*	Prospective	Power	Group Assignment	Blinding	Group Comparability	Treatment Integrity	Measurement	Investigator Bias	*Quality*	Participants	Intervention and Expertise	Compliance and Adherence	Analysis	*Applicability Study*
Rother (2007)	WOMAC Pain	6	Topical Ketoprofen versus Celecoxib	●	●	○	●	○	●	●	○	**Moderate**	○	○	●	●	**Moderate**
Rother (2007)	WOMAC Pain	6	Topical Ketoprofen versus Placebo	●	●	○	●	○	●	●	○	**Moderate**	○	○	●	●	**Moderate**
Rother (2007)	WOMAC Pain	6	Celecoxib versus Placebo	●	●	○	●	○	●	●	○	**Moderate**	○	○	●	●	**Moderate**
Bookman (2004)	WOMAC Pain	4	Topical Diclofenac versus vehicle control	●	●	●	●	●	●	●	○	**High**	○	○	●	●	**Moderate**

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Study	*Outcome*	*Week*	*Comparison*	**Prospective**	**Power**	**Group Assignment**	**Blinding**	**Group Comparability**	**Treatment Integrity**	**Measurement**	**Investigator Bias**	*Quality*	**Participants**	**Intervention and Expertise**	**Compliance and Adherence**	**Analysis**	*Applicability Study*
Bookman (2004)	WOMAC Pain	4	Topical Diclofenac versus Placebo	●	●	●	●	●	●	●	○	**High**	○	○	●	●	**Moderate**
Bookman (2004)	WOMAC Pain on walking	4	Topical Diclofenac versus vehicle control	●	●	●	●	●	●	●	○	**High**	○	○	●	●	**Moderate**
Bookman (2004)	WOMAC Pain on walking	4	Topical Diclofenac versus Placebo	●	●	●	●	●	●	●	○	**High**	○	○	●	●	**Moderate**
Roth (2004)	WOMAC Stiffness	12	Topical Diclofenac versus vehicle control	●	●	●	●	●	●	●	○	**High**	○	○	●	●	**Moderate**

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Study	*Outcome*	*Week*	*Comparison*	**Prospective**	**Power**	**Group Assignment**	**Blinding**	**Group Comparability**	**Treatment Integrity**	**Measurement**	**Investigator Bias**	*Quality*	**Participants**	**Intervention and Expertise**	**Compliance and Adherence**	**Analysis**	*Applicability Study*
Baer (2005)	WOMAC Stiffness	6	Pennsaid (topical Diclofenac solution) versus vehicle control solution	●	●	●	●	●	●	●	○	**High**	○	○	●	●	**Moderate**
Bookman (2004)	WOMAC Stiffness	4	Topical Diclofenac versus Placebo	●	●	●	●	●	●	●	○	**High**	○	○	●	●	**Moderate**
Bookman (2004)	WOMAC Stiffness	4	Topical Diclofenac versus vehicle control	●	○ *	●	●	●	●	●	○	**High**	○	○	●	●	**Moderate**

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Study	*Outcome*	*Week*	*Comparison*	Prospective	Power	Group Assignment	Blinding	Group Comparability	Treatment Integrity	Measurement	Investigator Bias	*Quality*	Participants	Intervention and Expertise	Compliance and Adherence	Analysis	*Applicability Study*
Torri (1994)	WOMAC averaged VAS Pain	12	Aceclofenac versus Piroxicam	●	●	○	●	●	●	●	○	**Moderate**	○	○	●	●	**Moderate**
Ayral (2003)	Physician Global Assessment	52	Tenidap 120mg versus Piroxicam 20mg	●	◐	○	●	○	●	●	○	**Moderate**	○	○	○	●	●
Ayral (2003)	Physician Global Assessment	52	Tenidap 40mg versus Piroxicam 20mg	●	◐	○	●	○	●	●	○	**Moderate**	○	○	●	●	**Moderate**
Ayral (2003)	Patient Global Assessment	52	Tenidap 120mg versus Piroxicam 20mg	●	◐	○	●	○	●	●	○	**Moderate**	○	○	●	●	**Moderate**
Ayral (2003)	Patient Global Assessment	52	Tenidap 40mg versus Placebo	●	◐	○	●	○	●	●	○	**Moderate**	○	○	●	●	**Moderate**

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Study	*Outcome*	*Week*	*Comparison*	**Prospective**	**Power**	**Group Assignment**	**Blinding**	**Group Comparability**	**Treatment Integrity**	**Measurement**	**Investigator Bias**	*Quality*	**Participants**	**Intervention and Expertise**	**Compliance and Adherence**	**Analysis**	*Applicability Study*
Ayral (2003)	Physician Global Assessment	52	Tenidap 40mg versus Tenidap 120mg	●	◐	○	●	○	●	●	○	**Moderate**	○	○	●	●	**Moderate**
Ayral (2003)	Patient Global Assessment	52	Tenidap 40mg versus vehicle control	●	◐	○	●	○	●	●	○	**Moderate**	○	○	●	●	**Moderate**
Kivits (2004)	Vomiting	6	Rofecoxib 12.5mg versus Nabumetone 1000mg	●	●	○	●	●	●	●	○	**Moderate**	○	○	●	●	**Moderate**
Kivits (2004)	At least one adverse event	6	nabumetone 1000 versus Placebo	●	◐	●	●	●	●	●	○	**High**	●	○	●	●	**Moderate**

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Study	*Outcome*	*Week*	*Comparison*	Prospective	Power	Group Assignment	Blinding	Group Comparability	Treatment Integrity	Measurement	Investigator Bias	*Quality*	Participants	Intervention and Expertise	Compliance and Adherence	Analysis	*Applicability Study*
Kivits (2002)	Physician Global Assessment	6	Naproxen versus Placebo	●	●	○	●	●	●	●	○	**Moderate**	○	○	●	●	**Moderate**
Kivits (2002)	Physician Global Assessment	12	Naproxen versus Placebo	●	●	○	●	●	●	●	○	**Moderate**	○	○	●	●	**Moderate**
Kivitz (2004)	Patient Global Assessment of Response to Treatment	6	Nabumetone versus Placebo	●	●	●	●	●	●	●	○	**High**	●	○	●	●	**Moderate**
Lee (1985)	Adverse events	6	High dose diflunisal (NSAID) versus Placebo	●	◐	○	●	●	●	●	○	**Moderate**	○	○	●	○	**Moderate**

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Study	*Outcome*	*Week*	*Comparison*	**Prospective**	**Power**	**Group Assignment**	**Blinding**	**Group Comparability**	**Treatment Integrity**	**Measurement**	**Investigator Bias**	*Quality*	**Participants**	**Intervention and Expertise**	**Compliance and Adherence**	**Analysis**	*Applicability Study*
Lee (1985)	Adverse events	6	Low dose diflunisal (NSAID) versus Placebo	●	◐	○	●	●	●	●	○	**Moderate**	○	○	●	○	**Moderate**
Lohmander (2005)	Patient Assessment of Treatment Response	6	Naproxcinod versus Naproxen	●	●	○	●	○	○	●	○	**Low**	○	○	●	○	**Moderate**
Lohmander (2005)	Patient Global Assessment of Response to Treatment	6	Naproxcinod versus Placebo	●	●	○	●	○	○	●	○	**Low**	○	○	●	○	**Moderate**

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Study	*Outcome*	*Week*	*Comparison*	Prospective	Power	Group Assignment	Blinding	Group Comparability	Treatment Integrity	Measurement	Investigator Bias	*Quality*	Participants	Intervention and Expertise	Compliance and Adherence	Analysis	*Applicability Study*
Lohmander (2005)	Patient Global Assessment of Response to Treatment	6	Naproxen versus Placebo	●	●	○	●	○	○	●	○	**Low**	○	○	●	○	**Moderate**
Lohmander (2005)	Adverse events	6	Naproxcinod 750mg versus Piroxicam	●	●	○	●	○	○	●	○	**Moderate**	○	○	●	○	**Moderate**
Lohmander (2005)	Adverse events	6	Naproxcinod 750mg versus Placebo	●	◐	○	●	○	○	●	○	**Moderate**	○	○	●	○	**Moderate**
Lohmander (2005)	Adverse events	6	Naproxen 500mg versus Placebo	●	◐	○	●	○	○	●	○	**Moderate**	○	○	●	○	**Moderate**
Mckenna (2001)	Patient Global Assessment	6	Diclofenac versus Placebo	●	●	○	●	●	●	●	○	**Moderate**	○	○	●	●	**Moderate**

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Study	*Outcome*	*Week*	*Comparison*	Prospective	Power	Group Assignment	Blinding	Group Comparability	Treatment Integrity	Measurement	Investigator Bias	*Quality*	Participants	Intervention and Expertise	Compliance and Adherence	Analysis	*Applicability Study*
McKenna (2001)	Alt increased	6	Celecoxib 100mg versus Diclofenac 50mg	●	●	○	●	●	●	●	○	**Moderate**	○	○	●	●	**Moderate**
McKenna (2001)	Anaemia	6	Celecoxib 100mg versus Diclofenac 50mg	●	●	○	●	●	●	●	○	**Moderate**	○	○	●	●	**Moderate**
McKenna (2001)	Back pain	6	Celecoxib 100mg versus Diclofenac 50mg	●	●	○	●	●	●	●	○	**Moderate**	○	○	●	●	**Moderate**
McKenna (2001)	Constipation	6	Celecoxib 100mg versus Diclofenac 50mg	●	●	○	●	●	●	●	○	**Moderate**	○	○	●	●	**Moderate**

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Study	*Outcome*	*Week*	*Comparison*	Prospective	Power	Group Assignment	Blinding	Group Comparability	Treatment Integrity	Measurement	Investigator Bias	*Quality*	Participants	Intervention and Expertise	Compliance and Adherence	Analysis	*Applicability Study*
McKenna (2001)	Diarrhea	6	Celecoxib 100mg versus Diclofenac 50mg	●	●	○	●	●	●	●	○	**Moderate**	○	○	●	●	**Moderate**
McKenna (2001)	Dizziness	6	Celecoxib 100mg versus Diclofenac 50mg	●	●	○	●	●	●	●	○	**Moderate**	○	○	●	●	**Moderate**
McKenna (2001)	Dyspepsia	6	Celecoxib 100mg versus Diclofenac 50mg	●	●	○	●	●	●	●	○	**Moderate**	○	○	●	●	**Moderate**
McKenna (2001)	Flatulence	6	Celecoxib 100mg versus Diclofenac 50mg	●	●	○	●	●	●	●	○	**Moderate**	○	○	●	●	**Moderate**

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Study	*Outcome*	*Week*	*Comparison*	**Prospective**	**Power**	**Group Assignment**	**Blinding**	**Group Comparability**	**Treatment Integrity**	**Measurement**	**Investigator Bias**	*Quality*	**Participants**	**Intervention and Expertise**	**Compliance and Adherence**	**Analysis**	*Applicability Study*
McKenna (2001)	Headache	6	Celecoxib 100mg versus Diclofenac 50mg	●	●	○	●	●	●	●	○	**Moderate**	○	○	●	●	**Moderate**
McKenna (2001)	Accidental injury	6	Celecoxib 100mg versus Diclofenac 50mg	●	●	○	●	●	●	●	○	**Moderate**	○	○	●	●	**Moderate**
McKenna (2001)	Myalgia	6	Celecoxib 100mg versus Diclofenac 50mg	●	●	○	●	●	●	●	○	**Moderate**	○	○	●	●	**Moderate**
McKenna (2001)	Nausea	6	Celecoxib 100mg versus Diclofenac 50mg	●	●	○	●	●	●	●	○	**Moderate**	○	○	●	●	**Moderate**

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Study	*Outcome*	*Week*	*Comparison*	**Prospective**	**Power**	**Group Assignment**	**Blinding**	**Group Comparability**	**Treatment Integrity**	**Measurement**	**Investigator Bias**	*Quality*	**Participants**	**Intervention and Expertise**	**Compliance and Adherence**	**Analysis**	*Applicability Study*
McKenna (2001)	Peripheral Oedema	6	Celecoxib 100mg versus Diclofenac 50mg	●	●	○	●	●	●	●	○	**Moderate**	○	○	●	●	**Moderate**
Mckenna (2001)	Physician Global Assessment	6	Diclofenac versus Placebo	●	●	○	●	●	●	●	○	**Moderate**	○	○	●	●	**Moderate**
Roth(2004)	Patient Global Assessment	12	Topical Diclofenac versus Placebo	●	●	●	●	●	●	●	○	**High**	○	○	●	●	**Moderate**
Schnitzer (2005)	Patient Assessment of Treatment Response	6	Naproxcinod 125mg versus Naproxcinod 375mg	●	●	○	●	○	●	●	○	**Moderate**	○	○	○	●	**Moderate**

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Study	*Outcome*	*Week*	*Comparison*	**Prospective**	**Power**	**Group Assignment**	**Blinding**	**Group Comparability**	**Treatment Integrity**	**Measurement**	**Investigator Bias**	*Quality*	**Participants**	**Intervention and Expertise**	**Compliance and Adherence**	**Analysis**	*Applicability Study*
Schnitzer (2005)	Patient Global Assessment of Disease Status	6	Naproxcinod 125mg versus Naproxcinod 750mg	●	●	○	●	○	●	●	○	**Moderate**	○	○	○	●	**Moderate**
Schnitzer (2005)	Patient Assessment of Treatment Response	6	Naproxcinod 125mg versus Naproxcinod 750mg	●	●	○	●	○	●	●	○	**Moderate**	○	○	○	●	**Moderate**
Schnitzer (2005)	Patient Global Assessment of Disease Status	6	Naproxcinod 375mg versus Naproxcinod 750mg	●	◐	○	●	○	●	●	○	**Moderate**	○	○	○	●	**Moderate**
Schnitzer (2005)	Patient Assessment of Treatment Response	6	Naproxcinod 375mg versus Naproxcinod 750mg	●	◐	○	●	○	●	●	○	**Moderate**	○	○	○	●	**Moderate**

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Study	*Outcome*	*Week*	*Comparison*	Prospective	Power	Group Assignment	Blinding	Group Comparability	Treatment Integrity	Measurement	Investigator Bias	*Quality*	Participants	Intervention and Expertise	Compliance and Adherence	Analysis	*Applicability Study*
Schnitzer (2005)	Patient Global Assessment of Disease Status	6	Naproxcinod 125mg versus Naproxen 500mg	●	●	○	●	○	●	●	○	**Moderate**	○	○	○	●	**Moderate**
Schnitzer (2005)	Patient Assessment of Treatment Response	6	Naproxcinod 125mg versus Naproxen 500mg	●	●	○	●	○	●	●	○	**Moderate**	○	○	○	●	**Moderate**
Schnitzer (2005)	Patient Global Assessment of Disease Status	6	Naproxcinod 375mg versus Naproxen 500mg	●	◐	○	●	○	●	●	○	**Moderate**	○	○	○	●	**Moderate**
Schnitzer (2005)	Patient Assessment of Treatment Response	6	Naproxcinod 375mg versus Naproxen 500mg	●	◐	○	●	○	●	●	○	**Moderate**	○	○	○	●	**Moderate**

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Study	*Outcome*	*Week*	*Comparison*	Prospective	Power	Group Assignment	Blinding	Group Comparability	Treatment Integrity	Measurement	Investigator Bias	*Quality*	Participants	Intervention and Expertise	Compliance and Adherence	Analysis	*Applicability Study*
Schnitzer (2005)	Patient Global Assessment of Disease Status	6	Naproxcinod 750mg versus Naproxen 500mg	●	◐	○	●	○	●	●	○	**Moderate**	○	○	○	●	**Moderate**
Schnitzer (2005)	Patient Assessment of Treatment Response	6	Naproxcinod 750mg versus Naproxen 500mg	●	◐	○	●	○	●	●	○	**Moderate**	○	○	○	●	**Moderate**
Schnitzer (2005)	Patient Global Assessment of Response to Treatment	6	Naproxcinod 125mg versus Placebo	●	◐	○	●	○	●	●	○	**Moderate**	○	○	○	●	**Moderate**

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◐: Moderate power

Study	*Outcome*	*Week*	*Comparison*	**Prospective**	**Power**	**Group Assignment**	**Blinding**	**Group Comparability**	**Treatment Integrity**	**Measurement**	**Investigator Bias**	*Quality*	**Participants**	**Intervention and Expertise**	**Compliance and Adherence**	**Analysis**	*Applicability Study*
Schnitzer (2005)	Patient Global Assessment of Disease Status	6	Naproxcinod 125mg versus Placebo	●	◐	○	●	○	●	●	○	**Moderate**	○	○	○	●	**Moderate**
Schnitzer (2005)	Patient Global Assessment of Disease Status	6	Naproxcinod 125mg versus Placebo	●	◐	○	●	○	●	●	○	**Moderate**	○	○	○	●	**Moderate**
Schnitzer (2005)	Patient Global Assessment of Response to Treatment	6	Naproxcinod 375mg versus Placebo	●	●	○	●	○	●	●	○	**Moderate**	○	○	○	●	**Moderate**

●: Domain free of flaws

○: Domain flaws present

◐: Moderate power

Study	*Outcome*	*Week*	*Comparison*	**Prospective**	**Power**	**Group Assignment**	**Blinding**	**Group Comparability**	**Treatment Integrity**	**Measurement**	**Investigator Bias**	*Quality*	**Participants**	**Intervention and Expertise**	**Compliance and Adherence**	**Analysis**	*Applicability Study*
Schnitzer (2005)	Patient Global Assessment of Disease Status	6	Naproxcinod 375mg versus Placebo	●	●	○	●	○	●	●	○	**Moderate**	○	○	○	●	**Moderate**
Schnitzer (2005)	Patient Global Assessment of Response to Treatment	6	Naproxcinod 750mg versus Placebo	●	●	○	●	○	●	●	○	**Moderate**	○	○	○	●	**Moderate**
Schnitzer (2005)	Patient Global Assessment of Disease Status	6	Naproxcinod 750mg versus Placebo	●	●	○	●	○	●	●	○	**Moderate**	○	○	○	●	**Moderate**

●: Domain free of flaws

○: Domain flaws present

◐: Moderate power

Study	*Outcome*	*Week*	*Comparison*	**Prospective**	**Power**	**Group Assignment**	**Blinding**	**Group Comparability**	**Treatment Integrity**	**Measurement**	**Investigator Bias**	*Quality*	**Participants**	**Intervention and Expertise**	**Compliance and Adherence**	**Analysis**	*Applicability Study*
Schnitzer (2005)	Patient Global Assessment of Response to Treatment	6	Naproxen 500mg versus Placebo	●	●	○	●	○	●	●	○	**Moderate**	○	○	○	●	**Moderate**
Schnitzer (2005)	Patient Global Assessment of Disease Status	6	Naproxen 500mg versus Placebo	●	●	○	●	○	●	●	○	**Moderate**	○	○	○	●	**Moderate**

Table 150. Quality and Applicability: Cox-2s Versus NSAIDs

●: Domain free of flaws

○: Domain flaws present

◐: Moderate power

Study	*Outcome*	*Week*	*Comparison*	Prospective	Power	Group Assignment	Blinding	Group Comparability	Treatment Integrity	Measurement	Investigator Bias	*Quality*	Participants	Intervention and Expertise	Compliance and Adherence	Analysis	*Applicability Study*
Gibofsky (2003)	Adverse events	6	Celecoxib 200mg versus Aceclofenac	●	◐	○	●	●	●	●	○	**Moderate**	○	○	●	○	**Moderate**
Gibofsky (2003)	Adverse events	6	Celecoxib 200mg versus Aceclofenac	●	◐	○	●	●	●	●	○	**Moderate**	○	○	●	○	**Moderate**
Kivits (2002)	VAS Pain	12	Valdecoxib 5mg versus Naproxen 5mg	●	●	○	●	●	●	●	○	**Moderate**	○	○	●	●	**Moderate**

●: Domain free of flaws

○: Domain flaws present

◐: Moderate power

Study	*Outcome*	*Week*	*Comparison*	**Prospective**	**Power**	**Group Assignment**	**Blinding**	**Group Comparability**	**Treatment Integrity**	**Measurement**	**Investigator Bias**	*Quality*	**Participants**	**Intervention and Expertise**	**Compliance and Adherence**	**Analysis**	*Applicability Study*
Kivits (2002)	VAS Pain	6	Valdecoxib 5mg versus Naproxen 5mg	●	●	○	●	●	●	●	○	**Moderate**	○	○	●	●	**Moderate**
Kivits (2002)	VAS Pain	12	Valdecoxib 5mg versus Naproxen 5mg	●	●	○	●	●	●	●	○	**Moderate**	○	○	●	●	**Moderate**
Kivits (2002)	VAS Pain	6	Valdecoxib 5mg versus Naproxen 5mg	●	●	○	●	●	●	●	○	**Moderate**	○	○	●	●	**Moderate**

●: Domain free of flaws

○: Domain flaws present

◐: Moderate power

Study	*Outcome*	*Week*	*Comparison*	**Prospective**	**Power**	**Group Assignment**	**Blinding**	**Group Comparability**	**Treatment Integrity**	**Measurement**	**Investigator Bias**	*Quality*	**Participants**	**Intervention and Expertise**	**Compliance and Adherence**	**Analysis**	*Applicability Study*
Kivits (2002)	VAS Pain	12	Valdecoxib 5mg versus Naproxen 5mg	●	●	○	●	●	●	●	○	**Moderate**	○	○	●	●	**Moderate**
Kivits (2002)	VAS Pain	6	Valdecoxib 5mg versus Naproxen 5mg	●	●	○	●	●	●	●	○	**Moderate**	○	○	●	●	**Moderate**
Kivits (2002)	WOMAC Stiffness	6	Valdecoxib 10mg versus Naproxen 10mg	●	●	○	●	●	●	●	○	**Moderate**	○	○	●	●	**Moderate**

●: Domain free of flaws

○: Domain flaws present

◐: Moderate power

Study	*Outcome*	*Week*	*Comparison*	**Prospective**	**Power**	**Group Assignment**	**Blinding**	**Group Comparability**	**Treatment Integrity**	**Measurement**	**Investigator Bias**	*Quality*	**Participants**	**Intervention and Expertise**	**Compliance and Adherence**	**Analysis**	*Applicability Study*
Kivits (2002)	WOMAC Stiffness	12	Valdecoxib 10mg versus Naproxen 10mg	●	●	○	●	●	●	●	○	**Moderate**	○	○	●	●	**Moderate**
Kivits (2002)	WOMAC Stiffness	12	Valdecoxib 20mg versus Naproxen 20mg	●	●	○	●	●	●	●	○	**Moderate**	○	○	●	●	**Moderate**
Kivits (2002)	WOMAC Stiffness	6	Valdecoxib 20mg versus Naproxen 20mg	●	●	○	●	●	●	●	○	**Moderate**	○	○	●	●	**Moderate**

●: Domain free of flaws

○: Domain flaws present

◐: Moderate power

Study	*Outcome*	*Week*	*Comparison*	Prospective	Power	Group Assignment	Blinding	Group Comparability	Treatment Integrity	Measurement	Investigator Bias	*Quality*	Participants	Intervention and Expertise	Compliance and Adherence	Analysis	*Applicability Study*
Kivits (2002)	WOMAC Stiffness	12	Valdecoxib 5mg versus Naproxen 5mg	●	●	○	●	●	●	●	○	**Moderate**	○	○	●	●	**Moderate**
Kivits (2002)	WOMAC Stiffness	6	Valdecoxib 5mg versus Naproxen 5mg	●	●	○	●	●	●	●	○	**Moderate**	○	○	●	●	**Moderate**
Kivits (2002)	WOMAC Total	12	Valdecoxib 10mg versus Naproxen 10mg	●	●	○	●	●	●	●	○	**Moderate**	○	○	●	●	**Moderate**

●: Domain free of flaws

○: Domain flaws present

◐: Moderate power

Study	*Outcome*	*Week*	*Comparison*	**Prospective**	**Power**	**Group Assignment**	**Blinding**	**Group Comparability**	**Treatment Integrity**	**Measurement**	**Investigator Bias**	*Quality*	**Participants**	**Intervention and Expertise**	**Compliance and Adherence**	**Analysis**	*Applicability Study*
Kivits (2002)	WOMAC Total	6	Valdecoxib 10mg versus Naproxen 10mg	●	●	○	●	●	●	●	○	**Moderate**	○	○	●	●	**Moderate**
Kivits (2002)	WOMAC Total	6	Valdecoxib 20mg versus Naproxen 20mg	●	●	○	●	●	●	●	○	**Moderate**	○	○	●	●	**Moderate**
Kivits (2002)	WOMAC Total	12	Valdecoxib 20mg versus Naproxen 20mg	●	●	○	●	●	●	●	○	**Moderate**	○	○	●	●	**Moderate**

●: Domain free of flaws

○: Domain flaws present

◐: Moderate power

Study	*Outcome*	*Week*	*Comparison*	**Prospective**	**Power**	**Group Assignment**	**Blinding**	**Group Comparability**	**Treatment Integrity**	**Measurement**	**Investigator Bias**	*Quality*	**Participants**	**Intervention and Expertise**	**Compliance and Adherence**	**Analysis**	*Applicability Study*
Kivits (2002)	WOMAC Total	12	Valdecoxib 5mg versus Naproxen 5mg	●	●	○	●	●	●	●	○	**Moderate**	○	○	●	●	**Moderate**
Kivits (2002)	WOMAC Total	6	Valdecoxib 5mg versus Naproxen 5mg	●	●	○	●	●	●	●	○	**Moderate**	○	○	●	●	**Moderate**
Kivits (2002)	Abdominal pain	12	Valdecoxib 20mg versus Naproxen 500mg	●	◐	○	●	●	●	●	○	**Moderate**	○	○	●	●	**Moderate**

●: Domain free of flaws

○: Domain flaws present

◐: Moderate power

Study	*Outcome*	*Week*	*Comparison*	**Prospective**	**Power**	**Group Assignment**	**Blinding**	**Group Comparability**	**Treatment Integrity**	**Measurement**	**Investigator Bias**	*Quality*	**Participants**	**Intervention and Expertise**	**Compliance and Adherence**	**Analysis**	*Applicability Study*
Kivits (2002)	Abdominal pain	12	Valdecoxib 10mg versus Naproxen 500mg	●	◐	○	●	●	●	●	○	**Moderate**	○	○	●	●	**Moderate**
Kivits (2002)	Abdominal pain	12	Valdecoxib 5mg versus Naproxen 500mg	●	◐	○	●	●	●	●	○	**Moderate**	○	○	●	●	**Moderate**
Kivits (2002)	Accidental injury	12	Valdecoxib 20mg versus Naproxen 500mg	●	◐	○	●	●	●	●	○	**Moderate**	○	○	●	●	**Moderate**

●: Domain free of flaws

○: Domain flaws present

◐: Moderate power

Study	*Outcome*	*Week*	*Comparison*	**Prospective**	**Power**	**Group Assignment**	**Blinding**	**Group Comparability**	**Treatment Integrity**	**Measurement**	**Investigator Bias**	*Quality*	**Participants**	**Intervention and Expertise**	**Compliance and Adherence**	**Analysis**	*Applicability Study*
Kivits (2002)	Accidental injury	12	Valdecoxib 10mg versus Naproxen 500mg	●	◐	○	●	●	●	●	○	**Moderate**	○	○	●	●	**Moderate**
Kivits (2002)	Accidental injury	12	Valdecoxib 5mg versus Naproxen 500mg	●	◐	○	●	●	●	●	○	**Moderate**	○	○	●	●	**Moderate**
Kivits (2002)	Constipation	12	Valdecoxib 20mg versus Naproxen 500mg	●	◐	○	●	●	●	●	○	**Moderate**	○	○	●	●	**Moderate**

●: Domain free of flaws

○: Domain flaws present

◐: Moderate power

Study	*Outcome*	*Week*	*Comparison*	**Prospective**	**Power**	**Group Assignment**	**Blinding**	**Group Comparability**	**Treatment Integrity**	**Measurement**	**Investigator Bias**	*Quality*	**Participants**	**Intervention and Expertise**	**Compliance and Adherence**	**Analysis**	*Applicability Study*
Kivits (2002)	Constipation	12	Valdecoxib 10mg versus Naproxen 500mg	●	◐	○	●	●	●	●	○	**Moderate**	○	○	●	●	**Moderate**
Kivits (2002)	Constipation	12	Valdecoxib 5mg versus Naproxen 500mg	●	◐	○	●	●	●	●	○	**Moderate**	○	○	●	●	**Moderate**
Kivits (2002)	Diarrhea	12	Valdecoxib 20mg versus Naproxen 500mg	●	◐	○	●	●	●	●	○	**Moderate**	○	○	●	●	**Moderate**

●: Domain free of flaws

○: Domain flaws present

◐: Moderate power

Study	*Outcome*	*Week*	*Comparison*	Prospective	Power	Group Assignment	Blinding	Group Comparability	Treatment Integrity	Measurement	Investigator Bias	*Quality*	Participants	Intervention and Expertise	Compliance and Adherence	Analysis	*Applicability Study*
Kivits (2002)	Diarrhea	12	Valdecoxib 10mg versus Naproxen 500mg	●	◐	○	●	●	●	●	○	**Moderate**	○	○	●	●	**Moderate**
Kivits (2002)	Diarrhea	12	Valdecoxib 5mg versus Naproxen 500mg	●	◐	○	●	●	●	●	○	**Moderate**	○	○	●	●	**Moderate**
Kivits (2002)	Dyspepsia	12	Valdecoxib 20mg versus Naproxen 500mg	●	◐	○	●	●	●	●	○	**Moderate**	○	○	●	●	**Moderate**

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○: Domain flaws present

◐: Moderate power

Study	*Outcome*	*Week*	*Comparison*	Prospective	Power	Group Assignment	Blinding	Group Comparability	Treatment Integrity	Measurement	Investigator Bias	*Quality*	Participants	Intervention and Expertise	Compliance and Adherence	Analysis	*Applicability Study*
Kivits (2002)	Dyspepsia	12	Valdecoxib 10mg versus Naproxen 500mg	●	◐	○	●	●	●	●	○	**Moderate**	○	○	●	●	**Moderate**
Kivits (2002)	Dyspepsia	12	Valdecoxib 5mg versus Naproxen 500mg	●	◐	○	●	●	●	●	○	**Moderate**	○	○	●	●	**Moderate**
Kivits (2002)	Flatulence	12	Valdecoxib 20mg versus Naproxen 500mg	●	◐	○	●	●	●	●	○	**Moderate**	○	○	●	●	**Moderate**

●: Domain free of flaws

○: Domain flaws present

◐: Moderate power

Study	*Outcome*	*Week*	*Comparison*	**Prospective**	**Power**	**Group Assignment**	**Blinding**	**Group Comparability**	**Treatment Integrity**	**Measurement**	**Investigator Bias**	*Quality*	**Participants**	**Intervention and Expertise**	**Compliance and Adherence**	**Analysis**	*Applicability Study*
Kivits (2002)	Flatulence	12	Valdecoxib 10mg versus Naproxen 500mg	●	◐	○	●	●	●	●	○	**Moderate**	○	○	●	●	**Moderate**
Kivits (2002)	Flatulence	12	Valdecoxib 5mg versus Naproxen 500mg	●	◐	○	●	●	●	●	○	**Moderate**	○	○	●	●	**Moderate**
Kivits (2002)	Headache	12	Valdecoxib 20mg versus Naproxen 500mg	●	◐	○	●	●	●	●	○	**Moderate**	○	○	●	●	**Moderate**

●: Domain free of flaws

○: Domain flaws present

◐: Moderate power

Study	*Outcome*	*Week*	*Comparison*	Prospective	Power	Group Assignment	Blinding	Group Comparability	Treatment Integrity	Measurement	Investigator Bias	*Quality*	Participants	Intervention and Expertise	Compliance and Adherence	Analysis	*Applicability Study*
Kivits (2002)	Headache	12	Valdecoxib 10mg versus Naproxen 500mg	●	◐	○	●	●	●	●	○	**Moderate**	○	○	●	●	**Moderate**
Kivits (2002)	Headache	12	Valdecoxib 5mg versus Naproxen 500mg	●	◐	○	●	●	●	●	○	**Moderate**	○	○	●	●	**Moderate**
Kivits (2002)	Myalgia	12	Valdecoxib 20mg versus Naproxen 500mg	●	◐	○	●	●	●	●	○	**Moderate**	○	○	●	●	**Moderate**

●: Domain free of flaws

○: Domain flaws present

◐: Moderate power

Study	*Outcome*	*Week*	*Comparison*	**Prospective**	**Power**	**Group Assignment**	**Blinding**	**Group Comparability**	**Treatment Integrity**	**Measurement**	**Investigator Bias**	*Quality*	**Participants**	**Intervention and Expertise**	**Compliance and Adherence**	**Analysis**	*Applicability Study*
Kivits (2002)	Myalgia	12	Valdecoxib 10mg versus Naproxen 500mg	●	◐	○	●	●	●	●	○	**Moderate**	○	○	●	●	**Moderate**
Kivits (2002)	Myalgia	12	Valdecoxib 5mg versus Naproxen 500mg	●	◐	○	●	●	●	●	○	**Moderate**	○	○	●	●	**Moderate**
Kivits (2002)	Nausea	12	Valdecoxib 20mg versus Naproxen 500mg	●	◐	○	●	●	●	●	○	**Moderate**	○	○	●	●	**Moderate**

●: Domain free of flaws

○: Domain flaws present

◐: Moderate power

Study	*Outcome*	*Week*	*Comparison*	Prospective	Power	Group Assignment	Blinding	Group Comparability	Treatment Integrity	Measurement	Investigator Bias	*Quality*	Participants	Intervention and Expertise	Compliance and Adherence	Analysis	*Applicability Study*
Kivits (2002)	Nausea	12	Valdecoxib 10mg versus Naproxen 500mg	●	◐	○	●	●	●	●	○	**Moderate**	○	○	●	●	**Moderate**
Kivits (2002)	Nausea	12	Valdecoxib 5mg versus Naproxen 500mg	●	◐	○	●	●	●	●	○	**Moderate**	○	○	●	●	**Moderate**
Kivits (2002)	Upper respiratory tract infections	12	Valdecoxib 20mg versus Naproxen 500mg	●	◐	○	●	●	●	●	○	**Moderate**	○	○	●	●	**Moderate**

●: Domain free of flaws

○: Domain flaws present

◐: Moderate power

Study	*Outcome*	*Week*	*Comparison*	**Prospective**	**Power**	**Group Assignment**	**Blinding**	**Group Comparability**	**Treatment Integrity**	**Measurement**	**Investigator Bias**	*Quality*	**Participants**	**Intervention and Expertise**	**Compliance and Adherence**	**Analysis**	*Applicability Study*
Kivits (2002)	Upper respiratory tract infections	12	Valdecoxib 10mg versus Naproxen 500mg	●	◐	○	●	●	●	●	○	**Moderate**	○	○	●	●	**Moderate**
Kivits (2002)	Upper respiratory tract infections	12	Valdecoxib 5mg versus Naproxen 500mg	●	◐	○	●	●	●	●	○	**Moderate**	○	○	●	●	**Moderate**
Kivits (2002)	Abdominal pain	12	Valdecoxib 20mg versus Naproxen 500mg	●	●	○	●	●	●	●	○	**Moderate**	○	○	●	●	**Moderate**

●: Domain free of flaws

○: Domain flaws present

◐: Moderate power

Study	*Outcome*	*Week*	*Comparison*	**Prospective**	**Power**	**Group Assignment**	**Blinding**	**Group Comparability**	**Treatment Integrity**	**Measurement**	**Investigator Bias**	*Quality*	**Participants**	**Intervention and Expertise**	**Compliance and Adherence**	**Analysis**	*Applicability Study*
Kivits (2002)	Accidental injury	12	Valdecoxib 20mg versus Naproxen 500mg	●	◐	○	●	●	●	●	○	**Moderate**	○	○	●	●	**Moderate**
Kivits (2002)	Constipation	12	Valdecoxib 20mg versus Naproxen 500mg	●	◐	○	●	●	●	●	○	**Moderate**	○	○	●	●	**Moderate**
Kivits (2002)	Diarrhea	12	Valdecoxib 20mg versus Naproxen 500mg	●	◐	○	●	●	●	●	○	**Moderate**	○	○	●	●	**Moderate**

●: Domain free of flaws

○: Domain flaws present

◐: Moderate power

Study	*Outcome*	*Week*	*Comparison*	Prospective	Power	Group Assignment	Blinding	Group Comparability	Treatment Integrity	Measurement	Investigator Bias	*Quality*	Participants	Intervention and Expertise	Compliance and Adherence	Analysis	*Applicability Study*
Kivits (2002)	Dyspepsia	12	Valdecoxib 20mg versus Naproxen 500mg	●	●	○	●	●	●	●	○	**Moderate**	○	○	●	●	**Moderate**
Kivits (2002)	Flatulence	12	Valdecoxib 20mg versus Naproxen 500mg	●	◐	○	●	●	●	●	○	**Moderate**	○	○	●	●	**Moderate**
Kivits (2002)	Headache	12	Valdecoxib 20mg versus Naproxen 500mg	●	◐	○	●	●	●	●	○	**Moderate**	○	○	●	●	**Moderate**

●: Domain free of flaws

○: Domain flaws present

◐: Moderate power

Study	*Outcome*	*Week*	*Comparison*	Prospective	Power	Group Assignment	Blinding	Group Comparability	Treatment Integrity	Measurement	Investigator Bias	*Quality*	Participants	Intervention and Expertise	Compliance and Adherence	Analysis	*Applicability Study*
Kivits (2002)	Myalgia	12	Valdecoxib 20mg versus Naproxen 500mg	●	◐	○	●	●	●	●	○	**Moderate**	○	○	●	●	**Moderate**
Kivits (2002)	Nausea	12	Valdecoxib 20mg versus Naproxen 500mg	●	◐	○	●	●	●	●	○	**Moderate**	○	○	●	●	**Moderate**
Kivits (2002)	Upper respiratory tract infections	12	Valdecoxib 20mg versus Naproxen 500mg	●	◐	○	●	●	●	●	○	**Moderate**	○	○	●	●	**Moderate**

●: Domain free of flaws

○: Domain flaws present

◐: Moderate power

Study	*Outcome*	*Week*	*Comparison*	Prospective	Power	Group Assignment	Blinding	Group Comparability	Treatment Integrity	Measurement	Investigator Bias	*Quality*	Participants	Intervention and Expertise	Compliance and Adherence	Analysis	*Applicability Study*
Kivits (2004)	Acid reflux	6	Rofecoxib 12.5mg versus Nabumetone 1000mg	●	●	●	●	●	●	●	○	**High**	●	○	●	●	**Moderate**
Kivits (2004)	At least one adverse event	6	Rofecoxib 12.5mg versus Naproxen	●	●	●	●	●	●	●	○	**High**	●	○	●	●	**Moderate**
Kivits (2004)	Dyspepsia	6	Rofecoxib 12.5mg versus Nabumetone 1000mg	●	●	●	●	●	●	●	○	**High**	●	○	●	●	**Moderate**
Kivits (2004)	Epigastric discomfort	6	Rofecoxib 12.5mg versus Nabumetone 1000mg	●	●	●	●	●	●	●	○	**High**	●	○	●	●	**Moderate**

●: Domain free of flaws

○: Domain flaws present

◐: Moderate power

Study	*Outcome*	*Week*	*Comparison*	Prospective	Power	Group Assignment	Blinding	Group Comparability	Treatment Integrity	Measurement	Investigator Bias	*Quality*	Participants	Intervention and Expertise	Compliance and Adherence	Analysis	*Applicability Study*
Kivits (2004)	GI events	6	Rofecoxib 12.5mg versus Nabumetone 1000mg	●	●	●	●	●	●	●	○	**High**	●	○	●	●	**Moderate**
Kivits (2004)	Heartburn	6	Rofecoxib 12.5mg versus Nabumetone 1000mg	●	●	●	●	●	●	●	○	**High**	●	○	●	●	**Moderate**
Kivits (2004)	Nausea	6	Rofecoxib 12.5mg versus Nabumetone 1000mg	●	●	●	●	●	●	●	○	**High**	●	○	●	●	**Moderate**

●: Domain free of flaws

○: Domain flaws present

◐: Moderate power

Study	*Outcome*	*Week*	*Comparison*	**Prospective**	**Power**	**Group Assignment**	**Blinding**	**Group Comparability**	**Treatment Integrity**	**Measurement**	**Investigator Bias**	*Quality*	**Participants**	**Intervention and Expertise**	**Compliance and Adherence**	**Analysis**	*Applicability Study*
Kivits (2004)	Vomiting	6	Rofecoxib 12.5mg versus Nabumetone 1000mg	●	●	●	●	●	●	●	○	**High**	●	○	●	●	**Moderate**
Kivits (2004)	Acid reflux	6	Rofecoxib 12.5mg versus Nabumetone 1000mg	●	◐	●	●	●	●	●	○	**High**	●	○	●	●	**Moderate**
Kivits (2004)	At least one adverse event	6	Rofecoxib 12.5mg versus Naproxen	●	◐	●	●	●	●	●	○	**High**	●	○	●	●	**Moderate**
Kivits (2004)	Dyspepsia	6	Rofecoxib 12.5mg versus Nabumetone 1000mg	●	◐	●	●	●	●	●	○	**High**	●	○	●	●	**Moderate**

●: Domain free of flaws

○: Domain flaws present

◐: Moderate power

Study	*Outcome*	*Week*	*Comparison*	**Prospective**	**Power**	**Group Assignment**	**Blinding**	**Group Comparability**	**Treatment Integrity**	**Measurement**	**Investigator Bias**	*Quality*	**Participants**	**Intervention and Expertise**	**Compliance and Adherence**	**Analysis**	*Applicability Study*
Kivits (2004)	Epigastric discomfort	6	Rofecoxib 12.5mg versus Nabumetone 1000mg	●	◐	●	●	●	●	●	○	**High**	●	○	●	●	**Moderate**
Kivits (2004)	GI events	6	Rofecoxib 12.5mg versus Nabumetone 1000mg	●	◐	●	●	●	●	●	○	**High**	●	○	●	●	**Moderate**
Kivits (2004)	Heartburn	6	Rofecoxib 12.5mg versus Nabumetone 1000mg	●	◐	●	●	●	●	●	○	**High**	●	○	●	●	**Moderate**

●: Domain free of flaws

○: Domain flaws present

◐: Moderate power

Study	*Outcome*	*Week*	*Comparison*	Prospective	Power	Group Assignment	Blinding	Group Comparability	Treatment Integrity	Measurement	Investigator Bias	*Quality*	Participants	Intervention and Expertise	Compliance and Adherence	Analysis	*Applicability Study*
Kivits (2004)	Nausea	6	Rofecoxib 12.5mg versus Nabumetone 1000mg	●	◐	●	●	●	●	●	○	**High**	●	○	●	●	**Moderate**
Kivits (2004)	Vomiting	6	Rofecoxib 12.5mg versus Nabumetone 1000mg	●	◐	●	●	●	●	●	○	**High**	●	○	●	●	**Moderate**
Kivits (2002)	Physician Global Assessment	6	Valdecoxib 10mg versus Naproxen	●	◐	○	●	●	●	●	○	**Moderate**	○	○	●	●	**Moderate**
Kivits (2002)	Physician Global Assessment	12	Valdecoxib 10mg versus Naproxen	●	◐	○	●	●	●	●	○	**Moderate**	○	○	●	●	**Moderate**

●: Domain free of flaws

○: Domain flaws present

◐: Moderate power

Study	*Outcome*	*Week*	*Comparison*	**Prospective**	**Power**	**Group Assignment**	**Blinding**	**Group Comparability**	**Treatment Integrity**	**Measurement**	**Investigator Bias**	*Quality*	**Participants**	**Intervention and Expertise**	**Compliance and Adherence**	**Analysis**	*Applicability Study*
Kivits (2002)	Physician Global Assessment	6	Valdecoxib 20mg versus Naproxen	●	◐	○	●	●	●	●	○	**Moderate**	○	○	●	●	**Moderate**
Kivits (2002)	Physician Global Assessment	12	Valdecoxib 20mg versus Naproxen	●	◐	○	●	●	●	●	○	**Moderate**	○	○	●	●	**Moderate**
Kivits (2002)	Physician Global Assessment	6	Valdecoxib 5mg versus Naproxen	●	◐	○	●	●	●	●	○	**Moderate**	○	○	●	●	**Moderate**
Kivits (2002)	Physician Global Assessment	12	Valdecoxib 5mg versus Naproxen	●	◐	○	●	●	●	●	○	**Moderate**	○	○	●	●	**Moderate**

●: Domain free of flaws

○: Domain flaws present

◐: Moderate power

Study	*Outcome*	*Week*	*Comparison*	Prospective	Power	Group Assignment	Blinding	Group Comparability	Treatment Integrity	Measurement	Investigator Bias	*Quality*	Participants	Intervention and Expertise	Compliance and Adherence	Analysis	*Applicability Study*
Kivitz (2004)	Patient Assessment of Treatment Response (Good or Excellent)	6	Rofecoxib 12.5mg versus Nabumetone	●	●	●	●	●	●	●	○	**High**	●	○	●	●	**Moderate**
Lücker (1994)	VAS Pain	4	Nimesulide 100mg versus Etodolac	●	●	○	●	●	●	●	○	**Moderate**	○	○	●	○	**Moderate**
Lücker (1994)	VAS Pain	8	Nimesulide 100mg versus Etodolac	●	●	○	●	●	●	●	○	**Moderate**	○	○	●	○	**Moderate**
Lücker (1994)	VAS Pain	12	Nimesulide 100mg versus Etodolac	●	●	○	●	●	●	●	○	**Moderate**	○	○	●	○	**Moderate**

●: Domain free of flaws

○: Domain flaws present

◐: Moderate power

Study	*Outcome*	*Week*	*Comparison*	**Prospective**	**Power**	**Group Assignment**	**Blinding**	**Group Comparability**	**Treatment Integrity**	**Measurement**	**Investigator Bias**	*Quality*	**Participants**	**Intervention and Expertise**	**Compliance and Adherence**	**Analysis**	*Applicability Study*
Lücker (1994)	Lequesne index	4	Nimesulide 100mg versus Etodolac	●	◐	○	●	●	●	●	○	**Moderate**	○	○	●	○	**Moderate**
Lücker (1994)	Lequesne index	8	Nimesulide 100mg versus Etodolac	●	◐	○	●	●	●	●	○	**Moderate**	○	○	●	○	**Moderate**
Lücker (1994)	Lequesne index	12	Nimesulide 100mg versus Etodolac	●	◐	○	●	●	●	●	○	**Moderate**	○	○	●	○	**Moderate**
Mckenna (2001)	Patient Global Assessment	6	Celecoxib versus Diclofenac	●	◐	○	●	●	●	●	○	**Moderate**	○	○	●	●	**Moderate**

●: Domain free of flaws

○: Domain flaws present

◐: Moderate power

Study	*Outcome*	*Week*	*Comparison*	**Prospective**	**Power**	**Group Assignment**	**Blinding**	**Group Comparability**	**Treatment Integrity**	**Measurement**	**Investigator Bias**	*Quality*	**Participants**	**Intervention and Expertise**	**Compliance and Adherence**	**Analysis**	*Applicability Study*
McKenna (2001)	Nausea	6	Rofecoxib 25mg versus Naproxcinod 125mg	●	◐	○	●	●	●	●	○	**Moderate**	○	○	●	●	**Moderate**
Mckenna (2001)	WOMAC Function	6	Celecoxib 100mg versus Diclofenac 100mg	●	●	○	●	●	●	●	○	**Moderate**	○	○	●	●	**Moderate**
Mckenna (2001)	WOMAC Pain	6	Celecoxib 100mg versus Diclofenac 100mg	●	●	○	●	●	●	●	○	**Moderate**	○	○	●	●	**Moderate**

●: Domain free of flaws

○: Domain flaws present

◐: Moderate power

Study	*Outcome*	*Week*	*Comparison*	**Prospective**	**Power**	**Group Assignment**	**Blinding**	**Group Comparability**	**Treatment Integrity**	**Measurement**	**Investigator Bias**	*Quality*	**Participants**	**Intervention and Expertise**	**Compliance and Adherence**	**Analysis**	*Applicability Study*
Mckenna (2001)	VAS Pain	6	Celecoxib 100mg versus Diclofenac 100mg	●	●	○	●	●	●	●	○	**Moderate**	○	○	●	●	**Moderate**
Mckenna (2001)	WOMAC Stiffness	6	Celecoxib 100mg versus Diclofenac 100mg	●	●	○	●	●	●	●	○	**Moderate**	○	○	●	●	**Moderate**
Mckenna (2001)	WOMAC Total	6	Celecoxib 100mg versus Diclofenac 100mg	●	●	○	●	●	●	●	○	**Moderate**	○	○	●	●	**Moderate**

●: Domain free of flaws

○: Domain flaws present

◐: Moderate power

Study	*Outcome*	*Week*	*Comparison*	**Prospective**	**Power**	**Group Assignment**	**Blinding**	**Group Comparability**	**Treatment Integrity**	**Measurement**	**Investigator Bias**	*Quality*	**Participants**	**Intervention and Expertise**	**Compliance and Adherence**	**Analysis**	*Applicability Study*
Mckenna (2001)	Physician Global Assessment	6	Celecoxib versus Diclofenac (NSAID)	●	●	○	●	●	●	●	○	**Moderate**	○	○	●	●	**Moderate**
Schnitzer (2005)	Patient Global Assessment of Disease responders	6	Rofecoxib 25mg versus Naproxcinod 125mg	●	●	○	●	○	●	●	○	**Moderate**	○	○	○	●	**Moderate**
Schnitzer (2005)	Patient Global Assessment of Disease responders	6	Rofecoxib 25mg versus Naproxcinod 375mg	●	◐	○	●	○	●	●	○	**Moderate**	○	○	○	●	**Moderate**

●: Domain free of flaws

○: Domain flaws present

◐: Moderate power

Study	*Outcome*	*Week*	*Comparison*	**Prospective**	**Power**	**Group Assignment**	**Blinding**	**Group Comparability**	**Treatment Integrity**	**Measurement**	**Investigator Bias**	*Quality*	**Participants**	**Intervention and Expertise**	**Compliance and Adherence**	**Analysis**	*Applicability Study*
Schnitzer (2005)	Patient Global Assessment of Disease responders	6	Rofecoxib 25mg versus Naproxcinod 750mg	●	◐	○	●	○	●	●	○	**Moderate**	○	○	○	●	**Moderate**
Schnitzer (2005)	Patient Assessment of Treatment Response (Good or Excellent)	6	Rofecoxib 25mg versus Naproxcinod 125mg	●	●	○	●	○	●	●	○	**Moderate**	○	○	○	●	**Moderate**

●: Domain free of flaws

○: Domain flaws present

◐: Moderate power

Study	*Outcome*	*Week*	*Comparison*	**Prospective**	**Power**	**Group Assignment**	**Blinding**	**Group Comparability**	**Treatment Integrity**	**Measurement**	**Investigator Bias**	*Quality*	**Participants**	**Intervention and Expertise**	**Compliance and Adherence**	**Analysis**	*Applicability Study*
Schnitzer (2005)	Patient Assessment of Treatment Response (Good or Excellent)	6	Rofecoxib 25mg versus Naproxcinod 375mg	●	◐	○	●	○	●	●	○	**Moderate**	○	○	○	●	**Moderate**
Schnitzer (2005)	Patient Assessment of Treatment Response (good or excellent)	6	Rofecoxib 25mg versus Naproxcinod 750mg	●	●	○	●	○	●	●	○	**Moderate**	○	○	○	●	**Moderate**

Table 151. Quality and Applicability: Acetaminophen Versus Control

●: Domain free of flaws

○: Domain flaws present

◐: Moderate power

Study	*Outcome*	*Week*	*Comparison*	Prospective	Power	Group Assignment	Blinding	Group Comparability	Treatment Integrity	Measurement	Investigator Bias	*Quality*	Participants	Intervention and Expertise	Compliance and Adherence	Analysis	*Applicability Study*
Gualda (2007)	Physician Global Assessment	6	Paracetamol versus Aceclofenac 100mg	●	●	●	●	●	●	●	○	**High**	○	○	●	●	**Moderate**
Gualda (2007)	Patient Global Assessment	6	Paracetamol 1000mg versus acelofenac 100mg	●	●	●	●	●	●	●	○	**High**	○	○	●	●	**Moderate**
Gualda (2007)	Adverse events	6	Paracetamol 1000mg versus Celecoxib 200mg	●	◐	●	●	●	●	●	○	**High**	○	○	●	●	**Moderate**

●: Domain free of flaws

○: Domain flaws present

◐: Moderate power

Study	*Outcome*	*Week*	*Comparison*	**Prospective**	**Power**	**Group Assignment**	**Blinding**	**Group Comparability**	**Treatment Integrity**	**Measurement**	**Investigator Bias**	*Quality*	**Participants**	**Intervention and Expertise**	**Compliance and Adherence**	**Analysis**	*Applicability Study*
Schnitzer (2005)	Patient Assessment of Treatment Response	6	Acetaminophen 4000mg versus Rofecoxib 12.5mg	○	●	○	○	○	●	●	○	**Low**	○	○	●	●	**Moderate**
Schnitzer (2009)	Physician Assessment of Treatment Response	4	Acetaminophen 1300mg versus Rofecoxib 25mg	●	●	○	●	○	●	●	○	**Moderate**	○	○	●	○	**Moderate**
Schnitzer (2009)	Physician Assessment of Treatment Response	4	Acetaminophen 1300mg versus Rofecoxib 12.5mg	●	●	○	●	○	●	●	○	**Moderate**	○	○	●	○	**Moderate**

●: Domain free of flaws

○: Domain flaws present

◐: Moderate power

Study	*Outcome*	*Week*	*Comparison*	Prospective	Power	Group Assignment	Blinding	Group Comparability	Treatment Integrity	Measurement	Investigator Bias	*Quality*	Participants	Intervention and Expertise	Compliance and Adherence	Analysis	*Applicability Study*
Schnitzer (2005)	Any clinical adverse event, VACT2	6	Acetaminophen 1000mg versus Rofecoxib 12.5mg	○	◐	○	○	○	●	●	○	**Low**	○	○	●	●	**Moderate**
Schnitzer (2005)	Patient Assessment of Treatment Response	6	Acetaminophen 4000mg versus Rofecoxib 25mg	○	●	○	○	○	●	●	○	**Low**	○	○	●	●	**Moderate**
Schnitzer (2005)	Patient Assessment of Treatment Response	6	Acetaminophen 4000mg versus Rofecoxib 25mg	○	●	○	○	○	●	●	○	**Low**	○	○	●	●	**Moderate**

●: Domain free of flaws

○: Domain flaws present

◐: Moderate power

Study	*Outcome*	*Week*	*Comparison*	Prospective	Power	Group Assignment	Blinding	Group Comparability	Treatment Integrity	Measurement	Investigator Bias	*Quality*	Participants	Intervention and Expertise	Compliance and Adherence	Analysis	*Applicability Study*
Schnitzer (2009)	Abdominal pain	4	Acetaminophen ER 1300mg versus Rofecoxib 12.5mg	●	◐	○	●	○	●	●	○	**Moderate**	○	○	●	○	**Moderate**
Schnitzer (2009)	Abdominal pain	4	Acetaminophen ER 1300mg versus Rofecoxib 25mg	●	◐	○	●	○	●	●	○	**Moderate**	○	○	●	○	**Moderate**
Schnitzer (2009)	Constipation	4	Acetaminophen ER 1300mg versus Rofecoxib 12.5mg	●	◐	○	●	○	●	●	○	**Moderate**	○	○	●	○	**Moderate**

●: Domain free of flaws

○: Domain flaws present

◐: Moderate power

Study	*Outcome*	*Week*	*Comparison*	Prospective	Power	Group Assignment	Blinding	Group Comparability	Treatment Integrity	Measurement	Investigator Bias	*Quality*	Participants	Intervention and Expertise	Compliance and Adherence	Analysis	*Applicability Study*
Schnitzer (2009)	Constipation	4	Acetaminophen ER 1300mg versus Rofecoxib 25mg	●	◐	○	●	○	●	●	○	**Moderate**	○	○	●	○	**Moderate**
Schnitzer (2009)	Diarrhea	4	Acetaminophen ER 1300mg versus Rofecoxib 12.5mg	●	◐	○	●	○	●	●	○	**Moderate**	○	○	●	○	**Moderate**
Schnitzer (2009)	Diarrhea	4	Acetaminophen ER 1300mg versus Rofecoxib 25mg	●	◐	○	●	○	●	●	○	**Moderate**	○	○	●	○	**Moderate**

●: Domain free of flaws

○: Domain flaws present

◐: Moderate power

Study	*Outcome*	*Week*	*Comparison*	**Prospective**	**Power**	**Group Assignment**	**Blinding**	**Group Comparability**	**Treatment Integrity**	**Measurement**	**Investigator Bias**	*Quality*	**Participants**	**Intervention and Expertise**	**Compliance and Adherence**	**Analysis**	*Applicability Study*
Schnitzer (2009)	Dizziness	4	Acetaminophen ER 1300mg versus Rofecoxib 12.5mg	●	◐	○	●	○	●	●	○	**Moderate**	○	○	●	○	**Moderate**
Schnitzer (2009)	Dizziness	4	Acetaminophen ER 1300mg versus Rofecoxib 25mg	●	◐	○	●	○	●	●	○	**Moderate**	○	○	●	○	**Moderate**
Schnitzer (2009)	Dyspepsia	4	Acetaminophen ER 1300mg versus Rofecoxib 12.5mg	●	◐	○	●	○	●	●	○	**Moderate**	○	○	●	○	**Moderate**

●: Domain free of flaws

○: Domain flaws present

◐: Moderate power

Study	*Outcome*	*Week*	*Comparison*	Prospective	Power	Group Assignment	Blinding	Group Comparability	Treatment Integrity	Measurement	Investigator Bias	*Quality*	Participants	Intervention and Expertise	Compliance and Adherence	Analysis	*Applicability Study*
Schnitzer (2009)	Dyspepsia	4	Acetaminophen ER 1300mg versus Rofecoxib 25mg	●	◐	○	●	○	●	●	○	**Moderate**	○	○	●	○	**Moderate**
Schnitzer (2009)	Flatulence	4	Acetaminophen ER 1300mg versus Rofecoxib 12.5mg	●	◐	○	●	○	●	●	○	**Moderate**	○	○	●	○	**Moderate**
Schnitzer (2009)	Flatulence	4	Acetaminophen ER 1300mg versus Rofecoxib 25mg	●	◐	○	●	○	●	●	○	**Moderate**	○	○	●	○	**Moderate**

●: Domain free of flaws

○: Domain flaws present

◐: Moderate power

Study	*Outcome*	*Week*	*Comparison*	Prospective	Power	Group Assignment	Blinding	Group Comparability	Treatment Integrity	Measurement	Investigator Bias	*Quality*	Participants	Intervention and Expertise	Compliance and Adherence	Analysis	*Applicability Study*
Schnitzer (2009)	Headache	4	Acetaminophen ER 1300mg versus Rofecoxib 12.5mg	●	◐	○	●	○	●	●	○	**Moderate**	○	○	●	○	**Moderate**
Schnitzer (2009)	Headache	4	Acetaminophen ER 1300mg versus Rofecoxib 25mg	●	◐	○	●	○	●	●	○	**Moderate**	○	○	●	○	**Moderate**
Schnitzer (2009)	Nausea	4	Acetaminophen ER 1300mg versus Rofecoxib 12.5mg	●	◐	○	●	○	●	●	○	**Moderate**	○	○	●	○	**Moderate**

●: Domain free of flaws

○: Domain flaws present

◐: Moderate power

Study	*Outcome*	*Week*	*Comparison*	Prospective	Power	Group Assignment	Blinding	Group Comparability	Treatment Integrity	Measurement	Investigator Bias	*Quality*	Participants	Intervention and Expertise	Compliance and Adherence	Analysis	*Applicability Study*
Schnitzer (2009)	Nausea	4	Acetaminophen ER 1300mg versus Rofecoxib 25mg	●	◐	○	●	○	●	●	○	**Moderate**	○	○	●	○	**Moderate**
Schnitzer (2009)	Pain	4	Acetaminophen ER 1300mg versus Rofecoxib 12.5mg	●	◐	○	●	○	●	●	○	**Moderate**	○	○	●	○	**Moderate**
Schnitzer (2009)	Pain	4	Acetaminophen ER 1300mg versus Rofecoxib 25mg	●	◐	○	●	○	●	●	○	**Moderate**	○	○	●	○	**Moderate**

●: Domain free of flaws

○: Domain flaws present

◐: Moderate power

Study	*Outcome*	*Week*	*Comparison*	Prospective	Power	Group Assignment	Blinding	Group Comparability	Treatment Integrity	Measurement	Investigator Bias	*Quality*	Participants	Intervention and Expertise	Compliance and Adherence	Analysis	*Applicability Study*
Schnitzer (2009)	Peripheral edema	4	Acetaminophen ER 1300mg versus Rofecoxib 12.5mg	●	◐	○	●	○	●	●	○	**Moderate**	○	○	●	○	**Moderate**
Schnitzer (2009)	Peripheral edema	4	Acetaminophen ER 1300mg versus Rofecoxib 25mg	●	◐	○	●	○	●	●	○	**Moderate**	○	○	●	○	**Moderate**
Schnitzer (2009)	Abdominal pain	4	Acetaminophen ER 1300mg versus Rofecoxib 12.5mg	●	◐	○	●	○	●	●	○	**Moderate**	○	○	●	○	**Moderate**

●: Domain free of flaws

○: Domain flaws present

◐: Moderate power

Study	*Outcome*	*Week*	*Comparison*	Prospective	Power	Group Assignment	Blinding	Group Comparability	Treatment Integrity	Measurement	Investigator Bias	*Quality*	Participants	Intervention and Expertise	Compliance and Adherence	Analysis	*Applicability Study*
Schnitzer (2009)	Abdominal pain	4	Acetaminophen ER 1300mg versus Rofecoxib 25mg	●	◐	○	●	○	●	●	○	**Moderate**	○	○	●	○	**Moderate**
Schnitzer (2009)	Constipation	4	Acetaminophen ER 1300mg versus Rofecoxib 12.5mg	●	◐	○	●	○	●	●	○	**Moderate**	○	○	●	○	**Moderate**
Schnitzer (2009)	Constipation	4	Acetaminophen ER 1300mg versus Rofecoxib 25mg	●	◐	○	●	○	●	●	○	**Moderate**	○	○	●	○	**Moderate**

●: Domain free of flaws

○: Domain flaws present

◐: Moderate power

Study	*Outcome*	*Week*	*Comparison*	Prospective	Power	Group Assignment	Blinding	Group Comparability	Treatment Integrity	Measurement	Investigator Bias	*Quality*	Participants	Intervention and Expertise	Compliance and Adherence	Analysis	*Applicability Study*
Schnitzer (2009)	Diarrhea	4	Acetaminophen ER 1300mg versus Rofecoxib 12.5mg	●	◐	○	●	○	●	●	○	**Moderate**	○	○	●	○	**Moderate**
Schnitzer (2005)	Any clinical adverse event, VACT2	6	Acetaminophen 1000mg versus Rofecoxib 25mg	○	●	○	○	○	●	●	○	**Low**	○	○	●	●	**Moderate**
Schnitzer (2009)	Patient Assessment of Treatment Response	4	Acetaminophen ER versus Diclofenac	●	●	○	●	○	●	●	○	**Moderate**	○	○	●	○	**Moderate**
Micelli (2004)	VAS Pain	6	Acetaminophen versus Placebo	●	◐	○	●	○	●	●	●	**Moderate**	○	○	●	●	**Moderate**

●: Domain free of flaws

○: Domain flaws present

◐: Moderate power

Study	*Outcome*	*Week*	*Comparison*	Prospective	Power	Group Assignment	Blinding	Group Comparability	Treatment Integrity	Measurement	Investigator Bias	*Quality*	Participants	Intervention and Expertise	Compliance and Adherence	Analysis	*Applicability Study*
Bradley (1991)	HAQ Disability	4	Acetaminophen versus Ibuprofen	●	◐	○	●	○	●	●	●	**Moderate**	○	○	●	●	**Moderate**
Bradley (1991)	HAQ Disability	4	Acetaminophen versus Ibuprofen	●	◐	○	●	○	●	●	●	**Moderate**	○	○	●	●	**Moderate**
Bradley (1991)	Health Assessment Questionnaire	4	Acetaminophen versus Ibuprofen	●	◐	○	●	○	●	●	●	**Moderate**	○	○	●	●	**Moderate**
Bradley (1991)	Health Assessment Questionnaire	4	Acetaminophen versus Ibuprofen	●	◐	○	●	○	●	●	●	**Moderate**	○	○	●	●	**Moderate**
Bradley (1991)	Walk time (sec) improvement	4	Acetaminophen versus Ibuprofen	●	◐	○	●	○	●	●	●	**Moderate**	○	○	●	●	**Moderate**

●: Domain free of flaws

○: Domain flaws present

◐: Moderate power

Study	*Outcome*	*Week*	*Comparison*	Prospective	Power	Group Assignment	Blinding	Group Comparability	Treatment Integrity	Measurement	Investigator Bias	*Quality*	Participants	Intervention and Expertise	Compliance and Adherence	Analysis	*Applicability Study*
Bradley (1991)	Walk time (sec)	4	Acetaminophen versus Ibuprofen	●	◐	○	●	○	●	●	●	**Moderate**	○	○	●	●	**Moderate**
Gualda (2007)	VAS Pain	6	Paracetamol versus Aceclofenac	●	●	●	●	●	●	●	○	**High**	○	○	●	●	**Moderate**
Micelli (2004)	VAS Pain	6	Acetaminophen versus Placebo	●	◐	○	●	○	●	●	●	**Moderate**	○	○	●	●	**Moderate**

Table 152. Quality and Applicability: Interleukin Versus Control

●: Domain free of flaws
○: Domain flaws present
◐: Moderate power

Study	*Outcome*	*Week*	*Comparison*	Prospective	Power	Group Assignment	Blinding	Group Comparability	Treatment Integrity	Measurement	Investigator Bias	*Quality*	Participants	Intervention and Expertise	Compliance and Adherence	Analysis	*Applicability Study*
Louthrenoo (2007)	WOMAC Function	4	Diacerein versus Piroxicam	●	●	○	●	○	●	●	○	**Moderate**	○	○	○	●	**Moderate**
Louthrenoo (2007)	WOMAC Function	8	Diacerein versus Piroxicam	●	●	○	●	○	●	●	○	**Moderate**	○	○	○	●	**Moderate**
Louthrenoo (2007)	WOMAC Function	12	Diacerein versus Piroxicam	●	●	○	●	○	●	●	○	**Moderate**	○	○	○	●	**Moderate**
Louthrenoo (2007)	WOMAC Function	16	Diacerein versus Piroxicam	●	●	○	●	○	●	●	○	**Moderate**	○	○	○	●	**Moderate**
Louthrenoo (2007)	WOMAC Function	20	Diacerein versus Piroxicam	●	●	○	●	○	●	●	○	**Moderate**	○	○	○	●	**Moderate**

●: Domain free of flaws
○: Domain flaws present
◐: Moderate power

Study	*Outcome*	*Week*	*Comparison*	**Prospective**	**Power**	**Group Assignment**	**Blinding**	**Group Comparability**	**Treatment Integrity**	**Measurement**	**Investigator Bias**	*Quality*	**Participants**	**Intervention and Expertise**	**Compliance and Adherence**	**Analysis**	*Applicability Study*
Louthrenoo (2007)	WOMAC Function	24	Diacerein versus Piroxicam	●	●	○	●	○	●	●	○	**Moderate**	○	○	○	●	**Moderate**
Louthrenoo (2007)	WOMAC Pain	4	Diacerein versus Piroxicam	●	●	○	●	○	●	●	○	**Moderate**	○	○	○	●	**Moderate**
Louthrenoo (2007)	WOMAC Pain	8	Diacerein versus Piroxicam	●	●	○	●	○	●	●	○	**Moderate**	○	○	○	●	**Moderate**
Louthrenoo (2007)	WOMAC Pain	12	Diacerein versus Piroxicam	●	●	○	●	○	●	●	○	**Moderate**	○	○	○	●	**Moderate**
Louthrenoo (2007)	WOMAC Pain	16	Diacerein versus Piroxicam	●	●	○	●	○	●	●	○	**Moderate**	○	○	○	●	**Moderate**
Louthrenoo (2007)	WOMAC Pain	20	Diacerein versus Piroxicam	●	●	○	●	○	●	●	○	**Moderate**	○	○	○	●	**Moderate**

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Study	*Outcome*	*Week*	*Comparison*	Prospective	Power	Group Assignment	Blinding	Group Comparability	Treatment Integrity	Measurement	Investigator Bias	*Quality*	Participants	Intervention and Expertise	Compliance and Adherence	Analysis	*Applicability Study*
Louthrenoo (2007)	WOMAC Pain	24	Diacerein versus Piroxicam	●	●	○	●	○	●	●	○	**Moderate**	○	○	○	●	**Moderate**
Louthrenoo (2007)	Paracetamol intake pills per day	4	Diacerein versus Piroxicam	●	●	○	●	○	●	●	○	**Moderate**	○	○	○	●	**Moderate**
Louthrenoo (2007)	Paracetamol intake pills per day	8	Diacerein versus Piroxicam	●	●	○	●	○	●	●	○	**Moderate**	○	○	○	●	**Moderate**
Louthrenoo (2007)	Paracetamol intake pills per day	12	Diacerein versus Piroxicam	●	●	○	●	○	●	●	○	**Moderate**	○	○	○	●	**Moderate**
Louthrenoo (2007)	Paracetamol intake pills per day	16	Diacerein versus Piroxicam	●	●	○	●	○	●	●	○	**Moderate**	○	○	○	●	**Moderate**
Louthrenoo (2007)	Paracetamol intake pills per day	20	Diacerein versus Piroxicam	●	●	○	●	○	●	●	○	**Moderate**	○	○	○	●	**Moderate**

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Study	*Outcome*	*Week*	*Comparison*	Prospective	Power	Group Assignment	Blinding	Group Comparability	Treatment Integrity	Measurement	Investigator Bias	*Quality*	Participants	Intervention and Expertise	Compliance and Adherence	Analysis	*Applicability Study*
Louthrenoo (2007)	Paracetamol intake pills per day	24	Diacerein versus Piroxicam	●	●	○	●	○	●	●	○	**Moderate**	○	○	○	●	**Moderate**
Louthrenoo (2007)	SF-36 sum score	16	Diacerein versus Piroxicam	●	●	○	●	○	●	●	○	**Moderate**	○	○	○	●	**Moderate**
Louthrenoo (2007)	SF-36 sum score	24	Diacerein versus Piroxicam	●	●	○	●	○	●	●	○	**Moderate**	○	○	○	●	**Moderate**
Louthrenoo (2007)	WOMAC Stiffness	4	Diacerein versus Piroxicam	●	●	○	●	○	●	●	○	**Moderate**	○	○	○	●	**Moderate**
Louthrenoo (2007)	WOMAC Stiffness	8	Diacerein versus Piroxicam	●	●	○	●	○	●	●	○	**Moderate**	○	○	○	●	**Moderate**
Louthrenoo (2007)	WOMAC Stiffness	12	Diacerein versus Piroxicam	●	●	○	●	○	●	●	○	**Moderate**	○	○	○	●	**Moderate**

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○: Domain flaws present
◐: Moderate power

Study	*Outcome*	*Week*	*Comparison*	Prospective	Power	Group Assignment	Blinding	Group Comparability	Treatment Integrity	Measurement	Investigator Bias	*Quality*	Participants	Intervention and Expertise	Compliance and Adherence	Analysis	*Applicability Study*
Louthrenoo (2007)	WOMAC Stiffness	16	Diacerein versus Piroxicam	●	●	○	●	○	●	●	○	**Moderate**	○	○	○	●	**Moderate**
Louthrenoo (2007)	WOMAC Stiffness	20	Diacerein versus Piroxicam	●	●	○	●	○	●	●	○	**Moderate**	○	○	○	●	**Moderate**
Louthrenoo (2007)	WOMAC Stiffness	24	Diacerein versus Piroxicam	●	●	○	●	○	●	●	○	**Moderate**	○	○	○	●	**Moderate**
Louthrenoo (2007)	WOMAC Total	4	Diacerein versus Piroxicam	●	●	○	●	○	●	●	○	**Moderate**	○	○	○	●	**Moderate**
Louthrenoo (2007)	WOMAC Total	8	Diacerein versus Piroxicam	●	●	○	●	○	●	●	○	**Moderate**	○	○	○	●	**Moderate**
Louthrenoo (2007)	WOMAC Total	12	Diacerein versus Piroxicam	●	●	○	●	○	●	●	○	**Moderate**	○	○	○	●	**Moderate**

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○: Domain flaws present
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Study	*Outcome*	*Week*	*Comparison*	Prospective	Power	Group Assignment	Blinding	Group Comparability	Treatment Integrity	Measurement	Investigator Bias	*Quality*	Participants	Intervention and Expertise	Compliance and Adherence	Analysis	*Applicability Study*
Louthrenoo (2007)	WOMAC Total	16	Diacerein versus Piroxicam	●	●	○	●	○	●	●	○	**Moderate**	○	○	○	●	**Moderate**
Louthrenoo (2007)	WOMAC Total	20	Diacerein versus Piroxicam	●	●	○	●	○	●	●	○	**Moderate**	○	○	○	●	**Moderate**
Louthrenoo (2007)	WOMAC Total	24	Diacerein versus Piroxicam	●	●	○	●	○	●	●	○	**Moderate**	○	○	○	●	**Moderate**
Louthrenoo (2007)	Upper respiratory infection	12	Diacerein versus Piroxicam	●	◐	○	●	○	●	●	○	**Moderate**	○	○	○	●	**Moderate**
Louthrenoo (2007)	Dyspepsia	12	Diacerein versus Piroxicam	●	◐	○	●	○	●	●	○	**Moderate**	○	○	○	●	**Moderate**
Louthrenoo (2007)	Diarrhea	12	Diacerein versus Piroxicam	●	◐	○	●	○	●	●	○	**Moderate**	○	○	○	●	**Moderate**

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○: Domain flaws present
◐: Moderate power

Study	*Outcome*	*Week*	*Comparison*	Prospective	Power	Group Assignment	Blinding	Group Comparability	Treatment Integrity	Measurement	Investigator Bias	*Quality*	Participants	Intervention and Expertise	Compliance and Adherence	Analysis	*Applicability Study*
Louthrenoo (2007)	Abdominal pain	12	Diacerein versus Piroxicam	●	◐	○	●	○	●	●	○	**Moderate**	○	○	○	●	**Moderate**
Louthrenoo (2007)	Bowel motility disorders	12	Diacerein versus Piroxicam	●	◐	○	●	○	●	●	○	**Moderate**	○	○	○	●	**Moderate**
Louthrenoo (2007)	Constipation	12	Diacerein versus Piroxicam	●	◐	○	●	○	●	●	○	**Moderate**	○	○	○	●	**Moderate**
Louthrenoo (2007)	Nausea	12	Diacerein versus Piroxicam	●	◐	○	●	○	●	●	○	**Moderate**	○	○	○	●	**Moderate**
Louthrenoo (2007)	Hypertension	12	Diacerein versus Piroxicam	●	◐	○	●	○	●	●	○	**Moderate**	○	○	○	●	**Moderate**
Louthrenoo (2007)	Myalgia	12	Diacerein versus Piroxicam	●	◐	○	●	○	●	●	○	**Moderate**	○	○	○	●	**Moderate**

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◐: Moderate power

Study	*Outcome*	*Week*	*Comparison*	Prospective	Power	Group Assignment	Blinding	Group Comparability	Treatment Integrity	Measurement	Investigator Bias	*Quality*	Participants	Intervention and Expertise	Compliance and Adherence	Analysis	*Applicability Study*
Louthrenoo (2007)	Arthropathy	12	Diacerein versus Piroxicam	●	◐	○	●	○	●	●	○	**Moderate**	○	○	○	●	**Moderate**
Louthrenoo (2007)	Oedema	12	Diacerein versus Piroxicam	●	◐	○	●	○	●	●	○	**Moderate**	○	○	○	●	**Moderate**
Louthrenoo (2007)	Dizziness	12	Diacerein versus Piroxicam	●	◐	○	●	○	●	●	○	**Moderate**	○	○	○	●	**Moderate**
Pavelka (2007)	WOMAC Function	8	Diacerein versus Placebo	●	○	○	●	●	●	●	○	**Moderate**	○	○	●	●	**Moderate**
Pavelka (2007)	WOMAC Function	16	Diacerein versus Placebo	●	●	○	●	●	●	●	○	**Moderate**	○	○	●	●	**Moderate**
Pavelka (2007)	WOMAC Function	20	Diacerein versus Placebo	●	●	○	●	●	●	●	○	**Moderate**	○	○	●	●	**Moderate**

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Study	*Outcome*	*Week*	*Comparison*	Prospective	Power	Group Assignment	Blinding	Group Comparability	Treatment Integrity	Measurement	Investigator Bias	*Quality*	Participants	Intervention and Expertise	Compliance and Adherence	Analysis	*Applicability Study*
Pavelka (2007)	WOMAC Function	24	Diacerein versus Placebo	●	●	○	●	●	●	●	○	**Moderate**	○	○	●	●	**Moderate**
Pavelka (2007)	WOMAC Pain	8	Diacerein versus Placebo	●	○	○	●	●	●	●	○	**Moderate**	○	○	●	●	**Moderate**
Pavelka (2007)	WOMAC Pain	12	Diacerein versus Placebo	●	●	○	●	●	●	●	○	**Moderate**	○	○	●	●	**Moderate**
Pavelka (2007)	WOMAC Pain	16	Diacerein versus Placebo	●	●	○	●	●	●	●	○	**Moderate**	○	○	●	●	**Moderate**
Pavelka (2007)	WOMAC Pain	20	Diacerein versus Placebo	●	●	○	●	●	●	●	○	**Moderate**	○	○	●	●	**Moderate**
Pavelka (2007)	WOMAC Pain	24	Diacerein versus Placebo	●	●	○	●	●	●	●	○	**Moderate**	○	○	●	●	**Moderate**

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Study	*Outcome*	*Week*	*Comparison*	Prospective	Power	Group Assignment	Blinding	Group Comparability	Treatment Integrity	Measurement	Investigator Bias	*Quality*	Participants	Intervention and Expertise	Compliance and Adherence	Analysis	*Applicability Study*
Pavelka (2007)	WOMAC Stiffness	4	Diacerein versus Placebo	●	●	○	●	●	●	●	○	**Moderate**	○	○	●	●	**Moderate**
Pavelka (2007)	WOMAC Stiffness	8	Diacerein versus Placebo	●	●	○	●	●	●	●	○	**Moderate**	○	○	●	●	**Moderate**
Pavelka (2007)	WOMAC Stiffness	16	Diacerein versus Placebo	●	●	○	●	●	●	●	○	**Moderate**	○	○	●	●	**Moderate**
Pavelka (2007)	WOMAC Stiffness	20	Diacerein versus Placebo	●	●	○	●	●	●	●	○	**Moderate**	○	○	●	●	**Moderate**
Pavelka (2007)	WOMAC Stiffness	24	Diacerein versus Placebo	●	●	○	●	●	●	●	○	**Moderate**	○	○	●	●	**Moderate**
Pavelka (2007)	Paracetamol intake pills per day	4	Diacerein versus Placebo	●	●	○	●	●	●	●	○	**Moderate**	○	○	●	●	**Moderate**

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Study	*Outcome*	*Week*	*Comparison*	Prospective	Power	Group Assignment	Blinding	Group Comparability	Treatment Integrity	Measurement	Investigator Bias	*Quality*	Participants	Intervention and Expertise	Compliance and Adherence	Analysis	*Applicability Study*
Pavelka (2007)	Paracetamol intake pills per day	8	Diacerein versus Placebo	●	●	○	●	●	●	●	○	**Moderate**	○	○	●	●	**Moderate**
Pavelka (2007)	Paracetamol intake pills per day	12	Diacerein versus Placebo	●	●	○	●	●	●	●	○	**Moderate**	○	○	●	●	**Moderate**
Pavelka (2007)	Paracetamol intake pills per day	16	Diacerein versus Placebo	●	●	○	●	●	●	●	○	**Moderate**	○	○	●	●	**Moderate**
Pavelka (2007)	Paracetamol intake pills per day	20	Diacerein versus Placebo	●	●	○	●	●	●	●	○	**Moderate**	○	○	●	●	**Moderate**
Pavelka (2007)	Paracetamol intake pills per day	24	Diacerein versus Placebo	●	●	○	●	●	●	●	○	**Moderate**	○	○	●	●	**Moderate**
Pavelka (2007)	WOMAC Total	4	Diacerein versus Placebo	●	●	○	●	●	●	●	○	**Moderate**	○	○	●	●	**Moderate**

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○: Domain flaws present
◐: Moderate power

Study	*Outcome*	*Week*	*Comparison*	**Prospective**	**Power**	**Group Assignment**	**Blinding**	**Group Comparability**	**Treatment Integrity**	**Measurement**	**Investigator Bias**	*Quality*	**Participants**	**Intervention and Expertise**	**Compliance and Adherence**	**Analysis**	*Applicability Study*
Pavelka (2007)	WOMAC Total	8	Diacerein versus Placebo	●	○	○	●	●	●	●	○	**Moderate**	○	○	●	●	**Moderate**
Pavelka (2007)	WOMAC Total	16	Diacerein versus Placebo	●	●	○	●	●	●	●	○	**Moderate**	○	○	●	●	**Moderate**
Pavelka (2007)	WOMAC Total	20	Diacerein versus Placebo	●	●	○	●	●	●	●	○	**Moderate**	○	○	●	●	**Moderate**
Pavelka (2007)	WOMAC Total	24	Diacerein versus Placebo	●	●	○	●	●	●	●	○	**Moderate**	○	○	●	●	**Moderate**
Zheng (2006)	VAS Pain on walking improvement	12	Diacerein versus Diclofenac	●	●	○	●	●	●	●	○	**Moderate**	○	○	●	●	**Moderate**

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○: Domain flaws present
◐: Moderate power

Study	*Outcome*	*Week*	*Comparison*	Prospective	Power	Group Assignment	Blinding	Group Comparability	Treatment Integrity	Measurement	Investigator Bias	*Quality*	Participants	Intervention and Expertise	Compliance and Adherence	Analysis	*Applicability Study*
Zheng (2006)	VAS Pain on walking	12 to 16	Diacerein versus Diclofenac	●	●	○	●	●	●	●	○	**Moderate**	○	○	●	●	**Moderate**
Zheng (2006)	WOMAC Total VAS improvement	12	Diacerein versus Diclofenac	●	●	○	●	●	●	●	○	**Moderate**	○	○	●	●	**Moderate**
Zheng (2006)	WOMAC Total	12 to 16	Diacerein versus Diclofenac	●	●	○	●	●	●	●	○	**Moderate**	○	○	●	●	**Moderate**
Zheng (2006)	Pain on walking	4	Diacerein versus Diclofenac	●	●	○	●	●	●	●	○	**Moderate**	○	○	●	○	**Moderate**
Zheng (2006)	Pain on walking	8	Diacerein versus Diclofenac	●	●	○	●	●	●	●	○	**Moderate**	○	○	●	○	**Moderate**

●: Domain free of flaws
○: Domain flaws present
◐: Moderate power

Study	*Outcome*	*Week*	*Comparison*	Prospective	Power	Group Assignment	Blinding	Group Comparability	Treatment Integrity	Measurement	Investigator Bias	*Quality*	Participants	Intervention and Expertise	Compliance and Adherence	Analysis	*Applicability Study*
Zheng (2006)	Pain on walking	12	Diacerein versus Diclofenac	●	●	○	●	●	●	●	○	**Moderate**	○	○	●	○	**Moderate**
Zheng (2006)	Pain on walking	16	Diacerein versus Diclofenac	●	●	○	●	●	●	●	○	**Moderate**	○	○	●	○	**Moderate**
Zheng (2006)	WOMAC Total	4	Diacerein versus Diclofenac	●	●	○	●	●	●	●	○	**Moderate**	○	○	●	○	**Moderate**
Zheng (2006)	WOMAC Total	8	Diacerein versus Diclofenac	●	●	○	●	●	●	●	○	**Moderate**	○	○	●	○	**Moderate**
Zheng (2006)	WOMAC Total	12	Diacerein versus Diclofenac	●	●	○	●	●	●	●	○	**Moderate**	○	○	●	○	**Moderate**
Zheng (2006)	WOMAC Total	16	Diacerein versus Diclofenac	●	●	○	●	●	●	●	○	**Moderate**	○	○	●	○	**Moderate**

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○: Domain flaws present
◐: Moderate power

Study	*Outcome*	*Week*	*Comparison*	Prospective	Power	Group Assignment	Blinding	Group Comparability	Treatment Integrity	Measurement	Investigator Bias	*Quality*	Participants	Intervention and Expertise	Compliance and Adherence	Analysis	*Applicability Study*
Zheng (2006)	Adverse events	16	Diacerein versus Diclofenac	●	◐	○	●	●	●	●	○	**Moderate**	○	○	●	○	**Moderate**
Zheng (2006)	GI adverse events	16	Diacerein versus Diclofenac	●	◐	○	●	●	●	●	○	**Moderate**	○	○	●	○	**Moderate**
Louthrenoo (2007)	WOMAC Function	4	Diacerein versus Piroxicam	●	●	○	●	○	●	●	○	**Moderate**	○	○	○	●	**Moderate**
Louthrenoo (2007)	WOMAC Function	8	Diacerein versus Piroxicam	●	●	○	●	○	●	●	○	**Moderate**	○	○	○	●	**Moderate**
Louthrenoo (2007)	WOMAC Function	12	Diacerein versus Piroxicam	●	●	○	●	○	●	●	○	**Moderate**	○	○	○	●	**Moderate**

Table 153. Quality and Applicability: Tramadol Versus Control

●: Domain free of flaws
○: Domain flaws present
◐: Moderate power

Study	*Outcome*	*Week*	*Comparison*	Prospective	Power	Group Assignment	Blinding	Group Comparability	Treatment Integrity	Measurement	Investigator Bias	*Quality*	Participants	Intervention and Expertise	Compliance and Adherence	Analysis	*Applicability Study*
Babul (2004)	WOMAC Function	12	Tramadol ER versus Placebo	●	●	○	●	○	●	●	○	**Moderate**	○	○	●	●	**Moderate**
Babul (2004)	Patients' global	12	Tramadol ER versus Placebo	●	●	○	●	○	●	●	○	**Moderate**	○	○	●	●	**Moderate**
Babul (2004)	VAS	12	Tramadol ER versus Placebo	●	●	○	●	○	●	●	○	**Moderate**	○	○	●	●	**Moderate**
Babul (2004)	WOMAC Pain	12	Tramadol ER versus Placebo	●	●	○	●	○	●	●	○	**Moderate**	○	○	●	●	**Moderate**
Babul (2004)	WOMAC Stiffness	12	Tramadol ER versus Placebo	●	●	○	●	○	●	●	○	**Moderate**	○	○	●	●	**Moderate**

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Study	*Outcome*	*Week*	*Comparison*	Prospective	Power	Group Assignment	Blinding	Group Comparability	Treatment Integrity	Measurement	Investigator Bias	*Quality*	Participants	Intervention and Expertise	Compliance and Adherence	Analysis	*Applicability Study*
Beaulieu (2008)	WOMAC Stiffness	6	CR Tramadol versus SR Diclofenac	●	○	○	●	○	●	●	○	**Moderate**	○	○	●	●	**Moderate**
Beaulieu (2008)	WOMAC Function	6	CR Tramadol versus SR Diclofenac	●	○	○	●	○	●	●	○	**Moderate**	○	○	●	●	**Moderate**
Beaulieu (2008)	Mean change in WOMAC Pain	6	Tramadol versus Diclofenac	●	○	○	●	○	●	●	○	**Moderate**	○	○	●	●	**Moderate**
Burch (2007)	Improvement in pain intensity numerical rating scale	12	Tramadol Contramid OAD versus Placebo	●	●	○	●	○	●	●	○	**Moderate**	○	○	●	●	**Moderate**

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Study	*Outcome*	*Week*	*Comparison*	Prospective	Power	Group Assignment	Blinding	Group Comparability	Treatment Integrity	Measurement	Investigator Bias	*Quality*	Participants	Intervention and Expertise	Compliance and Adherence	Analysis	*Applicability Study*
Fishman (2007)	WOMAC Pain, percent improvement from baseline	12	Tramadol Contramid versus Placebo	●	◐	●	●	●	●	●	○	**High**	○	○	●	●	**Moderate**
Fishman (2007)	WOMAC Pain, percent improvement from baseline	12	Tramadol Contramid versus Placebo	●	◐	●	●	●	●	●	○	**High**	○	○	●	●	**Moderate**

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○: Domain flaws present
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Study	*Outcome*	*Week*	*Comparison*	Prospective	Power	Group Assignment	Blinding	Group Comparability	Treatment Integrity	Measurement	Investigator Bias	*Quality*	Participants	Intervention and Expertise	Compliance and Adherence	Analysis	*Applicability Study*
Fishman (2007)	WOMAC Pain, percent improvement from baseline	12	Tramadol Contramid versus Placebo	●	●	●	●	●	●	●	○	**High**	○	○	●	●	**Moderate**
Fishman (2007)	WOMAC Pain, percent improvement from baseline	12	Tramadol Contramid 100mg versus Tramadol Contramid 200mg	●	◐	●	●	●	●	●	○	**High**	○	○	●	●	**Moderate**

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◐: Moderate power

Study	*Outcome*	*Week*	*Comparison*	Prospective	Power	Group Assignment	Blinding	Group Comparability	Treatment Integrity	Measurement	Investigator Bias	*Quality*	Participants	Intervention and Expertise	Compliance and Adherence	Analysis	*Applicability Study*
Fishman (2007)	WOMAC Pain, percent improvement from baseline	12	Tramadol Contramid 100mg versus Tramadol Contramid 300mg	●	◐	●	●	●	●	●	○	**High**	○	○	●	●	**Moderate**
Fishman (2007)	WOMAC Pain, percent improvement from baseline	12	Tramadol Contramid 200mg versus Tramadol Contramid 300mg	●	◐	●	●	●	●	●	○	**High**	○	○	●	●	**Moderate**
Fleischmann (2001)	WOMAC Function	13	Tramadol versus Placebo	●	●	●	●	●	●	●	○	**High**	○	○	●	●	**Moderate**

●: Domain free of flaws
○: Domain flaws present
◐: Moderate power

Study	*Outcome*	*Week*	*Comparison*	Prospective	Power	Group Assignment	Blinding	Group Comparability	Treatment Integrity	Measurement	Investigator Bias	*Quality*	Participants	Intervention and Expertise	Compliance and Adherence	Analysis	*Applicability Study*
Fleischmann (2001)	WOMAC Pain	13	Tramadol versus Placebo	●	●	●	●	●	●	●	○	**High**	○	○	●	●	**Moderate**
Fleischmann (2001)	WOMAC Stiffness	13	Tramadol versus Placebo	●	●	●	●	●	●	●	○	**High**	○	○	●	●	**Moderate**
Schnitzer (1999)	Minimum effective Naproxen dose	8	Tramadol versus Placebo	●	◐	○	●	○	●	●	○	**Moderate**	○	○	●	●	**Moderate**

Table 154. Quality and Applicability: Orgotein Versus Control

●: Domain free of flaws

○: Domain flaws present

◐: Moderate power

Study	*Outcome*	*Week*	*Comparison*	Prospective	Power	Group Assignment	Blinding	Group Comparability	Treatment Integrity	Measurement	Investigator Bias	*Quality*	Participants	Intervention and Expertise	Compliance and Adherence	Analysis	*Applicability Study*
McIlwain (1989)	Patient Assessment of Treatment Response	12	Orgotein 8mg x3 versus Orgotein 16 mg x 3	●	◐	○	●	●	●	●	○	**Moderate**	○	○	○	●	**Moderate**

FINDINGS

Table 155. Cox-2s Versus Placebo

Type	Study	Outcome	N	Sufficient Power	Week	Group 1	Group 2	Effect Size	Lower CI	Upper CI	Favors (NS=Not Significant)	Clinical Significance
	Fleischmann (2006)	WOMAC Function	693	Yes	13	Lumiracoxib	Placebo	-0.48571	-0.64572	-0.3257	Lumiracoxib	Possibly clinically significant
	Fleischmann (2006)	WOMAC Function	694	Yes	13	Lumiracoxib	Placebo	-0.46178	-0.62153	-0.30203	Lumiracoxib	Possibly clinically significant
	Tannenbaum (2004)	WOMAC Function	724	Yes	13	Celecoxib	Placebo	-0.25686	-0.41168	-0.10203	Celecoxib	Possibly clinically significant
	Tannenbaum (2004)	WOMAC Function	730	Yes	13	Lumiracoxib	Placebo	-0.29966	-0.45437	-0.14496	Lumiracoxib	Possibly clinically significant
	Tannenbaum (2004)	WOMAC Function	734	Yes	13	Lumiracoxib	Placebo	-0.28331	-0.43772	-0.1289	Lumiracoxib	Possibly clinically significant
	Gibofsky (2003)	WOMAC Function	285	Yes	6	Celecoxib	Placebo	-0.48333	-0.7322	-0.23446	Celecoxib	Possibly clinically significant
	Gibofsky (2003)	WOMAC Function	286	Yes	6	Rofecoxib	Placebo	-0.40069	-0.64833	-0.15305	Rofecoxib	Possibly clinically significant
	Mckenna (2001)	WOMAC Function	399	Yes	6	Celecoxib	Placebo	-0.39924	-0.59745	-0.20104	Celecoxib	Possibly clinically significant

	Williams (2000)	WOMAC Function	453	No	6	Celecoxib 200mg QD	Placebo	0.004811	-0.1794	0.189022	NS	True negative
	Ehrich (1999)	WOMAC Function	145	No	6	Rofecoxib	Placebo	-1.11169	-1.46213	-0.76126	Rofecoxib	Clinically significant
Lequesne index	Williams (2001)	Lequesne index	484	Unclear	6	Celecoxib	Placebo	-43.2659	-46.0084	-40.5234	Celecoxib	Unclear
	Williams (2001)	Lequesne index	474	Unclear	6	Celecoxib	Placebo	-37.7525	-40.1724	-35.3325	Celecoxib	Unclear
	Williams (2000)	Lequesne index	462	Unclear	6	Celecoxib 100mg BID	Placebo	-0.32841	-0.51202	-0.1448	Celecoxib 100mg BID	Unclear
	Williams (2000)	Lequesne index	453	Unclear	6	Celecoxib 200mg QD	Placebo	-0.39366	-0.57966	-0.20766	Celecoxib 200mg QD	Unclear
	Fleischmann (2006)	VAS Pain improvement	693	Yes	13	Lumiracoxib	Placebo	-0.26685	-0.42542	-0.10828	Lumiracoxib	Not clinically significant
	Fleischmann (2006)	VAS Pain improvement	694	Yes	13	Lumiracoxib	Placebo	-0.31161	-0.47035	-0.15288	Lumiracoxib	Not clinically significant
	Fleischmann (2006)	WOMAC Pain	693	Yes	13	Lumiracoxib	Placebo	-0.34431	-0.50329	-0.18533	Lumiracoxib	Possibly clinically significant
	Fleischmann (2006)	WOMAC Pain	694	Yes	13	Lumiracoxib	Placebo	-0.3443	-0.50322	-0.18538	Lumiracoxib	Possibly clinically significant
	Fleischmann (2006)	VAS Pain improvement	675	Yes	13	Celecoxib	Placebo	-0.22358	-0.38303	-0.06413	Celecoxib	Not clinically significant
	Fleischmann (2006)	WOMAC Pain	675	Yes	13	Celecoxib	Placebo	-0.29674	-0.45653	-0.13695	Celecoxib	Possibly clinically significant

	Tannenbaum (2004)	VAS Pain improvement	724	Yes	13	Celecoxib	Placebo	-0.21425	-0.3689	-0.0596	Celecoxib	Not clinically significant
	Tannenbaum (2004)	VAS Pain improvement	730	Yes	13	Lumiracoxib	Placebo	-0.18623	-0.34046	-0.03199	Lumiracoxib	Not clinically significant
	Tannenbaum (2004)	VAS Pain improvement	734	Yes	13	Lumiracoxib	Placebo	-0.3032	-0.45771	-0.14869	Lumiracoxib	Not clinically significant
	Tannenbaum (2004)	WOMAC Pain	724	Yes	13	Celecoxib	Placebo	-0.18402	-0.33857	-0.02947	Celecoxib	Not clinically significant
	Tannenbaum (2004)	WOMAC Pain	730	Yes	13	Lumiracoxib	Placebo	-0.19301	-0.34727	-0.03876	Lumiracoxib	Not clinically significant
	Tannenbaum (2004)	WOMAC Pain	734	Yes	13	Lumiracoxib	Placebo	-0.21031	-0.36442	-0.0562	Lumiracoxib	Not clinically significant
	Gibofsky (2003)	VAS Pain on walking improvement	285	Yes	6	Celecoxib	Placebo	-0.39492	-0.64272	-0.14712	Celecoxib	Not clinically significant
	Gibofsky (2003)	VAS Pain on walking improvement	286	Yes	6	Rofecoxib	Placebo	-0.32077	-0.56762	-0.07392	Rofecoxib	Not clinically significant

	Lehmann (2005)	VAS Pain improvement	844	Yes	13	Lumiracoxib (Cox-2) with loading dose	Placebo	-0.19962	-0.33488	-0.06435	Lumiracoxib (Cox-2) with loading dose	Not clinically significant
	Lehmann (2005)	WOMAC Pain	844	Yes	13	Lumiracoxib (Cox-2) with loading dose	Placebo	-0.17771	-0.31291	-0.04251	Lumiracoxib (Cox-2) with loading dose	Not clinically significant
	Gibofsky (2003)	WOMAC Pain	286	Yes	6	Rofecoxib	Placebo	-0.49078	-0.73953	-0.24204	Rofecoxib	Possibly clinically significant
	Lehmann (2005)	VAS Pain improvement	844	Yes	13	Celecoxib	Placebo	-0.21819	-0.35352	-0.08286	Celecoxib	Not clinically significant
	Lehmann (2005)	VAS Pain improvement	844	Yes	13	Lumiracoxib	Placebo	-0.22578	-0.36115	-0.09042	Lumiracoxib	Not clinically significant
	Lehmann (2005)	WOMAC Pain	844	Yes	13	Celecoxib	Placebo	-0.23041	-0.36579	-0.09503	Celecoxib	Not clinically significant
	Lehmann (2005)	WOMAC Pain	844	Yes	13	Lumiracoxib	Placebo	-0.22332	-0.35867	-0.08796	Lumiracoxib	Not clinically significant
	Gibofsky (2003)	WOMAC Pain	285	Yes	6	Celecoxib	Placebo	-0.51629	-0.76562	-0.26697	Celecoxib	Possibly clinically significant
	Kivits (2002)	VAS Pain improvement	406	Yes	6	Valdecoxib	Placebo	-0.24767	-0.44297	-0.05237	Valdecoxib	Not clinically significant
	Kivits (2002)	VAS Pain improvement	410	Yes	6	Valdecoxib	Placebo	-0.21281	-0.40695	-0.01867	Valdecoxib	Not clinically significant

	Kivits (2002)	VAS Pain improvement	406	Yes	6	Valdecoxib	Placebo	-0.29993	-0.49558	-0.10428	Valdecoxib	Not clinically significant
	Kivits (2002)	VAS Pain improvement	406	Yes	12	Valdecoxib	Placebo	-0.18084	-0.37579	0.014117	NS	True negative
	Kivits (2002)	VAS Pain improvement	410	Yes	12	Valdecoxib	Placebo	-0.18939	-0.38342	0.004641	NS	True negative
	Kivits (2002)	VAS Pain improvement	406	Yes	12	Valdecoxib	Placebo	-0.28608	-0.48164	-0.09053	Valdecoxib	Not clinically significant
	Mckenna (2001)	VAS Pain improvement	399	Yes	6	Celecoxib	Placebo	-0.41988	-0.6183	-0.22147	Celecoxib	Not clinically significant
	Mckenna (2001)	WOMAC Pain	399	Yes	6	Celecoxib	Placebo	-0.38937	-0.58748	-0.19125	Celecoxib	Possibly clinically significant
	Ehrich (1999)	WOMAC Pain	145	No	6	Rofecoxib	Placebo	-1.0773	-1.42626	-0.72833	Rofecoxib	Clinically significant
	Ehrich (1999)	VAS Pain improvement	145	Yes	6	Rofecoxib	Placebo	-1.12278	-1.4737	-0.77187	Rofecoxib	Possibly clinically significant
	Ehrich (1999)	VAS Pain improvement	145	Yes	6	Rofecoxib	Placebo	-0.96188	-1.30623	-0.61754	Rofecoxib	Possibly clinically significant
WOMAC Stiffness	Fleischmann (2006)	WOMAC Stiffness	693	Yes	13	Lumiracoxib	Placebo	-0.36238	-0.52148	-0.20329	Lumiracoxib	Possibly clinically significant

	Fleischmann (2006)	WOMAC Stiffness	694	Yes	13	Lumiracoxib	Placebo	-0.27036	-0.42889	-0.11184	Lumiracoxib	Possibly clinically significant
	Tannenbaum (2004)	WOMAC Stiffness	724	Yes	13	Celecoxib	Placebo	-0.17976	-0.3343	-0.02523	Celecoxib	Not clinically significant
	Tannenbaum (2004)	WOMAC Stiffness	730	Yes	13	Lumiracoxib	Placebo	-0.17263	-0.32682	-0.01843	Lumiracoxib	Not clinically significant
	Tannenbaum (2004)	WOMAC Stiffness	734	Yes	13	Lumiracoxib	Placebo	0	-0.15373	0.153728	NS	True negative
	Gibofsky (2003)	WOMAC Stiffness	285	Yes	6	Celecoxib	Placebo	-4.92792	-5.40363	-4.45221	Celecoxib	Clinically significant
	Gibofsky (2003)	WOMAC Stiffness	286	Yes	6	Rofecoxib	Placebo	-4.22771	-4.65426	-3.80116	Rofecoxib	Clinically significant
	Kivits (2002)	WOMAC Stiffness	406	Yes	6	Valdecoxib	Placebo	-0.12676	-0.32151	0.067988	NS	True negative
	Kivits (2002)	WOMAC Stiffness	410	Yes	6	Valdecoxib	Placebo	-0.23077	-0.42501	-0.03653	Valdecoxib	Possibly clinically significant
	Kivits (2002)	WOMAC Stiffness	406	Yes	6	Valdecoxib	Placebo	-0.23541	-0.43064	-0.04018	Valdecoxib	Possibly clinically significant
	Kivits (2002)	WOMAC Stiffness	406	Yes	12	Valdecoxib	Placebo	-0.11881	-0.31353	0.075918	NS	True negative
	Kivits (2002)	WOMAC Stiffness	410	Yes	12	Valdecoxib	Placebo	-0.16668	-0.36061	0.027253	NS	True negative
	Kivits (2002)	WOMAC Stiffness	406	Yes	12	Valdecoxib	Placebo	-0.1964	-0.39143	-0.00137	Valdecoxib	Possibly clinically significant

	Mckenna (2001)	WOMAC Stiffness	399	Yes	6	Celecoxib	Placebo	-0.39911	-0.59732	-0.2009	Celecoxib	Possibly clinically significant
	Ehrich (1999)	WOMAC Stiffness	145	No	6	Rofecoxib	Placebo	-1.09593	-1.44569	-0.74617	Rofecoxib	Clinically significant
WOMAC Total	Fleischmann (2006)	WOMAC Total	693	Yes	13	Lumiracoxib	Placebo	-0.47107	-0.63096	-0.31119	Lumiracoxib	Possibly clinically significant
	Fleischmann (2006)	WOMAC Total	694	Yes	13	Lumiracoxib	Placebo	-0.45161	-0.61127	-0.29194	Lumiracoxib	Possibly clinically significant
	Schnitzer (2010)	WOMAC Total	343	Yes	13	Naproxcinod	Placebo	-0.30757	-0.52305	-0.09209	Naproxcinod	Possibly clinically significant
	Schnitzer (2010)	WOMAC Total	333	Yes	13	Naproxcinod	Placebo	-0.35554	-0.57386	-0.13722	Naproxcinod	Possibly clinically significant
	Tannenbaum (2004)	WOMAC Total	724	Yes	13	Celecoxib	Placebo	-0.25129	-0.40609	-0.09649	Celecoxib	Possibly clinically significant
	Tannenbaum (2004)	WOMAC Total	730	Yes	13	Lumiracoxib	Placebo	-0.28334	-0.43797	-0.12872	Lumiracoxib	Possibly clinically significant
	Tannenbaum (2004)	WOMAC Total	734	Yes	13	Lumiracoxib	Placebo	-0.28217	-0.43657	-0.12776	Lumiracoxib	Possibly clinically significant
	Lehmann (2005)	WOMAC Total	844	Yes	13	Lumiracoxib	Placebo	-0.22095	-0.3563	-0.08561	Lumiracoxib	Not clinically significant

	Lehmann (2005)	WOMAC Total	844	Yes	13	Lumiracoxib	Placebo	-0.20165	-0.33693	-0.06638	Lumiracoxib	Not clinically significant
	Kivits (2002)	WOMAC Total	406	Yes	12	Valdecoxib	Placebo	-0.17728	-0.37222	0.017656	NS	True negative
	Kivits (2002)	WOMAC Total	410	Yes	12	Valdecoxib	Placebo	-0.20345	-0.39754	-0.00935	Valdecoxib	Not clinically significant
	Kivits (2002)	WOMAC Total	406	Yes	12	Valdecoxib	Placebo	-0.19789	-0.39292	-0.00286	Valdecoxib	Not clinically significant
	Kivits (2002)	WOMAC Total	406	Yes	6	Valdecoxib	Placebo	-0.13774	-0.33253	0.057042	NS	True negative
	Kivits (2002)	WOMAC Total	410	Yes	6	Valdecoxib	Placebo	-0.2076	-0.40172	-0.01348	Valdecoxib	Possibly clinically significant
	Kivits (2002)	WOMAC Total	406	Yes	6	Valdecoxib	Placebo	-0.24111	-0.43638	-0.04585	Valdecoxib	Possibly clinically significant
	Williams (2001)	WOMAC Total	484	Yes	6	Celecoxib	Placebo	-5.10879	-5.47781	-4.73978	Celecoxib	Clinically significant
	Williams (2001)	WOMAC Total	474	Yes	6	Celecoxib	Placebo	-5.59231	-5.9926	-5.19203	Celecoxib	Clinically significant
	Mckenna (2001)	WOMAC Total	399	Yes	6	Celecoxib	Placebo	-0.41279	-0.61113	-0.21445	Celecoxib	Possibly clinically significant
Global Assessment	Williams (2000)	Patient Global Assessment	453	Yes	6	Celecoxib 200mg	Placebo	-0.33159	-0.51707	-0.14611	Celecoxib 200mg	Not clinically significant

	Fleischmann (2006)	Patient Global Assessment	694	Yes	13	Lumiracoxib 400mg	Placebo	-0.34539	-0.50432	-0.18646	Lumiracoxib 400mg	Not clinically significant
	Fleischmann (2006)	Patient Global Assessment	693	Yes	13	Lumiracoxib 200mg	Placebo	-0.32586	-0.48473	-0.16699	Lumiracoxib 200mg	Not clinically significant
	Mckenna (2001)	Patient Global Assessment	399	Yes	6	Celecoxib	Placebo	-0.4335	-0.63206	-0.23495	Celecoxib	Not clinically significant
	Williams (2000)	Patient Global Assessment	462	Yes	6	Celecoxib 100mg	Placebo	-0.32841	-0.51202	-0.1448	Celecoxib 100mg	Not clinically significant
	Williams (2001)	Patient Global Assessment	484	Yes	6	Celecoxib 100mg	Placebo	-3.06211	-3.32529	-2.79893	Celecoxib 100mg	Clinically significant
	Williams (2001)	Patient Global Assessment	474	Yes	6	Celecoxib 200mg	Placebo	-6.11409	-6.54443	-5.68376	Celecoxib 200mg	Clinically significant
	Gibofsky (2003)	Patient Global Assessment	285	Yes	6	Celecoxib 200mg	Placebo	OR=2.50	1.47	4.26	Celecoxib 200mg	Clinically significant

	Gibofsky (2003)	Patient Global Assessment	286	Yes	6	Rofecoxib 25mg	Placebo	OR=2.04	1.2	3.49	Rofecoxib 25mg	Clinically significant
	Fleischmann (2006)	Physician Global Assessment	675	Yes	13	Celecoxib (Cox-2)	Placebo	-0.25204	-0.41161	-0.09247	Celecoxib (Cox-2)	Unclear
	Fleischmann (2006)	Physician Global Assessment	693	Yes	13	Lumiracoxib 200mg	Placebo	-0.35846	-0.51753	-0.1994	Lumiracoxib 200mg	Unclear
	Fleischmann (2006)	Physician Global Assessment	694	Yes	13	Lumiracoxib 400mg	Placebo	-0.34115	-0.50005	-0.18224	Lumiracoxib 400mg	Unclear
	Kivits (2002)	Physician Global Assessment	410	Yes	6	Valdecoxib 10mg (Cox-2)	Placebo	-0.2834	-0.47797	-0.08883	Valdecoxib 10mg (Cox-2)	Unclear
	Kivits (2002)	Physician Global Assessment	410	Yes	12	Valdecoxib 10mg (Cox-2)	Placebo	-0.28799	-0.48259	-0.09338	Valdecoxib 10mg (Cox-2)	Unclear
	Kivits (2002)	Physician Global Assessment	406	Unclear	6	Valdecoxib 20mg (Cox-2)	Placebo	-0.19324	-0.38825	0.001769	NS	Unclear

	Kivits (2002)	Physician Global Assessment	406	Yes	12	Valdecoxib 20mg (Cox-2)	Placebo	-0.22194	-0.4171	-0.02679	Valdecoxib 20mg (Cox-2)	Unclear
	Kivits (2002)	Physician Global Assessment	406	Yes	6	Valdecoxib 5mg (Cox-2)	Placebo	-0.22375	-0.41892	-0.02859	Valdecoxib 5mg (Cox-2)	Unclear
	Kivits (2002)	Physician Global Assessment	406	Yes	12	Valdecoxib 5mg (Cox-2)	Placebo	-0.19912	-0.39416	-0.00408	Valdecoxib 5mg (Cox-2)	Unclear
	Mckenna (2001)	Physician Global Assessment	399	Yes	6	Celecoxib (Cox-2)	Placebo	-0.3884	-0.5865	-0.19029	Celecoxib (Cox-2)	Unclear
	Williams (2001)	Physician Global Assessment	484	Yes	6	Celecoxib 100mg	Placebo	-4.99222	-5.35479	-4.62964	Celecoxib 100mg	Unclear
	Williams (2001)	Physician Global Assessment	474	Yes	6	Celecoxib 200mg	Placebo	-6.65607	-7.1181	-6.19404	Celecoxib 200mg	Unclear
	Gibofsky (2003)	Physician Global Assessment	285	Yes	6	Celecoxib 200mg	Placebo	OR=1.99	1.19	3.33	Celecoxib 200mg	Unclear

	Gibofsky (2003)	Physician Global Assessment	286	Unclear	6	Rofecoxib 25mg	Placebo	OR=1.59	0.95	2.66	NS	Unclear
	Lehmann (2005)	Patient Global Assessment of Disease	844	Yes	13	Celecoxib	Placebo	-0.1617	-0.29685	-0.02655	Celecoxib	Unclear
	Lehmann (2005)	Patient Global Assessment of Disease	844	Yes	13	Lumiracoxib	Placebo	-0.25402	-0.3895	-0.11855	Lumiracoxib	Unclear
	Tannenbaum (2004)	Patient Global Assessment of Disease	724	Yes	13	Celecoxib 200mg	Placebo	-0.25907	-0.41391	-0.10424	Celecoxib 200mg	Unclear
	Tannenbaum (2004)	Patient Global Assessment of Disease	730	Yes	13	Lumiracoxib 200mg	Placebo	-0.28128	-0.43589	-0.12666	Lumiracoxib 200mg	Unclear
	Tannenbaum (2004)	Patient Global Assessment of Disease	734	Yes	13	Lumiracoxib 400mg	Placebo	-0.33077	-0.48544	-0.17611	Lumiracoxib 400mg	Unclear

	Ehrich (1999)	Patient Global Assessment of Disease	145	Yes	6	Rofecoxib 125mg	Placebo	-1.21037	-1.56523	-0.85551	Rofecoxib 125mg	Unclear
	Ehrich (1999)	Patient Global Assessment of Disease	145	Yes	6	Rofecoxib 25mg	Placebo	-1.03651	-1.38379	-0.68923	Rofecoxib 25mg	Unclear
	Schnitzer (2005)	Patient Global Assessment of Disease	202	yes	6	Rofecoxib 25mg	Placebo	OR=2.74	1.55	4.85	Rofecoxib 25mg	Unclear
	Ehrich (1999)	Physician Global Assessment of Disease	145	Yes	6	Rofecoxib 125mg	Placebo	-1.24218	-1.59853	-0.88583	Rofecoxib 125mg	Unclear
	Ehrich (1999)	Physician Global Assessment of Disease	145	Yes	6	Rofecoxib 25mg	Placebo	-1.04206	-1.38957	-0.69455	Rofecoxib 25mg	Unclear
	Lehmann (2005)	Physician Global Assessment of Disease	844	Yes	13	Celecoxib 200mg	Placebo	-0.22744	-0.36281	-0.09208	Celecoxib 200mg	Unclear

	Lehmann (2005)	Physician Global Assessment of Disease	844	Yes	13	Lumiracoxib 100mg	Placebo	-0.26683	-0.40236	-0.1313	Lumiracoxib 100mg	Unclear
	Tannenbaum	Physician Global Assessment of Disease	724	Yes	13	Celecoxib 200mg	Placebo	-0.19281	-0.34739	-0.03823	Celecoxib 200mg	Unclear
	Tannenbaum	Physician Global Assessment of Disease	730	Yes	13	Lumiracoxib 200mg	Placebo	-0.21671	-0.37105	-0.06237	Lumiracoxib 200mg	Unclear
	Tannenbaum	Physician Global Assessment of Disease	734	Yes	13	Lumiracoxib 400mg	Placebo	-0.24974	-0.404	-0.09548	Lumiracoxib 400mg	Unclear
	Ehrich (1999)	Patient Global Assessment of Response to Treatment	145	Yes	6	Rofecoxib 125mg	Placebo	-1.4568	-1.82405	-1.08955	Rofecoxib 125mg	Unclear

	Ehrich (1999)	Patient Global Assessment of Response to Treatment	145	Yes	6	Rofecoxib 25mg	Placebo	-1.21549	-1.57058	-0.86039	Rofecoxib 25mg	Unclear
	Schnitzer (2005)	Patient Global Assessment of Response to Treatment	202	Yes	6	Rofecoxib 25mg	Placebo	OR=	2.458447	8.009691	Rofecoxib 25mg	Unclear
	Kivitz (2004)	Patient Global Assessment of Response to Treatment	625	Yes	6	Rofecoxib	Placebo	OR=	2.346792	4.842109	Rofecoxib 12.5mg	Unclear
	Gibofsky (2003)	Patient Global Assessment of Response to Treatment	285	Yes	6	Celecoxib 200mg	Placebo	OR=1.99	1.19	3.33	Celecoxib 200mg	Unclear

	Gibofsky (2003)	Patient Global Assessment of Response to Treatment	286	Unclear	6	Rofecoxib 25mg	Placebo	OR=1.59	0.95	2.66	NS	Unclear
	Ehrich (1999)	Physician Global Assessment of Response to Treatment	145	Yes	6	Rofecoxib 125mg	Placebo	-1.20414	-1.55871	-0.84957	Rofecoxib 125mg	Unclear
	Ehrich (1999)	Physician Global Assessment of Response to Treatment	145	Yes	6	Rofecoxib 25mg	Placebo	-1.09595	-1.4457	-0.74619	Rofecoxib 25mg	Unclear

Table 156. Cox-2s Versus Cox-2s

Type	Study	Outcome	N	Power	Week	Group 1	Group 2	ES	LCI	UCI	Favors (NS=Not Significant)	Clinical Importance
Function	Gibofsky (2003)	WOMAC Function improvement	379	Yes	6	Celecoxib 200mg	Rofecoxib	-0.14	-0.34	0.06	NS	True negative
	Lehmann (2005)	WOMAC Function improvement	844	Yes	13	Celecoxib 100mg	Lumiracoxib with loading dose	0.01	-0.13	0.14	NS	True negative
	Lehmann (2005)	WOMAC Function improvement	844	Yes	13	Lumiracoxib 100mg	Celecoxib	-0.02	-0.15	0.12	NS	True negative
	Lehmann (2005)	WOMAC Function improvement	844	Yes	13	Lumiracoxib 100mg	Lumiracoxib with loading dose	-0.01	-0.14	0.13	NS	True negative
	Schnitzer (2009)	WOMAC Function	206	No	4	Rofecoxib 12.5mg	Rofecoxib	0.21	-0.07	0.48	NS	Inconclusive
Lequesne index	Williams (2000)	Lequesne index	453	Unclear	6	Celecoxib 200mg	Celecoxib 100mg bid	-0.07	-0.25	0.12	NS	Unclear
	Williams (2001)	Lequesne index	472	Unclear	6	Celecoxib 100mg BID	Celecoxib 200mg qd	0	-0.18	0.18	NS	Unclear

Type	Study	Outcome	N	Power	Week	Group 1	Group 2	ES	LCI	UCI	Favors (NS=Not Significant)	Clinical Importance
Pain	Lehmann (2005)	VAS Pain improvement	844	Yes	13	Celecoxib 100mg	Lumiracoxib with loading dose	-0.02	-0.15	0.12	NS	True negative
	Luyten (2007)	WOMAC Pain	120	Unclear	24	Continuous Celecoxib	Intermittent Celecoxib	Mean difference=0	p>0.05	-	NS	Unclear
	Gibofsky (2003)	VAS Pain on walking improvement	379	Yes	6	Celecoxib 200mg	Rofecoxib	-0.08	-0.28	0.12	NS	True negative
	Gibofsky (2003)	WOMAC Pain improvement	379	Yes	6	Celecoxib 200mg	Rofecoxib	-0.02	-0.23	0.18	NS	True negative
	Lehmann (2005)	WOMAC Pain improvement	844	Yes	13	Celecoxib 100mg	Lumiracoxib with loading dose	-0.05	-0.19	0.08	NS	True negative
	Lehmann (2005)	VAS Pain improvement	844	Yes	13	Lumiracoxib 100mg	Celecoxib	-0.01	-0.14	0.13	NS	True negative

Type	Study	Outcome	N	Power	Week	Group 1	Group 2	ES	LCI	UCI	Favors (NS=Not Significant)	Clinical Importance
	Lehmann (2005)	VAS Pain improvement	844	Yes	13	Lumiracoxib 100mg	Lumiracoxib with loading dose	-0.03	-0.16	0.11	NS	True negative
	Lehmann (2005)	WOMAC Pain improvement	844	Yes	13	Lumiracoxib 100mg	Celecoxib	0	-0.13	0.13	NS	True negative
	Lehmann (2005)	WOMAC Pain improvement	844	Yes	13	Lumiracoxib 100mg	Lumiracoxib with loading dose	-0.05	-0.19	0.08	NS	True negative
	Schnitzer (2009)	WOMAC Pain	209	Yes	4	Rofecoxib 12.5mg	Rofecoxib	0.17	-0.1	0.44	NS	Inconclusive
Stiffness	Gibofsky (2003)	WOMAC Stiffness improvement	379	Yes	6	Celecoxib 200mg	Rofecoxib	-1	-1.21	-0.78	Celecoxib 200mg	Clinically significant
	Lehmann (2005)	WOMAC Stiffness improvement	844	Yes	13	Celecoxib 100mg	Lumiracoxib with loading dose	0	-0.13	0.13	NS	True negative
	Lehmann (2005)	WOMAC Stiffness improvement	844	Yes	13	Lumiracoxib 100mg	Celecoxib	-0.11	-0.25	0.02	NS	True negative

Type	Study	Outcome	N	Power	Week	Group 1	Group 2	ES	LCI	UCI	Favors (NS=Not Significant)	Clinical Importance
	Lehmann (2005)	WOMAC Stiffness improvement	844	Yes	13	Lumiracoxib 100mg	Lumiracoxib with loading dose	-0.11	-0.24	0.03	NS	True negative
	Schnitzer (2009)	WOMAC Stiffness	208	No	4	Rofecoxib 12.5mg	Rofecoxib	0.19	-0.08	0.47	NS	True negative
	Luyten (2007)	WOMAC Stiffness	120	Unclear	24	Continuous Celecoxib	Intermittent Celecoxib	Mean Difference = 0	p>0.05	-	NS	Unclear
WOMAC Total	Williams (2000)	WOMAC Total	453	Yes	6	Celecoxib 200mg	Celecoxib	0.04	-0.14	0.23	NS	True negative
	Williams (2001)	WOMAC Total	472	Yes	6	Celecoxib 100mg BID	Celecoxib 200mg qd	0.46	0.28	0.64	Celecoxib 200mg qd	Possibly clinically significant
	Lehmann (2005)	WOMAC Total	844	Yes	13	Celecoxib 100mg	Lumiracoxib with loading dose	0.01	-0.13	0.14	NS	True negative
	Lehmann (2005)	WOMAC Total	844	Yes	13	Lumiracoxib 100mg	Celecoxib	-0.03	-0.17	0.1	NS	True negative

Type	Study	Outcome	N	Power	Week	Group 1	Group 2	ES	LCI	UCI	Favors (NS=Not Significant)	Clinical Importance
	Lehmann (2005)	WOMAC Total	844	Yes	13	Lumiracoxib 100mg	Lumiracoxib with loading dose	-0.02	-0.16	0.11	NS	True negative
	Luyten (2007)	WOMAC Total	120	Unclear	24	Continuous Celecoxib	Intermittent Celecoxib	Mean Difference = 37	p>0.05	-	NS	Unclear
Global assessment	Williams (2000)	Patient Global Assessment	453	Unclear	6	Celecoxib 200mg	Celecoxib 100mg	0	-0.18	0.18	NS	True negative
	Fleischmann (2006)	Patient Global Assessment	906	Yes	13	Lumiracoxib 200mg	Celecoxib 200mg	-0.03	-0.16	0.1	NS	True negative
	Fleischmann (2006)	Patient Global Assessment	907	Yes	13	Lumiracoxib 400mg	Celecoxib 200mg	-0.05	-0.18	0.08	NS	True negative
	Williams (2000)	Patient Global Assessment	472	Yes	6	Celecoxib 100	Celecoxib 200mg	3.33	3.05	3.61	Celecoxib 200mg	Clinically significant

Type	Study	Outcome	N	Power	Week	Group 1	Group 2	ES	LCI	UCI	Favors (NS=Not Significant)	Clinical Importance
	Fleischmann (2006)	Patient Global Assessment	925	Yes	13	Lumiracoxib 200mg	Lumiracoxib 400mg	0.18	-0.11	0.15	NS	True negative
	Gibofsky (2003)	Patient Global Assessment	379	Unclear	6	Celecoxib 200mg	Rofecoxib 25mg	OR= 1.223	0.816	1.833	NS	Unclear
	Fleischmann (2006)	Physician Global Assessment	906	Yes	13	Lumiracoxib 200mg	Celecoxib 200mg	-0.11	-0.24	0.02	NS	Unclear
	Fleischmann (2006)	Physician Global Assessment	907	Yes	13	Lumiracoxib 400mg	Celecoxib 200mg	-0.09	-0.22	0.04	NS	Unclear
	Fleischmann (2006)	Physician Global Assessment	925	Yes	13	Lumiracoxib 200mg	Lumiracoxib 400mg	-0.02	-0.15	0.11	NS	Unclear
	Williams (2001)	Physician Global Assessment	472	Yes	6	Celecoxib 100mg	Celecoxib 200mg	1.66	1.45	1.87	Celecoxib 200mg	Unclear

Type	Study	Outcome	N	Power	Week	Group 1	Group 2	ES	LCI	UCI	Favors (NS=Not Significant)	Clinical Importance
	Gibofsky (2003)	Physician Global Assessment	379	Unclear	6	Celecoxib 200mg	Rofecoxib 25mg	OR=1.249	0.833	1.87	NS	Unclear
	Lehmann (2005)	Patient Global Assessment of Disease	844	Yes	13	Lumiracoxib	Celecoxib	-0.09	-0.23	0.04	NS	Unclear
	Gottesdiener (2002)	Patient Global Assessment of Disease	224	Unclear	6	Etoricoxib 60mg	Etoricoxib 90mg	-0.01	-0.27	0.25	NS	Unclear
	Gottesdiener (2002)	Patient Global Assessment of Disease	231	Unclear	6	Etoricoxib 5mg	Etoricoxib 10mg	-0.01	-0.27	0.25	NS	Unclear
	Gottesdiener (2002)	Patient Global Assessment of Disease	219	Unclear	6	Etoricoxib 5mg	Etoricoxib 30mg	0.09	-0.18	0.36	NS	Unclear

Type	Study	Outcome	N	Power	Week	Group 1	Group 2	ES	LCI	UCI	Favors (NS=Not Significant)	Clinical Importance
	Gottesdiener (2002)	Patient Global Assessment of Disease	229	Yes	6	Etoricoxib 5mg	Etoricoxib 60mg	0.36	0.1	0.62	Etoricoxib 60mg	Unclear
	Gottesdiener (2002)	Patient Global Assessment of Disease	229	Yes	6	Etoricoxib 5mg	Etoricoxib 90mg	0.27	0.01	0.53	Etoricoxib 90mg	Unclear
	Gottesdiener (2002)	Patient Global Assessment of Disease	216	Unclear	6	Etoricoxib 10mg	Etoricoxib 30mg	0.1	-0.17	0.36	NS	Unclear
	Gottesdiener (2002)	Patient Global Assessment of Disease	226	Yes	6	Etoricoxib 10mg	Etoricoxib 60mg	0.37	0.1	0.63	Etoricoxib 60mg	Unclear
	Gottesdiener (2002)	Patient Global Assessment of Disease	226	Yes	6	Etoricoxib 10mg	Etoricoxib 90mg	0.28	0.01	0.54	Etoricoxib 90mg	Unclear

Type	Study	Outcome	N	Power	Week	Group 1	Group 2	ES	LCI	UCI	Favors (NS=Not Significant)	Clinical Importance
	Gottesdiener (2002)	Patient Global Assessment of Disease	214	Yes	6	Etoricoxib 30mg	Etoricoxib 60mg	0.28	0.01	0.55	Etoricoxib 60mg	Unclear
	Gottesdiener (2002)	Patient Global Assessment of Disease	214	Unclear	6	Etoricoxib 30mg	Etoricoxib 90mg	0.19	-0.08	0.46	NS	Unclear
	Gottesdiener (2002)	Patient Global Assessment of Disease	224	Unclear	6	Etoricoxib 60mg	Etoricoxib 90mg	-0.1	-0.36	0.17	NS	Unclear
	Gottesdiener (2002)	Physician Global Assessment of Disease	231	Unclear	6	Etoricoxib 5mg	Etoricoxib 10mg	-0.01	-0.27	0.25	NS	Unclear
	Gottesdiener (2002)	Physician Global Assessment of Disease	219	Unclear	6	Etoricoxib 5mg	Etoricoxib 30mg	0.09	-0.18	0.36	NS	Unclear

Type	Study	Outcome	N	Power	Week	Group 1	Group 2	ES	LCI	UCI	Favors (NS=Not Significant)	Clinical Importance
	Gottesdiener (2002)	Physician Global Assessment of Disease	216	Unclear	6	Etoricoxib 10mg	Etoricoxib 30mg	0.1	-0.17	0.36	NS	Unclear
	Gottesdiener (2002)	Physician Global Assessment of Disease	229	Yes	6	Etoricoxib 5mg	Etoricoxib 60mg	0.36	0.1	0.62	Etoricoxib 60mg	Unclear
	Gottesdiener (2002)	Physician Global Assessment of Disease	226	Yes	6	Etoricoxib 10mg	Etoricoxib 60mg	0.37	0.1	0.63	Etoricoxib 60mg	Unclear
	Gottesdiener (2002)	Physician Global Assessment of Disease	214	Yes	6	Etoricoxib 30mg	Etoricoxib 60mg	0.28	0.01	0.55	Etoricoxib 60mg	Unclear
	Gottesdiener (2002)	Physician Global Assessment of Disease	229	Yes	6	Etoricoxib 5mg	Etoricoxib 90mg	0.27	0.01	0.53	Etoricoxib 90mg	Unclear

Type	Study	Outcome	N	Power	Week	Group 1	Group 2	ES	LCI	UCI	Favors (NS=Not Significant)	Clinical Importance
	Gottesdiener (2002)	Physician Global Assessment of Disease	226	Yes	6	Etoricoxib 10mg	Etoricoxib 90mg	0.28	0.01	0.54	Etoricoxib 90mg	Unclear
	Gottesdiener (2002)	Physician Global Assessment of Disease	214	Unclear	6	Etoricoxib 30mg	Etoricoxib 90mg	0.19	-0.08	0.46	NS	Unclear
	Gottesdiener (2002)	Physician Global Assessment of Disease	224	Unclear	6	Etoricoxib 60mg	Etoricoxib 90mg	-0.1	-0.36	0.17	NS	Unclear
	Lehmann (2005)	Physician Global Assessment of Disease	844	Unclear	13	Lumiracoxib 100mg	Celecoxib 200mg	-0.04	-0.18	0.09	NS	Unclear
	Schnitzer (2009)	Patient Assessment of Treatment Response	209	Unclear	4	Rofecoxib 12.5mg	Rofecoxib 25mg	0.19	-0.08	0.46	NS	Unclear

Type	Study	Outcome	N	Power	Week	Group 1	Group 2	ES	LCI	UCI	Favors (NS=Not Significant)	Clinical Importance
	Gottesdiener (2002)	Patient Assessment of Treatment Response	231	Unclear	6	Etoricoxib 5mg	Etoricoxib 10mg	0.04	-0.22	0.29	NS	Unclear
	Gottesdiener (2002)	Patient Assessment of Treatment Response	219	Unclear	6	Etoricoxib 5mg	Etoricoxib 30mg	0.09	-0.17	0.36	NS	Unclear
	Gottesdiener (2002)	Patient Assessment of Treatment Response	229	Yes	6	Etoricoxib 5mg	Etoricoxib 60mg	0.42	0.16	0.68	Etoricoxib 60mg	Unclear
	Gottesdiener (2002)	Patient Assessment of Treatment Response	229	Yes	6	Etoricoxib 5mg	Etoricoxib 90mg	0.32	0.06	0.58	Etoricoxib 90mg	Unclear

Type	Study	Outcome	N	Power	Week	Group 1	Group 2	ES	LCI	UCI	Favors (NS=Not Significant)	Clinical Importance
	Gottesdiener (2002)	Patient Assessment of Treatment Response	216	Unclear	6	Etoricoxib 10mg	Etoricoxib 30mg	0.05	-0.21	0.32	NS	Unclear
	Gottesdiener (2002)	Patient Assessment of Treatment Response	226	Yes	6	Etoricoxib 10mg	Etoricoxib 60mg	0.39	0.12	0.65	Etoricoxib 60mg	Unclear
	Gottesdiener (2002)	Patient Assessment of Treatment Response	226	Yes	6	Etoricoxib 10mg	Etoricoxib 90mg	0.28	0.02	0.55	Etoricoxib 90mg	Unclear
	Gottesdiener (2002)	Patient Assessment of Treatment Response	214	Yes	6	Etoricoxib 30mg	Etoricoxib 60mg	0.34	0.07	0.61	Etoricoxib 60mg	Unclear

Type	Study	Outcome	N	Power	Week	Group 1	Group 2	ES	LCI	UCI	Favors (NS=Not Significant)	Clinical Importance
	Gottesdiener (2002)	Patient Assessment of Treatment Response	214	Unclear	6	Etoricoxib 30mg	Etoricoxib 90mg	0.23	-0.04	0.5	NS	Unclear
	Gottesdiener (2002)	Patient Assessment of Treatment Response	224	Unclear	6	Etoricoxib 60mg	Etoricoxib 90mg	-0.1	-0.36	0.16	NS	Unclear
	Schnitzer (2005)	Patient Assessment of Treatment Response	782	Unclear	6	Celecoxib 200mg	Rofecoxib 12.5mg	OR= 1.051	0.78	1.416	NS	Unclear
	Schnitzer (2005)	Patient Assessment of Treatment Response	1050	Unclear	6	Celecoxib 200mg	Rofecoxib 25mg	OR= 0.827	0.649	1.054	NS	Unclear

Type	Study	Outcome	N	Power	Week	Group 1	Group 2	ES	LCI	UCI	Favors (NS=Not Significant)	Clinical Importance
	Schnitzer (2005)	Patient Assessment of Treatment Response	786	Unclear	6	Rofecoxib 12.5mg	Rofecoxib 25mg	OR= 0.786	0.584	1.059	NS	Unclear
	Gottesdiener (2002)	Patient Assessment of Treatment Response	231	Unclear	6	Etoricoxib 5mg	Etoricoxib 10mg	0.04	-0.22	0.3	NS	Unclear
	Gottesdiener (2002)	Physician Assessment of Treatment Response	219	Unclear	6	Etoricoxib 5mg	Etoricoxib 30mg	0.09	-0.18	0.36	NS	Unclear
	Gottesdiener (2002)	Physician Assessment of Treatment Response	216	Unclear	6	Etoricoxib 10mg	Etoricoxib 30mg	0.05	-0.22	0.32	NS	Unclear

Type	Study	Outcome	N	Power	Week	Group 1	Group 2	ES	LCI	UCI	Favors (NS=Not Significant)	Clinical Importance
	Gottesdiener (2002)	Physician Assessment of Treatment Response	229	Yes	6	Etoricoxib 5mg	Etoricoxib 60mg	0.37	0.11	0.63	Etoricoxib 60mg	Unclear
	Gottesdiener (2002)	Physician Assessment of Treatment Response	226	Yes	6	Etoricoxib 10mg	Etoricoxib 60mg	0.33	0.07	0.59	Etoricoxib 60mg	Unclear
	Gottesdiener (2002)	Physician Assessment of Treatment Response	214	Yes	6	Etoricoxib 30mg	Etoricoxib 60mg	0.28	0.01	0.55	Etoricoxib 60mg	Unclear
	Gottesdiener (2002)	Physician Assessment of Treatment Response	229	Yes	6	Etoricoxib 5mg	Etoricoxib 90mg	0.31	0.05	0.57	Etoricoxib 90mg	Unclear

Type	Study	Outcome	N	Power	Week	Group 1	Group 2	ES	LCI	UCI	Favors (NS=Not Significant)	Clinical Importance
	Gottesdiener (2002)	Physician Assessment of Treatment Response	226	Yes	6	Etoricoxib 10mg	Etoricoxib 90mg	0.27	0.01	0.53	Etoricoxib 90mg	Unclear
	Gottesdiener (2002)	Physician Assessment of Treatment Response	214	Unclear	6	Etoricoxib 30mg	Etoricoxib 90mg	0.23	-0.04	0.49	NS	Unclear
	Gottesdiener (2002)	Physician Assessment of Treatment Response	224	Unclear	6	Etoricoxib 60mg	Etoricoxib 90mg	-0.06	-0.32	0.2	NS	Unclear
	Schnitzer (2009)	Physician Assessment of Treatment Response	208	Unclear	4	Rofecoxib 12.5mg	Rofecoxib 25mg	0.17	-0.1	0.45	NS	Unclear

Table 157. NSAIDs Versus Placebo

Outcome Type	Study	Outcome	N	Sufficient Power	Week	Group 1	Group 2	Effect Size	Lower CI	Upper CI	Favors (NS=not Significant)	Clinical Importance
Additional Acetaminophen Use	Schnitzer (2010)	Rescue Acetaminophen	429	Unclear	12	Naproxen	Placebo	-0.28	-0.47	-0.09	Naproxen	Unclear
	Schnitzer (2010)	Rescue Acetaminophen	442	Unclear	13	Naproxcinod	Placebo	-0.22	-0.41	-0.03	Naproxcinod	Unclear
	Schnitzer (2010)	Rescue Acetaminophen	432	Unclear	13	Naproxcinod	Placebo	-0.53	-0.73	-0.33	Naproxcinod	Unclear
Function	Mckenna (2001)	WOMAC Function improvement	399	Yes	6	Diclofenac	Placebo	0.07	-0.15	0.29	Diclofenac	Possibly clinically significant
	Schnitzer (2010)	SF-36 MCS improvement	327	Unclear	12	Naproxen	Placebo	-0.52	-0.71	-0.33	NS	Unclear
	Schnitzer (2010)	WOMAC Function improvement	447	Yes	12	Naproxen	Placebo	-2	-2.55	-1.44	Naproxen	Possibly clinically significant
	Evcik (2003)	Health assessment questionnaire	76	Unclear	26	Tenoxicam	Placebo	0.11	-0.11	0.33	Tenoxicam	Unclear
	Schnitzer (2010)	SF-36 MCS improvement	337	Unclear	13	Naproxcinod	Placebo	0.09	-0.13	0.31	NS	Inconclusive
	Schnitzer (2010)	SF-36 MCS improvement	326	Unclear	13	Naproxcinod	Placebo	-0.03	-0.21	0.16	NS	Inconclusive
	Schnitzer (2010)	WOMAC Function	450	No	13	Naproxcinod	Placebo	-1.72	-2.25	-1.19		True negative
Lequesne index	Evcik (2003)	Lequesne index	76	Unclear	26	Tenoxicam	Placebo	-0.2	-0.39	0	Tenoxicam	Unclear

Pain	Kivits (2002)	VAS Pain	409	Yes	12	Naproxen	Placebo	-0.28	-0.48	-0.09	Naproxen	Not clinically significant
	Kivits (2002)	VAS Pain	409	Yes	6	Naproxen	Placebo	-0.48	-0.68	-0.28	Naproxen	Not clinically significant
	Mckenna (2001)	VAS Pain	399	Yes	6	Diclofenac	Placebo	-0.45	-0.64	-0.25	Diclofenac	Not clinically significant
	Mckenna (2001)	WOMAC Pain	399	Yes	6	Diclofenac	Placebo	-0.44	-0.66	-0.22	Diclofenac	Possibly clinically significant
	Schnitzer (2010)	VAS Pain	333	Yes	12	Naproxen	Placebo	-0.44	-0.66	-0.22	Naproxen	Not clinically significant
	Schnitzer (2010)	VAS Pain during walking improvement	333	Yes	12	Naproxen	Placebo	-1.68	-1.89	-1.46	Naproxen	Not clinically significant
	Schnitzer (2010)	WOMAC Pain	447	Yes	12	Naproxen	Placebo	-1.88	-2.42	-1.33	Naproxen	Clinically significant
	Evcik (2003)	VAS Ascending stairs	76	Yes	26	Tenoxicam	Placebo	-1.68	-2.21	-1.15	Tenoxicam	Clinically significant
	Evcik (2003)	VAS Descending stairs	76	Yes	26	Tenoxicam	Placebo	-1.36	-1.86	-0.86	Tenoxicam	Possibly clinically significant
	Evcik (2003)	VAS Walking	76	Yes	26	Tenoxicam	Placebo	-0.95	-1.42	-0.47	Tenoxicam	Possibly clinically significant
	Evcik (2003)	VAS At rest	76	Yes	26	Tenoxicam	Placebo	-0.25	-0.47	-0.04	Tenoxicam	Possibly clinically significant
	Schnitzer (2010)	VAS Pain at rest improvement	341	Yes	13	Naproxcinod 375mg	Placebo	-0.33	-0.55	-0.11	Naproxcinod	Not clinically significant

	Schnitzer (2010)	VAS Pain at rest improvement	330	Yes	13	Naproxcinod 750mg	Placebo	-0.28	-0.5	-0.06	Naproxcinod	Not clinically significant
	Schnitzer (2010)	VAS Pain during walking improvement	341	Yes	13	Naproxcinod 375mg	Placebo	-0.38	-0.6	-0.16	Naproxcinod	Not clinically significant
	Schnitzer (2010)	VAS Pain during walking	330	Yes	13	Naproxcinod 750mg	Placebo	-1.49	-1.7	-1.28	Naproxcinod	Not clinically significant
	Schnitzer (2010)	WOMAC Pain	461	Yes	13	Naproxcinod 375mg	Placebo	-1.55	-1.76	-1.34	Naproxcinod	Clinically significant
	Schnitzer (2010)	WOMAC Pain	450	Yes	13	Naproxcinod 750mg	Placebo	-0.22	-0.41	-0.02	Naproxcinod	Clinically significant
Stiffness	Kivits (2002)	WOMAC Stiffness	409	Yes	6	Naproxen	Placebo	-0.24	-0.44	-0.05	Naproxen	Possibly clinically significant
	Kivits (2002)	WOMAC Stiffness	409	Yes	12	Naproxen	Placebo	-0.57	-0.77	-0.37	Naproxen	Possibly clinically significant
	Mckenna (2001)	WOMAC Stiffness	399	Yes	6	Diclofenac	Placebo	-0.22	-0.42	-0.03	Diclofenac	Possibly clinically significant
WOMAC Total	Kivits (2002)	WOMAC Total	409	Yes	6	Naproxen	Placebo	-0.24	-0.43	-0.05	Naproxen	Possibly clinically significant
	Kivits (2002)	WOMAC Total	409	Yes	12	Naproxen	Placebo	-0.54	-0.74	-0.34	Naproxen	Possibly clinically significant
	Mckenna (2001)	WOMAC Total	399	Yes	6	Diclofenac	Placebo	-0.48	-0.7	-0.26	Diclofenac	Possibly clinically significant

	Schnitzer	WOMAC Total	332	Yes	12	Naproxen	Placebo	-0.28	-0.47	-0.09	Naproxen	Possibly clinically significant

Table 158. NSAIDs Versus NSAIDs

Type	Study	Outcome	N	Sufficient Power	Week	Group 1	Group 2	SMD	LCI (or p value)	UCI	Favors	Clinical Importance
Function	Bradley (1991)	HAQ Disability	122	Unclear	4	Ibuprofen 300mg	Ibuprofen 600mg	-0.07	-0.42	0.29	NS	Unclear
	Bradley (1991)	WOMAC Function	98	Unclear	12	Tenoxicam	Diclofenac	Mean difference =2.47	p>.05	-	NS	Unclear
	Ayral (2003)	WOMAC Function	416	No	52	Tenidap 120mg	Piroxicam 20mg	-0.07	-0.26	0.12	NS	Unclear
	Bradley (1991)	Health Assessment Questionnaire (HAQ)	122	Unclear	4	Ibuprofen 300mg	Ibuprofen 600	-0.06	-0.41	0.3	NS	Unclear
	Herrera (2007)	WOMAC Function	62	Unclear	4	Diclofenac CR 100mg	Diclofenac IR 50mg	Mean difference = 3.69	p>.05	-	NS	Unclear
	Schnitzer (2010)	WOMAC Function	455	Yes	13	Naproxcinod 750mg	Naproxen	0.12	-0.06	0.31	NS	True negative
	Schnitzer (2010)	WOMAC Function	465	Yes	13	Naproxcinod 375mg	Naproxen	0.18	0	0.36	NS	True negative

Type	Study	Outcome	N	Sufficient Power	Week	Group 1	Group 2	SMD	LCI (or p value)	UCI	Favors	Clinical Importance
	Schnitzer (2010)	SF-36 MCS	369	Unclear	13	Naproxcinod 750mg	Naproxen	0.09	-0.11	0.3	NS	Unclear
	Schnitzer (2010)	SF-36 MCS	380	Unclear	13	Naproxcinod 375mg	Naproxen	0.11	-0.09	0.31	NS	Unclear
Function-Task	Bradley (1991)	Walk time (seconds)	122	Unclear	4	Ibuprofen 300mg	Ibuprofen 600	0.06	-0.3	0.41	NS	Unclear
	Kogstad (1981)	Sequence A ability to walk (VAS)	156	Yes	4	Piroxicam 20mg	Naproxen 250mg	-0.39	-0.71	-0.07	Piroxicam 20mg	Unclear
	Kogstad (1981)	Sequence B ability to walk (VAS)	142	Yes	4	Piroxicam 20mg	Naproxen 250mg	1.33	0.96	1.69	Naproxen 250mg	Unclear
	Karbowski (1991)	Time to walk 50ft	61	Unclear	6	Etodolac 300mg	Indomethacin 50mg	Mean Difference = 0.5	p>0.05	-	NS	Unclear
	Dick (1992)	Time to walk 50ft	116	Unclear	6	Etodolac 300mgx2	Piroxicam 20mg	Mean difference =-.1	p>0.05	-	NS	Unclear

Type	Study	Outcome	N	Sufficient Power	Week	Group 1	Group 2	SMD	LCI (or p value)	UCI	Favors	Clinical Importance
	Astorga (1991)	Time to walk 50ft	220	Unclear	6	Etodolac 300mg	Piroxicam 20mg	Mean difference = -0.1	p>0.05	-	NS	Unclear
	Astorga (1991)	Time to walk 50ft	220	Unclear	6	Etodolac 300mg	Piroxicam 20mg	Mean difference = -.5	p>.05	-	NS	Unclear
	Astorga (1991)	Time to walk 50ft	220	Unclear	6	Etodolac 300mg	Piroxicam 20mg	Mean difference = -.2	p>.05	-	NS	Unclear
	Liang (2003)	Change in Lequesne index	64	Unclear	4	Etodolac sustained-release400mg	Diclofenac 50mg	0.01	-0.48	0.5	NS	Unclear
	Kogstad (1981)	Sequence A pain at night (VAS)	156	Yes	4	Piroxicam 20mg	Naproxen 250mg	-0.78	-1.11	-0.45	Piroxicam 20mg	Not clinically significant
	Kogstad (1981)	Sequence B pain at night (VAS)	142	Yes	4	Piroxicam 20mg	Naproxen 250mg	0.78	0.44	1.12	Naproxen 250mg	Not clinically significant

Type	Study	Outcome	N	Sufficient Power	Week	Group 1	Group 2	SMD	LCI (or p value)	UCI	Favors	Clinical Importance
	Tyson (1980)	Linear analogue pain scale	105	Unclear	8	Benoxaprofen	Ibuprofen	Mean difference = 37	p>0.05	-	NS	Unclear
	Tyson (1980)	Linear analogue pain scale	105	Unclear	12	Benoxaprofen	Ibuprofen	Mean Difference = -9.78	p<.05	-	Ibuprofen	Unclear
	Tyson (1980)	Linear analogue pain scale	105	Unclear	16	Benoxaprofen	Ibuprofen	Mean Difference = -5.53	p>.05	-	NS	Unclear
	Bellamy (1993)	WOMAC Pain	98	Unclear	12	Tenoxicam	Diclofenac	1.288	p>.05	-	NS	Unclear
	Ayral (2003)	WOMAC Pain	434	Yes	52	Tenidap 40mg	Tenidap 120mg	0.01	-0.17	0.2	NS	True negative
	Ayral (2003)	WOMAC Pain	437	Yes	52	Tenidap 40mg	Piroxicam 20mg	0.02	-0.17	0.21	NS	True negative
	Ayral (2003)	WOMAC Pain	427	Yes	52	Tenidap 120mg	Piroxicam 20mg	0.01	-0.18	0.2	NS	True negative
	Queiros (1990)	Pain at night (1 to 4)	60	Unclear	4	Piroxicam 20mg	Oxaprozin 1200mg	0	-0.51	0.51	NS	True negative
	Queiros (1990)	Walk pain in evening	60	Unclear	4	Piroxicam 20mg	Oxaprozin 1200mg	-0.31	-0.82	0.2	NS	True negative

Type	Study	Outcome	N	Sufficient Power	Week	Group 1	Group 2	SMD	LCI (or p value)	UCI	Favors	Clinical Importance
	Queiros (1990)	Walk pain in the morning	60	Unclear	4	Piroxicam 20mg	Oxaprozin 1200mg	-0.37	-0.88	0.15	NS	True negative
	Kogstad (1981)	Sequence A pain on movement (VAS)	156	Yes	4	Piroxicam 20mg	Naproxen 250mg	-1	-1.33	-0.66	Piroxicam 20mg	Possibly clinically significant
	Kogstad (1981)	Sequence B pain on movement (VAS)	142	Yes	4	Piroxicam 20mg	Naproxen 250mg	0.99	0.65	1.34	Naproxen 250mg	Possibly clinically significant
	La Montagna (1998)	Present pain index	106	Unclear	12	Piroxicam-beta-cyclodextrin 20mg	Diclofenac 100mg	0.17	-0.21	0.56	NS	Unclear
	La Montagna (1998)	present pain index	106	Unclear	24	Piroxicam-beta-cyclodextrin 20mg	Diclofenac 100mg	0.2	-0.19	0.58	NS	Unclear
	La Montagna (1998)	VAS Pain	106	Unclear	12	Piroxicam-beta-cyclodextrin 20mg	Diclofenac 100mg	0.14	-0.24	0.53	NS	True negative

Type	Study	Outcome	N	Sufficient Power	Week	Group 1	Group 2	SMD	LCI (or p value)	UCI	Favors	Clinical Importance
	La Montagna (1998)	VAS Pain	106	Unclear	24	Piroxicam-beta-cyclodextrin20mg	Diclofenac 100mg	-0.02	-0.4	0.36	NS	True negative
	Herrera (2007)	VAS Pain	62	Unclear	4	Diclofenac CR 100mg	Diclofenac IR 50mg	Mean difference = 4.35	p=.334	-	NS	Unclear
	Herrera (2007)	WOMAC Pain	62	Unclear	4	Diclofenac CR 100mg	Diclofenac IR 50mg	Mean difference = 0.73	p>.05	-	NS	Unclear
	Chubick (1987)	Improved Afternoon weight bearing pain	173	Unclear	4	Sulindac 300-400mg QD	Sulindac 300-400mg BID	OR=1.73	0.76	3.92	NS	Unclear
	Chubick (1987)	Improved night pain	173	Unclear	4	Sulindac 300-400mg QD	Sulindac 300-400mg BID	OR=1.42	0.64	3.12	NS	Unclear
	Chubick (1987)	Improved tenderness	173	Unclear	4	Sulindac 300-400mg QD	Sulindac 300-400mg BID	OR=1.30	0.69	2.47	NS	Unclear

Type	Study	Outcome	N	Sufficient Power	Week	Group 1	Group 2	SMD	LCI (or p value)	UCI	Favors	Clinical Importance
	Chubick (1987)	Improved afternoon weight bearing pain	173	Unclear	4	Sulindac 300-400mg QD	Sulindac 300-400mg BID	OR=1.73	0.76	3.92	NS	Unclear
	Schnitzer (2010)	WOMAC Pain	455	Yes	13	Naproxcinod 750mg	Naproxen	0.08	-0.1	0.27	NS	True negative
	Schnitzer (2010)	WOMAC Pain	466	Yes	13	Naproxcinod 375mg	Naproxen	0.12	-0.07	0.3	NS	True negative
	Schnitzer (2010)	VAS Pain during walking	375	Yes	13	Naproxcinod 750mg	Naproxen	-0.38	-0.59	-0.18	Naproxinod	Not clinically important
	Schnitzer (2010)	VAS Pain during walking	386	Yes	13	Naproxcinod 375mg	Naproxen	-0.28	-0.48	-0.08	Naproxinod	Not clinically important
	Schnitzer (2010)	VAS Pain at rest	375	Yes	13	Naproxcinod 750mg	Naproxen	-0.33	-0.54	-0.13	Naproxinod	Not clinically important
	Schnitzer (2010)	VAS Pain at rest	386	Yes	13	Naproxcinod 375mg	Naproxen	-0.25	-0.45	-0.05	Naproxinod	Not clinically important

Type	Study	Outcome	N	Sufficient Power	Week	Group 1	Group 2	SMD	LCI (or p value)	UCI	Favors	Clinical Importance
	Chubick (1987)	Afternoon weight bearing pain	173	Unclear	4	Sulindac 300-400mg QD	Sulindac 300-400mg BID	OR=1.33	0.53	3.35	NS	Unclear
Stiffness	Herrera (2007)	WOMAC Stiffness	62	Unclear	4	Diclofenac CR 100mg	Diclofenac IR 50mg	Mean difference = 0.71	p>.05	-	NS	Unclear
	Karbowski (1991)	Morning stiffness	61	Unclear	6	Etodolac 300mg	Indomethacin 50mg	Mean difference = -1.6	p>.05	-	NS	Unclear
	Dick (1992)	Morning stiffness	116	Unclear	6	Etodolac 300mgx2	Piroxicam 20mg	Mean difference = -10.3	p>0.05	-	NS	Unclear
	Astorga (1991)	Morning stiffness	220	Unclear	4	Etodolac 300mg	Piroxicam 20mg	Mean difference = -2.6	p>0.05	-	NS	Unclear
	Astorga (1991)	Morning stiffness	220	Unclear	6	Etodolac 300mg	Piroxicam 20mg	Mean difference = -1.4	p>0.05	-	NS	Unclear

Type	Study	Outcome	N	Sufficient Power	Week	Group 1	Group 2	SMD	LCI (or p value)	UCI	Favors	Clinical Importance
	Astorga (1991)	Morning stiffness	220	Unclear	8	Etodolac 300mg	Piroxicam 20mg	Mean difference = -2	p>0.05	-	NS	Unclear
	Astorga (1991)	Morning stiffness	220	Unclear	final follow-up	Etodolac 300mg	Piroxicam 20mg	Mean difference = -2.6	p>0.05	-	NS	Unclear
	Bellamy (1993)	WOMAC Stiffness	98	Unclear	12	Tenoxicam	Diclofenac	2.636	p>.05	-	NS	Unclear
	Ayral (2003)	WOMAC Stiffness	435	Yes	52	Tenidap 40mg	Tenidap 120mg	0.03	-0.16	0.22	NS	True negative
	Ayral (2003)	WOMAC Stiffness	438	Yes	52	Tenidap 40mg	Piroxicam 20	0.01	-0.18	0.2	NS	True negative
	Ayral (2003)	WOMAC Stiffness	429	Yes	52	Tenidap 120mg	Piroxicam 20	-0.02	-0.21	0.17	NS	True negative
WOMAC Total	Herrera (2007)	WOMAC Total	62	Unclear	4	Diclofenac CR 100mg	Diclofenac IR 50mg	Mean difference = 4.74	p=.334	-	NS	Unclear
	Ayral (2003)	WOMAC Total	415	Yes	52	Tenidap 40mg	Tenidap 120mg	0.06	-0.13	0.25	NS	True negative

Type	Study	Outcome	N	Sufficient Power	Week	Group 1	Group 2	SMD	LCI (or p value)	UCI	Favors	Clinical Importance
	Ayral (2003)	WOMAC Total	418	Yes	52	Tenidap 40mg	Piroxicam 20	0.04	-0.15	0.23	NS	True negative
	Ayral (2003)	WOMAC Total	411	Yes	52	Tenidap 120mg	Piroxicam 20	-0.02	-0.21	0.17	NS	True negative
	Schnitzer (2010)	WOMAC total	375	yes	13	Naproxcinod 750mg	Naproxen	0.13	-0.08	0.33	NS	True negative
	Schnitzer (2010)	WOMAC total	385	yes	13	Naproxcinod 375mg	Naproxen	0.17	-0.03	0.37	NS	True negative
Global Assessment	Ayral (2003)	Patient Global Assessment	436	Unclear	52	Tenidap 40mg	Piroxicam 20mg	0.02	-0.17	0.21	NS	Moderate
	Ayral (2003)	Patient Global Assessment	427	Unclear	52	Tenidap 120mg	Piroxicam 20mg	-0.05	-0.24	0.14	NS	Moderate
	Ayral (2003)	Patient Global Assessment	431	Unclear	52	Tenidap 40mg	Tenidap 120mg	0.07	-0.12	0.26	NS	Moderate
	Ayral (2003)	Physician Global Assessment	440	Unclear	52	Tenidap 40mg	Piroxicam 20mg	0.01	-0.17	0.2	NS	Moderate
	Ayral (2003)	Physician Global Assessment	435	Unclear	52	Tenidap 120mg	Piroxicam 20mg	-0.04	-0.22	0.15	NS	Moderate

Type	Study	Outcome	N	Sufficient Power	Week	Group 1	Group 2	SMD	LCI (or p value)	UCI	Favors	Clinical Importance
	Ayral (2003)	Physician Global Assessment	437	Unclear	52	Tenidap 40mg	Tenidap 120mg	0.05	-0.14	0.24	NS	Moderate
	Schnitzer (2010)	Patient Global Assessment of Disease	465	Unclear	13	Naproxen	Naproxcinod 375mg	-0.03	-0.21	0.16	NS	Moderate
	Schnitzer (2010)	Patient Global Assessment of Disease	454	Unclear	13	Naproxen	Naproxcinod 750mg	-0.02	-0.2	0.17	NS	Moderate
	Schnitzer (2005)	Patient Global Assessment of Disease	212	Unclear	6	Naproxcinod 125mg	Naproxcinod 375mg	OR=0.658	0.38	1.13	NS	Moderate
	Schnitzer (2005)	Patient Global Assessment of Disease	219	Yes	6	Naproxcinod 125mg	Naproxcinod 750mg	OR=0.471	0.28	0.81	Naproxcinod 750mg	Unclear
	Schnitzer (2005)	Patient Global Assessment of Disease	222	Yes	6	Naproxcinod 125mg	Naproxen 500mg	OR=0.540	0.32	0.92	Naproxen 500mg	Unclear
	Schnitzer (2005)	Patient Global Assessment of Disease	221	Unclear	6	Naproxcinod 375mg	Naproxcinod 750mg	OR=0.717	0.42	1.22	NS	Moderate

Type	Study	Outcome	N	Sufficient Power	Week	Group 1	Group 2	SMD	LCI (or p value)	UCI	Favors	Clinical Importance
	Schnitzer (2005)	Patient Global Assessment of Disease	224	Unclear	6	Naproxcinod 375mg	Naproxen 500mg	OR=0.821	0.48	1.39	NS	Moderate
	Schnitzer (2005)	Patient Global Assessment of Disease	231	Unclear	6	Naproxcinod 750mg	Naproxen 500mg	OR=1.146	0.68	1.94	NS	Moderate
	Schnitzer (2010)	Patient Global Assessment of Disease Status	454	Unclear	13	Naproxcinod 750mg	Naproxen	0.06	-0.13	0.24	NS	True negative
	Schnitzer (2010)	Patient Global Assessment of Disease Status	465	Unclear	13	Naproxcinod 375mg	Naproxen	0.05	-0.13	0.23	NS	True negative
	Schnitzer (2005)	Patient Assessment of Treatment Response	212	Yes	6	Naproxcinod 125mg	Naproxcinod 375mg	OR=0.564	0.33	0.97	Naproxcinod 375mg	Unclear
	Schnitzer (2005)	Patient Assessment of Treatment Response	219	Yes	6	Naproxcinod 125mg	Naproxcinod 750mg	OR=0.420	0.24	0.72	Naproxcinod 750mg	Unclear

Type	Study	Outcome	N	Sufficient Power	Week	Group 1	Group 2	SMD	LCI (or p value)	UCI	Favors	Clinical Importance
	Schnitzer (2005)	Patient Assessment of Treatment Response	221	Unclear	6	Naproxcinod 375mg	Naproxcino d 750mg	OR=0.744	0.44	1.27	NS	Moderate
	Schnitzer (2005)	Patient Assessment of Treatment Response	222	Yes	6	Naproxcinod 125mg	Naproxen 500mg	OR=0.360	0.21	0.62	Naproxe n 500mg	Unclear
	Schnitzer (2005)	Patient Assessment of Treatment Response	224	Unclear	6	Naproxcinod 375mg	Naproxen 500mg	OR=0.639	0.37	1.1	NS	Moderate
	Schnitzer (2005)	Patient Assessment of Treatment Response	231	Unclear	6	Naproxcinod 750mg	Naproxen 500mg	OR=0.858	0.5	1.47	NS	Moderate
	Lohmand er (2005)	Patient Assessment of Treatment Response	828	Yes	6	Naproxcinod	Naproxen	OR=1.042	0.77	1.42	NS	Low
Rescue Medicine	Schnitzer (2010)	Rescue acetaminophe n	441	Unclear	13	Naproxcinod 750mg	Naproxen	-0.22	-0.4	-0.03	Naproxi nod	Unclear

Type	Study	Outcome	N	Sufficient Power	Week	Group 1	Group 2	SMD	LCI (or p value)	UCI	Favors	Clinical Importance
	Schnitzer (2010)	Rescue acetaminophen	451	Unclear	13	Naproxcinod 375mg	Naproxen	-0.28	-0.47	-0.09	Naproxinod	Unclear

Table 159. Cox-2s Versus NSAIDs

	Study	Outcome	N	Power	Week	Cox-2	NSAID	ES	LCI	UCI	Favors	Clinical Importance
Function	Mckenna (2001)	WOMAC Function	398	Yes	6	Celecoxib 100mg	Diclofenac 100mg	0.14	-0.05	0.34	NS	True negative
Pain	Mckenna (2001)	WOMAC Pain	398	Yes	6	Celecoxib 100mg	Diclofenac 100mg	0.07	-0.12	0.27	NS	True negative
	Mckenna (2001)	VAS Pain	398	Yes	6	Celecoxib 100mg	Diclofenac 100mg	0.07	-0.13	0.26	NS	True negative
	Lücker (1994)	VAS Pain	186	Yes	4	Nimesulide 100mg	Etodolac	0.15	-0.14	0.43	NS	True negative
	Lücker (1994)	VAS Pain	180	Yes	8	Nimesulide 100mg	Etodolac	0.06	-0.23	0.36	NS	True negative
	Lücker (1994)	VAS Pain	167	Yes	12	Nimesulide 100mg	Etodolac	-0.08	-0.38	0.22	NS	True negative
	Kivits (2002)	VAS Pain	409	Yes	12	Valdecoxib 5mg	Naproxen 5mg	0.06	-0.13	0.25	NS	True negative
	Kivits (2002)	VAS Pain	409	Yes	6	Valdecoxib 5mg	Naproxen 5mg	0.07	-0.12	0.27	NS	True negative
	Kivits (2002)	VAS Pain	405	Yes	12	Valdecoxib 5mg	Naproxen 5mg	-0.04	-0.23	0.16	NS	True negative
	Kivits (2002)	VAS Pain	405	Yes	6	Valdecoxib 5mg	Naproxen 5mg	-0.02	-0.21	0.18	NS	True negative
	Kivits (2002)	VAS Pain	405	Yes	12	Valdecoxib 5mg	Naproxen 5mg	0.02	-0.18	0.21	NS	True negative
	Kivits (2002)	VAS Pain	405	Yes	6	Valdecoxib 5mg	Naproxen 5mg	0.04	-0.16	0.23	NS	True negative

	Study	Outcome	N	Power	Week	Cox-2	NSAID	ES	LCI	UCI	Favors	Clinical Importance
Stiffness	Mckenna (2001)	WOMAC Stiffness	398	Yes	6	Celecoxib 100mg	Diclofenac 100mg	0.17	-0.03	0.36	NS	True negative
	Kivits (2002)	WOMAC Stiffness	409	Yes	6	Valdecoxib 10mg	Naproxen 10mg	-0.01	-0.21	0.18	NS	True negative
	Kivits (2002)	WOMAC Stiffness	409	Yes	12	Valdecoxib 10mg	Naproxen 10mg	0.07	-0.12	0.27	NS	True negative
	Kivits (2002)	WOMAC Stiffness	405	Yes	12	Valdecoxib 20mg	Naproxen 20mg	0.05	-0.15	0.24	NS	True negative
	Kivits (2002)	WOMAC Stiffness	405	Yes	6	Valdecoxib 20mg	Naproxen 20mg	-0.02	-0.21	0.18	NS	True negative
	Kivits (2002)	WOMAC Stiffness	405	Yes	12	Valdecoxib 5mg	Naproxen 5mg	0.12	-0.08	0.31	NS	True negative
	Kivits (2002)	WOMAC Stiffness	405	Yes	6	Valdecoxib 5mg	Naproxen 5mg	0.09	-0.1	0.29	NS	True negative
WOMAC Total	Mckenna (2001)	WOMAC Total	398	Yes	6	Celecoxib 100mg	Diclofenac 100mg	0.14	-0.05	0.34	NS	True negative
	Kivits (2002)	WOMAC Total	409	Yes	12	Valdecoxib 10mg	Naproxen 10mg	0.04	-0.16	0.23	NS	True negative
	Kivits (2002)	WOMAC Total	409	Yes	6	Valdecoxib 10mg	Naproxen 10mg	0.01	-0.18	0.21	NS	True negative
	Kivits (2002)	WOMAC Total	405	Yes	6	Valdecoxib 20mg	Naproxen 20mg	-0.02	-0.21	0.18	NS	True negative
	Kivits (2002)	WOMAC Total	405	Yes	12	Valdecoxib 20mg	Naproxen 20mg	0.04	-0.15	0.24	NS	True negative
	Kivits (2002)	WOMAC Total	405	Yes	12	Valdecoxib 5mg	Naproxen 5mg	0.06	-0.13	0.26	NS	True negative

	Study	Outcome	N	Power	Week	Cox-2	NSAID	ES	LCI	UCI	Favors	Clinical Importance
	Kivits (2002)	WOMAC Total	405	Yes	6	Valdecoxib 5mg	Naproxen 5mg	0.08	-0.11	0.28	NS	True negative
Lequesne index	Lücker (1994)	Lequesne index	186	Unclear	4	Nimesulide 100mg	Etodolac	0.12	-0.17	0.41	NS	Unclear
	Lücker (1994)	Lequesne index	180	Unclear	8	Nimesulide 100mg	Etodolac	0.1	-0.19	0.4	NS	Unclear
	Lücker (1994)	Lequesne index	167	Unclear	12	Nimesulide 100mg	Etodolac	0	-0.31	0.3	NS	Unclear
Global Assessment	Mckenna (2001)	Patient Global Assessment	398	Unclear	6	Celecoxib	Diclofenac	-0.09	-0.29	0.11	NS	Unclear
	Kivits (2002)	Physician Global Assessment	409	Unclear	6	Valdecoxib 10mg	Naproxen	-0.05	-0.24	0.14	NS	Unclear
	Kivits (2002)	Physician Global Assessment	409	Unclear	12	Valdecoxib 10mg	Naproxen	-0.08	-0.28	0.11	NS	Unclear
	Kivits (2002)	Physician Global Assessment	405	Unclear	6	Valdecoxib 20mg	Naproxen	0.04	-0.15	0.24	NS	Unclear
	Kivits (2002)	Physician Global Assessment	405	Unclear	12	Valdecoxib 20mg	Naproxen	-0.02	-0.21	0.18	NS	Unclear
	Kivits (2002)	Physician Global Assessment	405	Unclear	6	Valdecoxib 5mg	Naproxen	0.01	-0.18	0.2	NS	Unclear

	Study	Outcome	N	Power	Week	Cox-2	NSAID	ES	LCI	UCI	Favors	Clinical Importance
	Kivits (2002)	Physician Global Assessment	405	Unclear	12	Valdecoxib 5mg	Naproxen	0	-0.19	0.19	NS	Unclear
	Mckenna (2001)	Physician Global Assessment	398	Yes	6	Celecoxib	Diclofenac (NSAID)	0.2	0	0.4	Diclofenac (NSAID)	Unclear
	Schnitzer (2005)	Patient Global Assessment of Disease responders	203	Yes	6	Rofecoxib 25mg	Naproxcinod 125mg	OR= 1.93	1.11	3.38	Rofecoxib 25mg	Unclear
	Schnitzer (2005)	Patient Global Assessment of Disease responders	205	Unclear	6	Rofecoxib 25mg	Naproxcinod 375mg	OR= 1.27	0.73	2.21	NS	Unclear
	Schnitzer (2005)	Patient Global Assessment of Disease responders	212	Unclear	6	Rofecoxib 25mg	Naproxcinod 750mg	OR= 0.91	0.52	1.58	NS	Unclear

	Study	Outcome	N	Power	Week	Cox-2	NSAID	ES	LCI	UCI	Favors	Clinical Importance
	Schnitzer (2005)	Patient Assessment of Treatment Response (good or excellent)	203	Yes	6	Rofecoxib 25mg	Naproxcinod 125mg	OR= 2.98	1.68	5.29	Rofecoxib 25mg	Unclear
	Schnitzer (2005)	Patient Assessment of Treatment Response (good or excellent)	205	Unclear	6	Rofecoxib 25mg	Naproxcinod 375mg	OR= 1.68	0.95	2.97	NS	Unclear
	Schnitzer (2005)	Patient Assessment of Treatment Response (good or excellent)	212	Unclear	6	Rofecoxib 25mg	Naproxcinod 750mg	OR= 1.25	0.71	2.2	NS	Unclear
	Kivitz (2004)	Patient Assessment of Treatment Response (good or excellent)	823	Yes	6	Rofecoxib 12.5mg	Nabumetone	OR= 1.371	1.042	1.803	Rofecoxib 12.5mg	Unclear

Table 160. Topical NSAIDs Versus Control

Type	Study	Outcome	N	Power	Week	Group 1	Group 2	ES	LCI	UCI	Favors	Clinical Significance
Concomitant Cedicine	Bookman (2004)	Acetaminophen consumption	163	Unclear	4	Topical Diclofenac	Vehicle control	-0.23	-0.54	0.08	NS	Unclear
	Bookman (2004)	Acetaminophen consumption	168	Unclear	4	Topical Diclofenac	Placebo	-0.3	-0.61	0	NS	Unclear
	Barthel (2009)	Weeks with No rescue drug	491	Yes	12	Diclofenac sodium 1% gel in DMSO	DMSO vehicle	0.2	0.02	0.38	Diclofenac sodium 1% gel in DMSO	Unclear
	Bookman (2004)	Acetaminophen consumption	163	Unclear	4	Topical Diclofenac	Vehicle control	-0.23	-0.54	0.08	NS	Unclear
	Bookman (2004)	Acetaminophen consumption	168	Unclear	4	Topical Diclofenac	Placebo	-0.3	-0.61	0	NS	Unclear
	Barthel (2009)	Weeks with No rescue drug	491	Yes	12	Diclofenac sodium 1% gel in DMSO	DMSO vehicle	0.2	0.02	0.38	Diclofenac sodium 1% gel in DMSO	Unclear
Function	Roth (2004)	WOMAC Function	321	Yes	12	Topical Diclofenac	Vehicle control	-0.36	-0.58	-0.14	Topical Diclofenac	Possibly clinically significant
	Baer (2005)	WOMAC Function	212	Yes	6	Pennsaid (topical Diclofenac solution)	Vehicle control solution	-0.44	-0.71	-0.16	Pennsaid (topical Diclofenac solution)	Possibly clinically significant
	Bookman (2004)	WOMAC Function	168	Yes	4	Topical Diclofenac	Placebo	-0.37	-0.67	-0.06	Topical Diclofenac	Possibly clinically significant

Type	Study	Outcome	N	Power	Week	Group 1	Group 2	ES	LCI	UCI	Favors	Clinical Significance
	Bookman (2004)	WOMAC Function	163	Yes	4	Topical Diclofenac	Vehicle control	-0.43	-0.74	-0.12	Topical Diclofenac	Possibly clinically significant
	Rother (2007)	WOMAC Function	270	Yes	6	Topical ketoprofen	Celecoxib	0.1	-0.14	0.33	NS	True negative
	Rother (2007)	WOMAC Function	265	Yes	6	Topical ketoprofen	Placebo	-0.21	-0.45	0.03	NS	Inconclusive
	Rother (2007)	WOMAC Function	259	Yes	6	Celecoxib	Placebo	-0.31	-0.56	-0.07	Celecoxib	Possibly clinically significant
	Bookman (2004)	WOMAC Function	168	Yes	4	Topical Diclofenac	Placebo	-0.37	-0.67	-0.06	Topical Diclofenac	Possibly clinically significant
	Bookman (2004)	WOMAC Function	163	Yes	4	Topical Diclofenac	Vehicle control	-0.43	-0.74	-0.12	Topical Diclofenac	Possibly clinically significant
Pain	Roth (2004)	WOMAC Pain	322	Yes	12	Topical Diclofenac	Vehicle control	-0.35	-0.57	-0.13	Topical Diclofenac	Possibly clinically significant
	Roth (2004)	WOMAC Pain on walking	322	Yes	12	Topical Diclofenac	Vehicle control	-0.28	-0.5	-0.07	Topical Diclofenac	Unclear
	Baer (2005)	WOMAC Pain	212	Yes	6	Pennsaid (topical Diclofenac solution)	Vehicle control solution	-0.41	-0.68	-0.13	Pennsaid (topical Diclofenac solution)	Possibly clinically significant

Type	Study	Outcome	N	Power	Week	Group 1	Group 2	ES	LCI	UCI	Favors	Clinical Significance
	Baer (2005)	WOMAC Pain on walking	212	Yes	6	Pennsaid (topical Diclofenac solution)	Vehicle control solution	-0.35	-0.62	-0.08	Pennsaid (topical Diclofenac solution)	Unclear
	Ottillinger (2001)	VAS Pain	118	Yes	4	Eltenac gel 0.3%	Eltenac gel 0.1%	-0.11	-0.47	0.25	NS	True negative
	Ottillinger (2001)	VAS Pain	118	Yes	5	Eltenac gel 0.3%	Eltenac gel 0.1%	-0.15	-0.51	0.21	NS	True negative
	Ottillinger (2001)	VAS Pain	118	Yes	6	Eltenac gel 0.3%	Eltenac gel 0.1%	-0.1	-0.46	0.26	NS	True negative
	Ottillinger (2001)	VAS Pain	116	Yes	4	Eltenac gel 1%	Eltenac gel 0.3%	-0.18	-0.54	0.19	NS	True negative
	Ottillinger (2001)	VAS Pain	116	Yes	4	Eltenac gel 1%	Eltenac gel 0.1%	-0.29	-0.66	0.07	NS	True negative
	Ottillinger (2001)	VAS Pain	116	Yes	5	Eltenac gel 1%	Eltenac gel 0.3%	-0.12	-0.49	0.24	NS	True negative
	Ottillinger (2001)	VAS Pain	116	Yes	5	Eltenac gel 1%	Eltenac gel 0.1%	-0.28	-0.65	0.08	NS	True negative
	Ottillinger (2001)	VAS Pain	116	Yes	6	Eltenac gel 1%	Eltenac gel 0.3%	-0.1	-0.46	0.27	NS	True negative
	Ottillinger (2001)	VAS Pain	116	Yes	6	Eltenac gel 1%	Eltenac gel 0.1%	-0.2	-0.56	0.17	NS	True negative
	Ottillinger (2001)	VAS Pain	118	Yes	4	Eltenac gel 0.1%	Placebo gel	0.17	-0.19	0.53	NS	True negative
	Ottillinger (2001)	VAS Pain	118	Yes	5	Eltenac gel 0.1%	Placebo gel	0.15	-0.21	0.52	NS	True negative
	Ottillinger (2001)	VAS Pain	118	Yes	6	Eltenac gel 0.1%	Placebo gel	0.06	-0.3	0.42	NS	True negative

Type	Study	Outcome	N	Power	Week	Group 1	Group 2	ES	LCI	UCI	Favors	Clinical Significance
	Ottillinger (2001)	VAS Pain	118	Yes	4	Eltenac gel 0.3%	Placebo gel	0.06	-0.3	0.42	NS	True negative
	Ottillinger (2001)	VAS Pain	118	Yes	5	Eltenac gel 0.3%	Placebo gel	0	-0.36	0.36	NS	True negative
	Ottillinger (2001)	VAS Pain	118	Yes	6	Eltenac gel 0.3%	Placebo gel	-0.04	-0.4	0.32	NS	True negative
	Ottillinger (2001)	VAS Pain	116	Yes	4	Eltenac gel 1%	Placebo gel	-0.13	-0.5	0.23	NS	True negative
	Ottillinger (2001)	VAS Pain	116	Yes	5	Eltenac gel 1%	Placebo gel	-0.12	-0.49	0.24	NS	True negative
	Ottillinger (2001)	VAS Pain	116	Yes	6	Eltenac gel 1%	Placebo gel	-0.13	-0.5	0.23	NS	True negative
	Bookman (2004)	WOMAC Pain	163	Yes	4	Topical Diclofenac	Vehicle control	-0.34	-0.65	-0.03	Topical Diclofenac	Possibly clinically significant
	Bookman (2004)	WOMAC Pain	168	Yes	4	Topical Diclofenac	Placebo	-0.37	-0.68	-0.07	Topical Diclofenac	Possibly clinically significant
	Bookman (2004)	WOMAC Pain on walking	163	Yes	4	Topical Diclofenac	Vehicle control	-0.47	-0.79	-0.16	Topical Diclofenac	Unclear
	Bookman (2004)	WOMAC Pain on walking	168	Yes	4	Topical Diclofenac	Placebo	-0.4	-0.7	-0.09	Topical Diclofenac	Unclear
	Rother (2007)	WOMAC Pain	270	Yes	6	Topical ketoprofen	Celecoxib	0.03	-0.21	0.27	NS	True negative
	Rother (2007)	WOMAC Pain	265	Yes	6	Topical ketoprofen	Placebo	-0.34	-0.58	-0.1	topical ketoprofen	Possibly clinically significant

Type	Study	Outcome	N	Power	Week	Group 1	Group 2	ES	LCI	UCI	Favors	Clinical Significance
	Rother (2007)	WOMAC Pain	259	Yes	6	Celecoxib	Placebo	-0.35	-0.6	-0.11	Celecoxib	Possibly clinically significant
	Bookman (2004)	WOMAC Pain	163	Yes	4	Topical Diclofenac	Vehicle control	-0.34	-0.65	-0.03	Topical Diclofenac	Possibly clinically significant
	Bookman (2004)	WOMAC Pain	168	Yes	4	Topical Diclofenac	Placebo	-0.37	-0.68	-0.07	Topical Diclofenac	Possibly clinically significant
	Bookman (2004)	WOMAC Pain on walking	163	Yes	4	Topical Diclofenac	Vehicle control	-0.47	-0.79	-0.16	Topical Diclofenac	
	Bookman (2004)	WOMAC Pain on walking	168	Yes	4	Topical Diclofenac	Placebo	-0.4	-0.7	-0.09	Topical Diclofenac	
Stiffness	Roth (2004)	WOMAC Stiffness	321	Yes	12	Topical Diclofenac	Vehicle control	-0.24	-0.46	-0.02	Topical Diclofenac	Possibly clinically significant
	Baer (2005)	WOMAC Stiffness	212	Yes	6	Pennsaid (topical Diclofenac solution)	Vehicle control solution	-0.44	-0.71	-0.16	Pennsaid (topical Diclofenac solution)	Possibly clinically significant
	Bookman (2004)	WOMAC Stiffness	168	Yes	4	Topical Diclofenac	Placebo	-0.42	-0.72	-0.11	Topical Diclofenac	Possibly clinically significant
	Bookman (2004)	WOMAC Stiffness	163	No	4	Topical Diclofenac	Vehicle control	-0.26	-0.56	0.05	NS	Inconclusive

Table 161. Interleukin Versus Control

Comparison	Study	Outcome	N	Power	Week	Group 1	Group 2	Effect Size	LCL	UCL	Favors	Clinical Importance
Interleukin Versus Placebo	Pavelka (2007)	Paracetamol intake pills per day	165	Yes	4	Diacerein	Placebo	-0.15	-0.45	0.16	NS	Unclear
	Pavelka (2007)	Paracetamol intake pills per day	165	Yes	8	Diacerein	Placebo	-0.08	-0.39	0.22	NS	Unclear
	Pavelka (2007)	Paracetamol intake pills per day	165	Yes	12	Diacerein	Placebo	-0.08	-0.38	0.23	NS	Unclear
	Pavelka (2007)	Paracetamol intake pills per day	165	Yes	16	Diacerein	Placebo	-0.31	-0.62	0	Diacerein	Unclear
	Pavelka (2007)	Paracetamol intake pills per day	165	Yes	20	Diacerein	Placebo	-0.4	-0.71	-0.1	Diacerein	Unclear
	Pavelka (2007)	Paracetamol intake pills per day	165	Yes	24	Diacerein	Placebo	-0.41	-0.72	-0.1	Diacerein	Unclear
	Pavelka (2007)	WOMAC Function	165	No	8	Diacerein	Placebo	-0.22	-0.53	0.08	NS	Inconclusive
	Pavelka (2007)	WOMAC Function	165	Yes	16	Diacerein	Placebo	-0.4	-0.7	-0.09	Diacerein	Possibly clinically significant
	Pavelka (2007)	WOMAC Function	165	Yes	20	Diacerein	Placebo	-0.54	-0.85	-0.23	Diacerein	Possibly clinically significant

Comparison	Study	Outcome	N	Power	Week	Group 1	Group 2	Effect Size	LCL	UCL	Favors	Clinical Importance
	Pavelka (2007)	WOMAC Function	165	Yes	24	Diacerein	Placebo	-0.42	-0.73	-0.11	Diacerein	Possibly clinically significant
	Pavelka (2007)	WOMAC Pain	165	No	8	Diacerein	Placebo	-0.21	-0.52	0.1	NS	Inconclusive
	Pavelka (2007)	WOMAC Pain	165	Yes	12	Diacerein	Placebo	-0.35	-0.66	-0.04	Diacerein	Possibly clinically significant
	Pavelka (2007)	WOMAC Pain	165	Yes	16	Diacerein	Placebo	-0.4	-0.7	-0.09	Diacerein	Possibly clinically significant
	Pavelka (2007)	WOMAC Pain	165	Yes	20	Diacerein	Placebo	-0.44	-0.75	-0.13	Diacerein	Possibly clinically significant
	Pavelka (2007)	WOMAC Pain	165	Yes	24	Diacerein	Placebo	-0.39	-0.7	-0.08	Diacerein	Possibly clinically significant
	Pavelka (2007)	WOMAC Stiffness	165	Yes	4	Diacerein	Placebo	-0.15	-0.46	0.15	NS	Inconclusive
	Pavelka (2007)	WOMAC Stiffness	165	Yes	8	Diacerein	Placebo	-0.18	-0.49	0.13	NS	Inconclusive
	Pavelka (2007)	WOMAC Stiffness	165	Yes	16	Diacerein	Placebo	-0.43	-0.74	-0.12	Diacerein	Possibly clinically significant
	Pavelka (2007)	WOMAC Stiffness	165	Yes	20	Diacerein	Placebo	-0.65	-0.97	-0.34	Diacerein	Possibly clinically significant

Comparison	Study	Outcome	N	Power	Week	Group 1	Group 2	Effect Size	LCL	UCL	Favors	Clinical Importance
	Pavelka (2007)	WOMAC Stiffness	165	Yes	24	Diacerein	Placebo	-0.43	-0.73	-0.12	Diacerein	Possibly clinically significant
	Pavelka (2007)	WOMAC Total	165	Yes	4	Diacerein	Placebo	-0.22	-0.52	0.09	NS	Inconclusive
	Pavelka (2007)	WOMAC Total	165	No	8	Diacerein	Placebo	-0.22	-0.53	0.09	NS	Inconclusive
	Pavelka (2007)	WOMAC Total	165	Yes	16	Diacerein	Placebo	-0.41	-0.72	-0.1	Diacerein	Possibly clinically significant
	Pavelka (2007)	WOMAC Total	165	Yes	20	Diacerein	Placebo	-0.55	-0.86	-0.24	Diacerein	Possibly clinically significant
	Pavelka (2007)	WOMAC Total	165	Yes	24	Diacerein	Placebo	-0.42	-0.73	-0.12	Diacerein	Possibly clinically significant
Interleukin Versus NSAID	Louthrenoo (2007)	Paracetamol intake pills per day	161	Yes	4	Diacerein	Piroxicam	0.19	-0.12	0.5	NS	Unclear
	Louthrenoo (2007)	Paracetamol intake pills per day	161	Yes	8	Diacerein	Piroxicam	0.2	-0.11	0.51	NS	Unclear
	Louthrenoo (2007)	Paracetamol intake pills per day	161	Yes	12	Diacerein	Piroxicam	0.3	-0.01	0.61	NS	Unclear
	Louthrenoo (2007)	Paracetamol intake pills per day	161	Yes	16	Diacerein	Piroxicam	0.31	0	0.62	Piroxicam	Unclear

Comparison	Study	Outcome	N	Power	Week	Group 1	Group 2	Effect Size	LCL	UCL	Favors	Clinical Importance
	Louthrenoo (2007)	Paracetamol intake pills per day	161	Yes	20	Diacerein	Piroxicam	-0.42	-0.73	-0.11	Diacerein	Unclear
	Louthrenoo (2007)	Paracetamol intake pills per day	161	Yes	24	Diacerein	Piroxicam	-0.46	-0.77	-0.14	Diacerein	Unclear
	Louthrenoo (2007)	WOMAC Function	161	Yes	4	Diacerein	Piroxicam	0.33	0.02	0.64	Piroxicam	Possibly clinically significant
	Louthrenoo (2007)	WOMAC Function	161	Yes	8	Diacerein	Piroxicam	0.23	-0.08	0.54	NS	Inconclusive
	Louthrenoo (2007)	WOMAC Function	161	Yes	12	Diacerein	Piroxicam	0.14	-0.17	0.45	NS	Inconclusive
	Louthrenoo (2007)	WOMAC Function	161	Yes	16	Diacerein	Piroxicam	0.13	-0.18	0.44	NS	Inconclusive
	Louthrenoo (2007)	WOMAC Function	161	No	20	Diacerein	Piroxicam	-0.37	-0.68	-0.05	Diacerein	Possibly clinically significant
	Louthrenoo (2007)	WOMAC Function	161	No	24	Diacerein	Piroxicam	-0.79	-1.11	-0.47	Diacerein	Clinically Significant
	Louthrenoo (2007)	SF-36 sum score	161	Yes	16	Diacerein	Piroxicam	-0.28	-0.59	0.03	NS	Unclear
	Louthrenoo (2007)	SF-36 sum score	161	Yes	24	Diacerein	Piroxicam	-0.11	-0.42	0.2	NS	Unclear
	Zheng (2006)	pain on walking	213	Yes	4	Diacerein	Diclofenac	0.08	-0.19	0.35	NS	True negative
	Zheng (2006)	Pain on walking	213	Yes	8	Diacerein	Diclofenac	0.06	-0.21	0.33	NS	True negative

Comparison	Study	Outcome	N	Power	Week	Group 1	Group 2	Effect Size	LCL	UCL	Favors	Clinical Importance
	Zheng (2006)	Pain on walking	213	Yes	12	Diacerein	Diclofenac	0.07	-0.2	0.34	NS	True negative
	Zheng (2006)	Pain on walking	213	Yes	16	Diacerein	Diclofenac	-0.15	-0.42	0.12	NS	True negative
	Zheng (2006)	VAS Pain on walking improvement	213	Yes	12	Diacerein	Diclofenac	0.19	-0.08	0.46	NS	True negative
	Zheng (2006)	VAS Pain on walking improvement	213	Yes		Diacerein	Diclofenac	-0.29	-0.56	-0.02	Diacerein	Not clinically significant
	Louthrenoo (2007)	WOMAC Pain	161	Yes	4	Diacerein	Piroxicam	0.36	0.05	0.68	Piroxicam	Possibly clinically significant
	Louthrenoo (2007)	WOMAC Pain	161	Yes	8	Diacerein	Piroxicam	0.2	-0.11	0.51	NS	Inconclusive
	Louthrenoo (2007)	WOMAC Pain	161	Yes	12	Diacerein	Piroxicam	0.17	-0.14	0.48	NS	Inconclusive
	Louthrenoo (2007)	WOMAC Pain	161	Yes	16	Diacerein	Piroxicam	0.18	-0.13	0.49	NS	Inconclusive
	Louthrenoo (2007)	WOMAC Pain	161	Yes	20	Diacerein	Piroxicam	-0.49	-0.81	-0.18	Diacerein	Possibly clinically significant
	Louthrenoo (2007)	WOMAC Pain	161	Yes	24	Diacerein	Piroxicam	-0.91	-1.24	-0.59	Diacerein	Clinically significant
	Louthrenoo (2007)	WOMAC Stiffness	161	Yes	4	Diacerein	Piroxicam	0.4	0.09	0.71	Piroxicam	Possibly clinically significant

Comparison	Study	Outcome	N	Power	Week	Group 1	Group 2	Effect Size	LCL	UCL	Favors	Clinical Importance
	Louthrenoo (2007)	WOMAC Stiffness	161	Yes	8	Diacerein	Piroxicam	0.21	-0.1	0.52	NS	Inconclusive
	Louthrenoo (2007)	WOMAC Stiffness	161	Yes	12	Diacerein	Piroxicam	0.17	-0.14	0.48	NS	Inconclusive
	Louthrenoo (2007)	WOMAC Stiffness	161	Yes	16	Diacerein	Piroxicam	0.23	-0.08	0.54	NS	Inconclusive
	Louthrenoo (2007)	WOMAC Stiffness	161	Yes	20	Diacerein	Piroxicam	-0.58	-0.9	-0.26	Diacerein	Possibly clinically significant
	Louthrenoo (2007)	WOMAC Stiffness	161	Yes	24	Diacerein	Piroxicam	-0.53	-0.84	-0.22	Diacerein	Possibly clinically significant
	Zheng (2006)	WOMAC Total	213	Yes	4	Diacerein	Diclofenac	0.21	-0.06	0.48	NS	Inconclusive
	Zheng (2006)	WOMAC Total	213	Yes	8	Diacerein	Diclofenac	0.07	-0.2	0.34	NS	True negative
	Zheng (2006)	WOMAC Total	213	Yes	12	Diacerein	Diclofenac	-0.05	-0.32	0.22	NS	True negative
	Zheng (2006)	WOMAC Total	213	Yes	16	Diacerein	Diclofenac	-0.24	-0.51	0.03	NS	Inconclusive
	Zheng (2006)	WOMAC Total	213	Yes	12	Diacerein	Diclofenac	-0.16	-0.43	0.11	NS	Inconclusive
	Zheng (2006)	WOMAC Total	213	Yes		Diacerein	Diclofenac	-0.37	-0.65	-0.1	Diacerein	Possibly clinically significant
	Louthrenoo (2007)	WOMAC Total	161	Yes	4	Diacerein	Piroxicam	0.35	0.04	0.67	Piroxicam	Possibly clinically significant

Comparison	Study	Outcome	N	Power	Week	Group 1	Group 2	Effect Size	LCL	UCL	Favors	Clinical Importance
	Louthrenoo (2007)	WOMAC Total	161	Yes	8	Diacerein	Piroxicam	0.23	-0.08	0.54	NS	Inconclusive
	Louthrenoo (2007)	WOMAC Total	161	Yes	12	Diacerein	Piroxicam	0.15	-0.16	0.46	NS	Inconclusive
	Louthrenoo (2007)	WOMAC Total	161	Yes	16-Jan	Diacerein	Piroxicam	0.15	-0.16	0.46	NS	Inconclusive
	Louthrenoo (2007)	WOMAC Total	161	Yes	20	Diacerein	Piroxicam	-0.43	-0.74	-0.11	Diacerein	Possibly clinically significant
	Louthrenoo (2007)	WOMAC Total	161	Yes	24	Diacerein	Piroxicam	-0.82	-1.15	-0.5	Diacerein	Clinically significant

Table 162. Acetaminophen Versus Control

Study	Outcome	N	Power	Week	Group 1	Group 2	Effect Size	LCL	UCL	Favors	Clinical Importance
Micelli (2004)	VAS Pain	774	Unclear	6	Acetaminophen	Placebo	Mean Difference=.8	-2.8	4.44	NS	Inconclusive
Bradley (1991)	HAQ Disability	121	Unclear	4	Acetaminophen	Ibuprofen	0	-0.36	0.36	NS	Unclear
Bradley (1991)	HAQ Disability	121	Unclear	4	Acetaminophen	Ibuprofen	-0.07	-0.43	0.29	NS	Unclear
Bradley (1991)	Health Assessment Questionnaire	121	Unclear	4	Acetaminophen	Ibuprofen	0.04	-0.32	0.39	NS	Unclear
Bradley (1991)	Health Assessment Questionnaire	121	Unclear	4	Acetaminophen	Ibuprofen	-0.02	-0.38	0.33	NS	Unclear
Bradley (1991)	Walk time (sec) improvement	121	Unclear	4	Acetaminophen	Ibuprofen	0	-0.36	0.36	NS	Unclear
Bradley (1991)	Walk time (sec)	121	Unclear	4	Acetaminophen	Ibuprofen	0.07	-0.28	0.43	NS	Unclear
Gualda (2007)	VAS Pain	168	Yes	6	Paracetamol	Aceclofenac	0.32	0.02	0.63	Aceclofenac	Unclear
Gualda (2007)	Lequesne index	168	Yes	6	Paracetamol	Aceclofenac	0.45	0.14	0.75	Aceclofenac	Unclear
Gualda (2007)	Patient Global Assessment	168	Yes	6	Paracetamol 1000mg	Aceclofenac 100mg	0.364933	0.059852	0.670014	Aceclofenac 100mg	Not Clinically Significant

Gualda (2007)	Physician Global Assessment	168	Yes	6	Paracetamol	Aceclofenac	0.304891	0.000583	0.6092	Aceclofenac	Unclear
Schnitzer (2009)	Patient Assessment of Treatment Response	203	Yes	4	Acetaminophen ER	Rofecoxib 25mg	0.368	0.231	0.505	Rofecoxib 25mg	Unclear
Schnitzer (2005)	Patient Assessment of Treatment Response	792	Yes	6	Acetaminophen 4000mg	Celecoxib 200mg	OR=0.663	0.492	0.893	Celecoxib 200mg	Unclear
Schnitzer (2005)	Patient Assessment of Treatment Response	528	Yes	6	Acetaminophen 4000mg	Rofecoxib 12.5mg	OR=0.697	0.494	0.984	Rofecoxib 12.5mg	Unclear
Schnitzer (2005)	Patient Assessment of Treatment Response	796	Yes	6	Acetaminophen 4000mg	Rofecoxib 25mg	OR=0.548	0.407	0.739	Rofecoxib 25mg	Unclear
Schnitzer (2009)	Physician Assessment of Treatment Response	211	Yes	4	Acetaminophen 1300mg	Rofecoxib 12.5mg	-0.18	-0.312	-0.045	Acetaminophen 1300mg	Unclear
Schnitzer (2009)	Physician Assessment of Treatment Response	203	Yes	4	Acetaminophen 1300mg	Rofecoxib 25mg	-0.354	-0.49	-0.21	Acetaminophen 1300mg	Unclear

Table 163. Tramadol Versus Control

Study	Outcome	N	Power	Week	Group 1	Group 2	Effect Size	LCL	UCL	Favors	Clinical Importance
Schnitzer (1999)	Minimum effective Naproxen dose: Naproxen responder subgroup	90	Unclear	8	Tramadol	Placebo	Mean difference=186 (p=.021)	-	-	Tramadol	Unclear
Schnitzer (1999)	Minimum effective Naproxen dose: Naproxen non-responder subgroup	147	Unclear	8	Tramadol	Placebo	Mean difference=23 (p=.706)	-	-	NS	Unclear
Fleischmann (2001)	WOMAC Function	129	Yes	13	Tramadol	Placebo	-0.33277	-0.68044	0.014912	NS	inconclusive
Babul (2004)	WOMAC Function	246	Yes	12	Tramadol ER	Placebo	Mean difference=-9.916 (p<.001)	-	-	Tramadol	Unclear
Babul (2004)	Patients' Global	246	Yes	12	Tramadol ER	Placebo	Mean difference=-14.8 (p<.001)	-	-	Tramadol	Unclear

Study	Outcome	N	Power	Week	Group 1	Group 2	Effect Size	LCL	UCL	Favors	Clinical Importance
Fishman (2007)	WOMAC Pain, percent improvement from baseline	322	Unclear	12	Tramadol Contramid	Placebo	0.179827	-0.05729	0.416943	NS	Unclear
Fishman (2007)	WOMAC Pain, percent improvement from baseline	330	Unclear	12	Tramadol Contramid	Placebo	0.219965	-0.01115	0.451077	NS	Unclear
Fishman (2007)	WOMAC Pain, percent improvement from baseline	327	Yes	12	Tramadol Contramid	Placebo	0.298874	0.065005	0.532742	Tramadol	Unclear
Fishman (2007)	WOMAC Pain, percent improvement from baseline	206	Unclear	12	Tramadol Contramid 100mg	Tramadol Contramid 200mg	-0.02477	-0.2981	0.248559	NS	Unclear
Fishman (2007)	WOMAC Pain, percent improvement from baseline	203	Unclear	12	Tramadol Contramid 100mg	Tramadol Contramid 300mg	-0.09695	-0.37232	0.178426	NS	Unclear

Study	Outcome	N	Power	Week	Group 1	Group 2	Effect Size	LCL	UCL	Favors	Clinical Importance
Fishman (2007)	WOMAC Pain, percent improvement from baseline	211	Unclear	12	Tramadol Contramid 200mg	Tramadol Contramid 300mg	-0.07361	-0.34359	0.196374	NS	Unclear
Burch (2007)	Improvement in pain intensity numerical rating scale	589	Yes	12	Tramadol Contramid OAD	Placebo	-0.35679	-0.5294	-0.18419	Tramadol	Unclear
Fleischmann (2001)	WOMAC Pain	129	Yes	13	Tramadol	Placebo	-0.43138	-0.78072	-0.08204	Tramadol	Possibly clinically significant
Babul (2004)	VAS	246	Yes	12	Tramadol ER	Placebo	Mean difference=-15.3 (p<.001)	-	-	Tramadol	Unclear
Babul (2004)	WOMAC Pain	246	Yes	12	Tramadol ER	Placebo	Mean difference=-2.76 (p<.001)	-	-	Tramadol	Unclear
Fleischmann (2001)	WOMAC Stiffness	129	Yes	13	Tramadol	Placebo	-0.358	-0.71	-0.01	Tramadol	Possibly clinically significant
Babul (2004)	WOMAC Stiffness	246	Yes	12	Tramadol ER	Placebo	Mean difference=-1.204 (p<.001)	-	-	Tramadol	Unclear
Beaulieu (2008)	WOMAC Pain	97	No	6	Tramadol	Diclofenac	. 067	-.33	.47	NS	Inconclusive

Study	Outcome	N	Power	Week	Group 1	Group 2	Effect Size	LCL	UCL	Favors	Clinical Importance
Beaulieu (2008)	WOMAC Function	97	No	6	Tramadol	Diclofenac	.061	-.34	.46	NS	Inconclusive
Beaulieu (2008)	WOMAC Stiffness	97	No	6	Tramadol	Diclofenac	.01	-.39	.41	NS	Inconclusive

Table 164. Active Treatments Versus Placebo: Patient and Physician Global Assessments

	Study	N	Sufficient Power	Week	Group 1	Group 2	Effect Size	Lower CI	Upper CI	Favors (NS=Not Significant)	Strength of Evidence
Patient Global Assessment	Williams (2000)	453	Yes	6	Celecoxib 200mg	Placebo	-0.33159	-0.51707	-0.14611	Celecoxib 200mg	Moderate
	Fleischmann (2004)	694	Yes	13	Lumiracoxib 400mg	Placebo	-0.34539	-0.50432	-0.18646	Lumiracoxib 400mg	Low
	Fleischmann (2004)	693	Yes	13	Lumiracoxib 200mg	Placebo	-0.32586	-0.48473	-0.16699	Lumiracoxib 200mg	Low
	Mckenna (2001)	399	Yes	6	Celecoxib	Placebo	-0.4335	-0.63206	-0.23495	Celecoxib	Moderate
	Mckenna (2001)	399	Yes	6	Diclofenac	Placebo	-0.52021	-0.71977	-0.32064	Diclofenac	Moderate
	Williams (2000)	462	Yes	6	Celecoxib 100mg	Placebo	-0.32841	-0.51202	-0.1448	Celecoxib 100mg	Moderate
	Williams (2001)	484	Yes	6	Celecoxib 100mg	Placebo	-3.06211	-3.32529	-2.79893	Celecoxib 100mg	Moderate

	Study	N	Sufficient Power	Week	Group 1	Group 2	Effect Size	Lower CI	Upper CI	Favors (NS=Not Significant)	Strength of Evidence
	Williams (2001)	474	Yes	6	Celecoxib 200mg	Placebo	-6.11409	-6.54443	-5.68376	Celecoxib 200mg	Moderate
	Roth(2004)	320	Yes	12	Topical Diclofenac	Placebo	-0.33255	-0.55321	-0.11188	Topical Diclofenac	High
	Gibofsky (2003)	285	Yes	6	Celecoxib 200mg	Placebo	OR=2.50	1.47	4.26	Celecoxib 200mg	Moderate
	Gibofsky (2003)	286	Yes	6	Rofecoxib 25mg	Placebo	OR=2.04	1.20	3.49	Rofecoxib 25mg	Moderate
Physician Global Assessment	Fleischmann (2006)	675	Yes	13	Celecoxib (Cox-2)	Placebo	-0.25204	-0.41161	-0.09247	Celecoxib (Cox-2)	Low
	Fleischmann (2006)	693	Yes	13	Lumiracoxib 200mg	Placebo	-0.35846	-0.51753	-0.1994	Lumiracoxib 200mg	Low
	Fleischmann (2006)	694	Yes	13	Lumiracoxib 400mg	Placebo	-0.34115	-0.50005	-0.18224	Lumiracoxib 400mg	Low
	Kivits (2002)	410	Yes	6	Valdecoxib 10mg (Cox-2)	Placebo	-0.2834	-0.47797	-0.08883	Valdecoxib 10mg (Cox-2)	Moderate
	Kivits (2002)	410	Yes	12	Valdecoxib 10mg (Cox-2)	Placebo	-0.28799	-0.48259	-0.09338	Valdecoxib 10mg (Cox-2)	Moderate
	Kivits (2002)	406	Unclear	6	Valdecoxib 20mg (Cox-2)	Placebo	-0.19324	-0.38825	0.001769	NS	Moderate
	Kivits (2002)	406	Yes	12	Valdecoxib 20mg (Cox-2)	Placebo	-0.22194	-0.4171	-0.02679	Valdecoxib 20mg (Cox-2)	Moderate
	Kivits (2002)	406	Yes	6	Valdecoxib 5mg (Cox-2)	Placebo	-0.22375	-0.41892	-0.02859	Valdecoxib 5mg (Cox-2)	Moderate
	Kivits (2002)	406	Yes	12	Valdecoxib 5mg (Cox-2)	Placebo	-0.19912	-0.39416	-0.00408	Valdecoxib 5mg (Cox-2)	Moderate
	Kivits (2002)	409	Yes	6	Naproxen	Placebo	-0.23307	-0.42757	-0.03858	Naproxen	Moderate

	Study	N	Sufficient Power	Week	Group 1	Group 2	Effect Size	Lower CI	Upper CI	Favors (NS=Not Significant)	Strength of Evidence
					(NSAID)					(NSAID)	
	Kivits (2002)	409	Yes	12	Naproxen (NSAID)	Placebo	-0.20185	-0.39618	-0.00753	Naproxen (NSAID)	Moderate
	Mckenna (2001)	399	Yes	6	Celecoxib (Cox-2)	Placebo	-0.3884	-0.5865	-0.19029	Celecoxib (Cox-2)	Moderate
	Mckenna (2001)	399	Yes	6	Diclofenac (NSAID)	Placebo	-0.55943	-0.75951	-0.35935	Diclofenac (NSAID)	Moderate
	Williams (2001)	484	Yes	6	Celecoxib 100mg	Placebo	-4.99222	-5.35479	-4.62964	Celecoxib 100mg	Moderate
	Williams (2001)	474	Yes	6	Celecoxib 200mg	Placebo	-6.65607	-7.1181	-6.19404	Celecoxib 200mg	Moderate
	Gibofsky (2003)	285	yes	6	Celecoxib 200mg	Placebo	OR=1.99	1.19	3.33	Celecoxib 200mg	Moderate
	Gibofsky (2003)	286	Unclear	6	Rofecoxib 25mg	Placebo	OR=1.59	0.95	2.66	NS	Moderate
Patient Global Assessment of Disease: Versus Placebo	Lehmann (2005)	844	Yes	13	Celecoxib	Placebo	-0.1617	-0.29685	-0.02655	Celecoxib	Low
	Lehmann (2005)	844	Yes	13	Lumiracoxib	Placebo	-0.25402	-0.3895	-0.11855	Lumiracoxib	Low
	Schnitzer (2010)	461	Yes	13	Naproxcinod 375mg	Placebo	-0.41661	-0.60131	-0.2319	Naproxcinod 375mg	Moderate
	Schnitzer (2010)	450	Yes	13	Naproxcinod 750mg	Placebo	-0.48149	-0.66899	-0.294	Naproxcinod 750mg	Moderate
	Schnitzer (2010)	446	Unclear	13	Naproxen	Placebo	-0.07352	-0.25921	0.11216	NS	Moderate

	Study	N	Sufficient Power	Week	Group 1	Group 2	Effect Size	Lower CI	Upper CI	Favors (NS=Not Significant)	Strength of Evidence
	Tannenbaum (2004)	724	Yes	13	Celecoxib 200mg	Placebo	-0.25907	-0.41391	-0.10424	Celecoxib 200mg	Moderate
	Tannenbaum (2004)	730	Yes	13	Lumiracoxib 200mg	Placebo	-0.28128	-0.43589	-0.12666	Lumiracoxib 200mg	Moderate
	Tannenbaum (2004)	734	Yes	13	Lumiracoxib 400mg	Placebo	-0.33077	-0.48544	-0.17611	Lumiracoxib 400mg	Moderate
	Ehrich (1999)	145	Yes	6	Rofecoxib 125mg	Placebo	-1.21037	-1.56523	-0.85551	Rofecoxib 125mg	Moderate
	Ehrich (1999)	145	Yes	6	Rofecoxib 25mg	Placebo	-1.03651	-1.38379	-0.68923	Rofecoxib 25mg	Moderate
	Schnitzer (2005)	209	Unclear	6	Naproxcinod 125mg	Placebo	OR=1.42	0.81	2.48	NS	Moderate
	Schnitzer (2005)	211	Yes	6	Naproxcinod 375mg	Placebo	OR=2.15	1.24	3.75	Naproxcinod 375mg	Moderate
	Schnitzer (2005)	218	Yes	6	Naproxcinod 750mg	Placebo	OR=3.01	1.73	5.22	Naproxcinod 750mg	Moderate
	Schnitzer (2005)	202	Yes	6	Rofecoxib 25mg	Placebo	OR=2.74	1.55	4.85	Rofecoxib 25mg	Moderate
	Schnitzer (2005)	221	Yes	6	Naproxen 500mg	Placebo	OR=2.62	1.52	4.53	Naproxen 500mg	Moderate
Physician Global Assessment of Disease: Versus	Ehrich (1999)	145	Yes	6	Rofecoxib 125mg	Placebo	-1.24218	-1.59853	-0.88583	Rofecoxib 125mg	Moderate
	Ehrich (1999)	145	Yes	6	Rofecoxib 25mg	Placebo	-1.04206	-1.38957	-0.69455	Rofecoxib 25mg	Moderate
	Lehmann	844	Yes	13	Celecoxib	Placebo	-0.22744	-0.36281	-0.09208	Celecoxib	Low

	Study	N	Sufficient Power	Week	Group 1	Group 2	Effect Size	Lower CI	Upper CI	Favors (NS=Not Significant)	Strength of Evidence
Placebo	(2005)				200mg					200mg	
	Lehmann (2005)	844	Yes	13	Lumiracoxib 100mg	Placebo	-0.26683	-0.40236	-0.1313	Lumiracoxib 100mg	Low
	Tannenbaum	724	Yes	13	Celecoxib 200mg	Placebo	-0.19281	-0.34739	-0.03823	Celecoxib 200mg	Moderate
	Tannenbaum	730	Yes	13	Lumiracoxib 200mg	Placebo	-0.21671	-0.37105	-0.06237	Lumiracoxib 200mg	Moderate
	Tannenbaum	734	Yes	13	Lumiracoxib 400mg	Placebo	-0.24974	-0.404	-0.09548	Lumiracoxib 400mg	Moderate
Patient Global Assessment of Response to Treatment: Versus Placebo	Ehrich (1999)	145	Yes	6	Rofecoxib 125mg	Placebo	-1.4568	-1.82405	-1.08955	Rofecoxib 125mg	Moderate
	Ehrich (1999)	145	Yes	6	Rofecoxib 25mg	Placebo	-1.21549	-1.57058	-0.86039	Rofecoxib 25mg	Moderate
	Schnitzer (2005)	209	Unclear	6	Naproxcinod 125mg	Placebo	OR= 1.49218	0.846163	2.631409	NS	Moderate
	Schnitzer (2005)	211	Yes	6	Naproxcinod 375mg	Placebo	OR= 2.644571	1.507841	4.638257	Naproxcinod 375mg	Moderate
	Schnitzer (2005)	218	Yes	6	Naproxcinod 750mg	Placebo	OR= 3.552502	2.02858	6.221234	Naproxcinod 750mg	Moderate
	Schnitzer (2005)	202	Yes	6	Rofecoxib 25mg	Placebo	OR= 4.4375	2.458447	8.009691	Rofecoxib 25mg	Moderate
	Schnitzer (2005)	221	Yes	6	Naproxen 500mg	Placebo	OR= 4.141667	2.359783	7.269059	Naproxen 500mg	Moderate
	Lohmander (2005)	532	Yes	6	Naproxcinod	Placebo	OR= 3.281416	2.128709	5.05832	Naproxcinod	Low

	Study	N	Sufficient Power	Week	Group 1	Group 2	Effect Size	Lower CI	Upper CI	Favors (NS=Not Significant)	Strength of Evidence
	Lohmander (2005)	516	Yes	6	Naproxen	Placebo	OR= 3.15	2.041247	4.860999	Naproxen	Low
	Kivitz (2004)	625	Yes	6	Rofecoxib 12.5mg	Placebo	OR= 3.370968	2.346792	4.842109	Rofecoxib 12.5mg	High
	Kivitz (2004)	614	Yes	6	Nabumetone	Placebo	OR= 2.459423	1.710647	3.535951	Nabumetone	High
	Gibofsky (2003)	285	Yes	6	Celecoxib 200mg	Placebo	OR=1.99	1.19	3.33	Celecoxib 200mg	Moderate
	Gibofsky (2003)	286	Unclear	6	Rofecoxib 25mg	Placebo	OR=1.59	0.95	2.66	NS	Moderate
Physician Global Assessment of Response to Treatment: Versus Placebo	Ehrich (1999)	145	Yes	6	Rofecoxib 125mg	Placebo	-1.20414	-1.55871	-0.84957	Rofecoxib 125mg	Moderate
	Ehrich (1999)	145	Yes	6	Rofecoxib 25mg	Placebo	-1.09595	-1.4457	-0.74619	Rofecoxib 25mg	Moderate

Table 165. Active Treatment Comparison: Patient and Physician Global Assessments

Outcome	Study	N	Sufficient Power	Week	Group 1	Group 2	Standardized Mean Differen	Lower Confidence	Upper Confidence	Favors (NS=Not Significant)	Strength of Evidence

							ce	Interval	Interval		
Patient Global Assessment	Ayral (2003)	436	Unclear	52	Tenidap 40mg	Piroxicam 20mg	0.018026	-0.16972	0.205768	NS	Moderate
	Ayral (2003)	427	Unclear	52	Tenidap 120mg	Piroxicam 20mg	-0.05034	-0.24009	0.139398	NS	Moderate
	Ayral (2003)	431	Unclear	52	Tenidap 40mg	Tenidap 120mg	0.066773	-0.12214	0.255683	NS	Moderate
	Gualda (2007)	168	Yes	6	Paracetamol 1000mg	Aceclofenac 100mg	0.364933	0.059852	0.670014	Aceclofenac 100mg	High
	Williams (2000)	453	Unclear	6	Celecoxib 200mg	Celecoxib 100mg	0	-0.18421	0.184211	NS	Moderate
	Fleischmann (2004)	906	Yes	13	Lumiracoxib 200mg	Celecoxib 200mg	-0.03012	-0.16038	0.100147	NS	Low
	Fleischmann (2004)	907	Yes	13	Lumiracoxib 400mg	Celecoxib 200mg	-0.04916	-0.17937	0.081048	NS	Low
	Williams (2000)	472	Yes	6	Celecoxib 100	Celecoxib 200mg	3.328012	3.048693	3.607332	Celecoxib 200mg	Moderate
	Mckenna (2001)	398	Unclear	6	Celecoxib	Diclofenac	-0.09074	-0.28733	0.105854	NS	Moderate

	Fleischmann (2004)	925	Yes	13	Lumiracoxib 200mg	Lumiracoxib 400mg	-1.79404	-1.94676	-1.64132	Lumiracoxib 200mg	Low
	Gibofsky (2003)	379	Unclear	6	Celecoxib 200mg	Rofecoxib 25mg	OR=1.223	0.816	1.833	NS	Moderate
Physician Global Assessment	Ayral (2003)	440	Unclear	52	Tenidap 40mg	Piroxicam 20mg	0.01343	-0.17345	0.200309	NS	Moderate
	Ayral (2003)	435	Unclear	52	Tenidap 120mg	Piroxicam 20mg	-0.03605	-0.22402	0.151914	NS	Moderate
	Ayral (2003)	437	Unclear	52	Tenidap 40mg	Tenidap 120mg	0.049571	-0.13799	0.237128	NS	Moderate
	Fleischmann (2006)	906	Yes	13	Lumiracoxib 200mg	Celecoxib 200mg	-0.11041	-0.24077	0.019947	NS	Low
	Fleischmann (2006)	907	Yes	13	Lumiracoxib 400mg	Celecoxib 200mg	-0.09055	-0.22081	0.039704	NS	Low
	Fleischmann (2006)	925	Yes	13	Lumiracoxib 200mg	Lumiracoxib 400mg	-0.02043	-0.14932	0.108461	NS	Low
	Gualda (2007)	168	Yes	6	Paracetamol	Aceclofenac	0.304891	0.000583	0.6092	Aceclofenac	High
	Kivits (2002)	409	Unclear	6	Valdecoxib 10mg (Cox-2)	Naproxen (NSAID)	-0.05067	-0.24453	0.143191	NS	Moderate
	Kivits (2002)	409	Unclear	12	Valdecoxib 10mg (Cox-	Naproxen	-0.08491	-0.27883	0.109002	NS	Moderate

					2)	(NSAID)					
	Kivits (2002)	405	Unclear	6	Valdecoxib 20mg	Naproxen	0.040733	-0.15408	0.235542	NS	Moderate
	Kivits (2002)	405	Unclear	12	Valdecoxib 20mg	Naproxen	-0.01896	-0.21375	0.175831	NS	Moderate
	Kivits (2002)	405	Unclear	6	Valdecoxib 5mg	Naproxen	0.010183	-0.18461	0.204973	NS	Moderate
	Kivits (2002)	405	Unclear	12	Valdecoxib 5mg	Naproxen	0	-0.19479	0.194788	NS	Moderate
	Mckenna (2001)	398	Yes	6	Celecoxib (Cox-2)	Diclofenac (NSAID)	0.200419	0.003434	0.397405	Diclofenac (NSAID)	Moderate
	Williams (2001)	472	Yes	6	Celecoxib 100mg	Celecoxib 200mg	1.664008	1.454409	1.873608	Celecoxib 200mg	Moderate
	Gibofsky (2003)	379	Unclear	6	Celecoxib 200mg	Rofecoxib 25mg	OR=1.249	0.833	1.872	NS	Moderate
Patient Global Assessment of Disease	Lehmann (2005)	844	Yes	13	Lumiracoxib	Celecoxib	-0.09042	-0.22542	0.044579	NS	Low
	Gottesdiener (2002)	224	Unclear	6	Etoricoxib 60mg	Etoricoxib 90mg	-0.01121	-0.27313	0.250699	NS	High
	Schnitzer (2010)	465	Unclear	13	Naproxen	Naproxcinod 375mg	-0.02577	-0.20765	0.156116	NS	Moderate

	Schnitzer (2010)	454	Unclear	13	Naproxen	Naproxcinod 750mg	-0.01771	-0.2017	0.166269	NS	Moderate
	Gottesdiener (2002)	231	Unclear	6	Etoricoxib 5mg	Etoricoxib 10mg	-0.0072	-0.26513	0.250735	NS	High
	Gottesdiener (2002)	219	Unclear	6	Etoricoxib 5mg	Etoricoxib 30mg	0.089384	-0.17626	0.355026	NS	High
	Gottesdiener (2002)	229	Yes	6	Etoricoxib 5mg	Etoricoxib 60mg	0.361565	0.10032 3	0.622807	Etoricoxib 60mg	High
	Gottesdiener (2002)	229	Yes	6	Etoricoxib 5mg	Etoricoxib 90mg	0.270129	0.00983 3	0.530426	Etoricoxib 90mg	High
	Gottesdiener (2002)	216	Unclear	6	Etoricoxib 10mg	Etoricoxib 30mg	0.0965	-0.17079	0.363787	NS	High
	Gottesdiener (2002)	226	Yes	6	Etoricoxib 10mg	Etoricoxib 60mg	0.367512	0.10452 2	0.630503	Etoricoxib 60mg	High
	Gottesdiener (2002)	226	Yes	6	Etoricoxib 10mg	Etoricoxib 90mg	0.276482	0.01445 7	0.538506	Etoricoxib 90mg	High
	Gottesdiener (2002)	214	Yes	6	Etoricoxib 30mg	Etoricoxib 60mg	0.283559	0.01393 8	0.55318	Etoricoxib 60mg	High
	Gottesdiener (2002)	214	Unclear	6	Etoricoxib 30mg	Etoricoxib 90mg	0.188602	-0.08026	0.457461	NS	High
	Gottesdiener	224	Unclear	6	Etoricoxib	Etoricoxib	-0.09502	-0.35709	0.167037	NS	High

	(2002)				60mg	90mg					
	Schnitzer (2005)	212	Unclear	6	Naproxcinod 125mg	Naproxcinod 375mg	OR=0.658	0.383	1.131	NS	Moderate
	Schnitzer (2005)	219	Yes	6	Naproxcinod 125mg	Naproxcinod 750mg	OR=0.471	0.275	0.809	Naproxcinod 750mg	Moderate
	Schnitzer (2005)	203	Yes	6	Naproxcinod 125mg	Rofecoxib 25mg	OR=0.517	0.296	0.904	Rofecoxib 25mg	Moderate
	Schnitzer (2005)	222	Yes	6	Naproxcinod 125mg	Naproxen 500mg	OR=0.540	0.317	0.921	Naproxen 500mg	Moderate
	Schnitzer (2005)	221	Unclear	6	Naproxcinod 375mg	Naproxcinod 750mg	OR=0.717	0.420	1.224	NS	Moderate
	Schnitzer (2005)	205	Unclear	6	Naproxcinod 375mg	Rofecoxib 25mg	OR=0.786	0.452	1.368	NS	Moderate
	Schnitzer (2005)	224	Unclear	6	Naproxcinod 375mg	Naproxen 500mg	OR=0.821	0.484	1.393	NS	Moderate
	Schnitzer (2005)	212	Unclear	6	Naproxcinod 750mg	Rofecoxib 25mg	OR=1.097	0.632	1.905	NS	Moderate
	Schnitzer (2005)	231	Unclear	6	Naproxcinod 750mg	Naproxen 500mg	OR=1.146	0.677	1.941	NS	Moderate
Physician Global Assessment of Disease	Gottesdiener	231	Unclear	6	Etoricoxib 5mg	Etoricoxib 10mg	-0.0072	-0.26513	0.250735	NS	High
	Gottesdiener	219	Unclear	6	Etoricoxib 5mg	Etoricoxib 30mg	0.089384	-0.17626	0.355026	NS	High
	Gottesdiener	216	Unclear	6	Etoricoxib 10mg	Etoricoxib 30mg	0.0965	-0.17079	0.363787	NS	High
	Gottesdiener	229	Yes	6	Etoricoxib	Etoricoxib	0.36156	0.10032	0.622807	Etoricoxib	High

	(2002)				5mg	60mg	5	3		60mg	
	Gottesdiener (2002)	226	Yes	6	Etoricoxib 10mg	Etoricoxib 60mg	0.367512	0.104522	0.630503	Etoricoxib 60mg	High
	Gottesdiener (2002)	214	Yes	6	Etoricoxib 30mg	Etoricoxib 60mg	0.283559	0.013938	0.55318	Etoricoxib 60mg	High
	Gottesdiener (2002)	229	Yes	6	Etoricoxib 5mg	Etoricoxib 90mg	0.270129	0.009833	0.530426	Etoricoxib 90mg	High
	Gottesdiener (2002)	226	Yes	6	Etoricoxib 10mg	Etoricoxib 90mg	0.276482	0.014457	0.538506	Etoricoxib 90mg	High
	Gottesdiener (2002)	214	Unclear	6	Etoricoxib 30mg	Etoricoxib 90mg	0.188602	-0.08026	0.457461	NS	High
	Gottesdiener (2002)	224	Unclear	6	Etoricoxib 60mg	Etoricoxib 90mg	-0.09502	-0.35709	0.167037	NS	High
	Lehmann (2005)	844	Unclear	13	Lumiracoxib 100mg	Celecoxib 200mg	-0.0413	-0.17625	0.093641	NS	Low
Patient Assessment of Treatment Response	Schnitzer (2009)	203	Yes	4	Acetaminophen ER	Rofecoxib 25mg	0.368	0.231	0.505	Rofecoxib 25mg	Moderate
	Schnitzer (2009)	209	Unclear	4	Rofecoxib 12.5mg	Rofecoxib 25mg	0.187256	-0.08475	0.459259	NS	Moderate
	Gottesdiener (2002)	231	Unclear	6	Etoricoxib 5mg	Etoricoxib 10mg	0.036058	-0.2219	0.294014	NS	High

	Gottesdiener (2002)	219	Unclear	6	Etoricoxib 5mg	Etoricoxib 30mg	0.091776	-0.17387	0.357425	NS	High
	Gottesdiener (2002)	229	Yes	6	Etoricoxib 5mg	Etoricoxib 60mg	0.422499	0.160477	0.68452	Etoricoxib 60mg	High
	Gottesdiener (2002)	229	Yes	6	Etoricoxib 5mg	Etoricoxib 90mg	0.319892	0.059114	0.58067	Etoricoxib 90mg	High
	Gottesdiener (2002)	216	Unclear	6	Etoricoxib 10mg	Etoricoxib 30mg	0.054969	-0.21221	0.32215	NS	High
	Gottesdiener (2002)	226	Yes	6	Etoricoxib 10mg	Etoricoxib 60mg	0.385586	0.122372	0.648801	Etoricoxib 60mg	High
	Gottesdiener (2002)	226	Yes	6	Etoricoxib 10mg	Etoricoxib 90mg	0.283165	0.021079	0.545251	Etoricoxib 90mg	High
	Gottesdiener (2002)	214	Yes	6	Etoricoxib 30mg	Etoricoxib 60mg	0.337582	0.067393	0.607771	Etoricoxib 60mg	High
	Gottesdiener (2002)	214	Unclear	6	Etoricoxib 30mg	Etoricoxib 90mg	0.233239	-0.03594	0.502418	NS	High
	Gottesdiener (2002)	224	Unclear	6	Etoricoxib 60mg	Etoricoxib 90mg	-0.10288	-0.36497	0.159209	NS	High
	Schnitzer (2005)	212	Yes	6	Naproxcinod 125mg	Naproxcinod 375mg	OR=0.564	0.327	0.973	Naproxcinod 375mg	Moderate
	Schnitzer (2005)	219	Yes	6	Naproxcinod 125mg	Naproxcinod 750mg	OR=0.420	0.244	0.723	Naproxcinod 750mg	Moderate

	Schnitzer (2005)	221	Unclear	6	Naproxcinod 375mg	Naproxcinod 750mg	OR=0.744	0.435	1.274	NS	Moderate
	Schnitzer (2005)	222	Yes	6	Naproxcinod 125mg	Naproxen 500mg	OR=0.360	0.209	0.621	Naproxen 500mg	Moderate
	Schnitzer (2005)	224	Unclear	6	Naproxcinod 375mg	Naproxen 500mg	OR=0.639	0.372	1.095	NS	Moderate
	Schnitzer (2005)	231	Unclear	6	Naproxcinod 750mg	Naproxen 500mg	OR=0.858	0.501	1.469	NS	Moderate
	Schnitzer (2005)	203	Yes	6	Naproxcinod 125mg	Rofecoxib 25mg	OR=0.336	0.189	0.597	Rofecoxib 25mg	Moderate
	Schnitzer (2005)	205	Unclear	6	Naproxcinod 375mg	Rofecoxib 25mg	OR=0.596	0.337	1.052	NS	Moderate
	Schnitzer (2005)	212	Unclear	6	Naproxcinod 750mg	Rofecoxib 25mg	OR=0.801	0.454	1.412	NS	Moderate
	Schnitzer (2005)	782	Unclear	6	Celecoxib 200mg	Rofecoxib 12.5mg	OR=1.051	0.780	1.416	NS	Moderate
	Schnitzer (2005)	1050	Unclear	6	Celecoxib 200mg	Rofecoxib 25mg	OR= 0.827	0.649	1.054	NS	Moderate
	Schnitzer (2005)	792	Yes	6	Acetaminophen 4000mg	Celecoxib 200mg	OR=0.663	0.492	0.893	Celecoxib 200mg	Moderate
	Schnitzer (2005)	528	Yes	6	Acetaminophen 4000mg	Rofecoxib 12.5mg	OR=0.697	0.494	0.984	Rofecoxib 12.5mg	Moderate
	Schnitzer (2005)	796	Yes	6	Acetaminophen 4000mg	Rofecoxib 25mg	OR=0.548	0.407	0.739	Rofecoxib 25mg	Moderate
	Schnitzer (2005)	786	Unclear	6	Rofecoxib 12.5mg	Rofecoxib 25mg	OR=0.786	0.584	1.059	NS	Moderate
	Lohmander (2005)	828	Yes	6	Naproxcinod	Naproxen	OR=1.042	0.767	1.415	NS	Low
	Kivitz (2004)	823	Yes	6	Rofecoxib 12.5mg	Nabumetone	OR=1.371	1.042	1.803	Rofecoxib 12.5mg	High

	McIlwain (1989)	65	Unclear	12	Orgotein 8x3	Orgotein 16x2	OR=0.783	0.272	2.253	NS	Moderate
	Gottesdiener (2002)	231	Unclear	6	Etoricoxib 5mg	Etoricoxib 10mg	0.03794	-0.22002	0.295898	NS	High
Physician Assessment of Treatment Response	Gottesdiener (2002)	219	Unclear	6	Etoricoxib 5mg	Etoricoxib 30mg	0.090097	-0.17555	0.355741	NS	High
	Gottesdiener (2002)	216	Unclear	6	Etoricoxib 10mg	Etoricoxib 30mg	0.051369	-0.21581	0.318544	NS	High
	Gottesdiener (2002)	229	Yes	6	Etoricoxib 5mg	Etoricoxib 60mg	0.36834	0.107018	0.629663	Etoricoxib 60mg	High
	Gottesdiener (2002)	226	Yes	6	Etoricoxib 10mg	Etoricoxib 60mg	0.329494	0.066939	0.592048	Etoricoxib 60mg	High
	Gottesdiener (2002)	214	Yes	6	Etoricoxib 30mg	Etoricoxib 60mg	0.283925	0.014301	0.55355	Etoricoxib 60mg	High
	Gottesdiener (2002)	229	Yes	6	Etoricoxib 5mg	Etoricoxib 90mg	0.311184	0.050496	0.571872	Etoricoxib 90mg	High
	Gottesdiener (2002)	226	Yes	6	Etoricoxib 10mg	Etoricoxib 90mg	0.272466	0.010478	0.534454	Etoricoxib 90mg	High
	Gottesdiener (2002)	214	Unclear	6	Etoricoxib 30mg	Etoricoxib 90mg	0.22585	-0.04327	0.494971	NS	High
	Gottesdiener (2002)	224	Unclear	6	Etoricoxib 60mg	Etoricoxib 90mg	-0.05728	-0.31925	0.204684	NS	High

	Schnitzer (2009)	211	Yes	4	Acetaminophen 1300mg	Rofecoxib 12.5mg	-0.18	-0.312	-0.045	Acetaminophen 1300mg	Moderate
	Schnitzer (2009)	203	Yes	4	Acetaminophen 1300mg	Rofecoxib 25mg	-0.354	-0.49	-0.21	Acetaminophen 1300mg	Moderate
	Schnitzer (2009)	208	Unclear	4	Rofecoxib 12.5mg	Rofecoxib 25mg	0.173523	-0.099	0.446042	NS	Moderate

Figure 47. Network Meta-Analysis: Analgesics Versus Placebo (Pain)

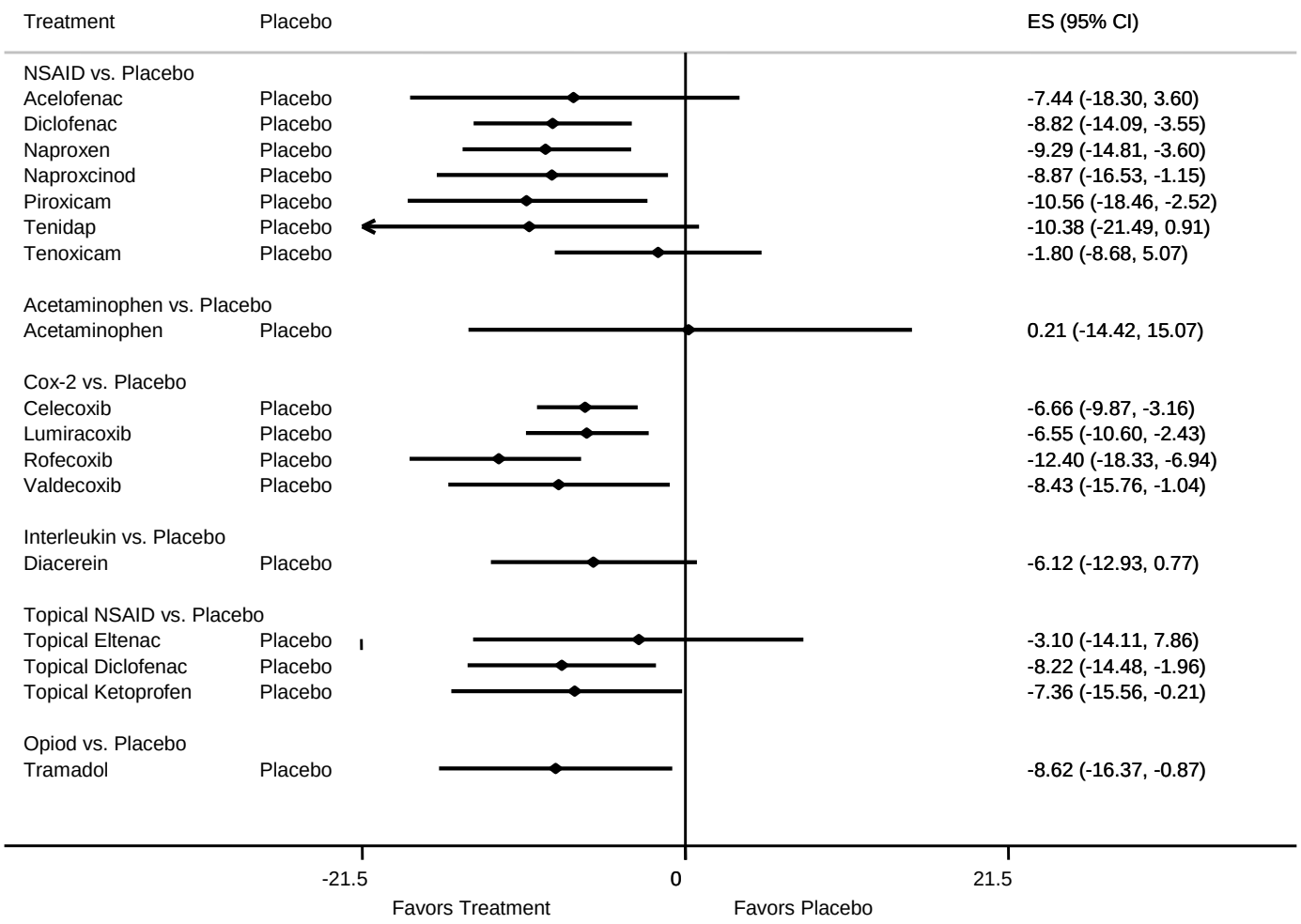


Figure 48. Network Meta-Analysis: Cox-2 Versus NSAIDS (Pain)

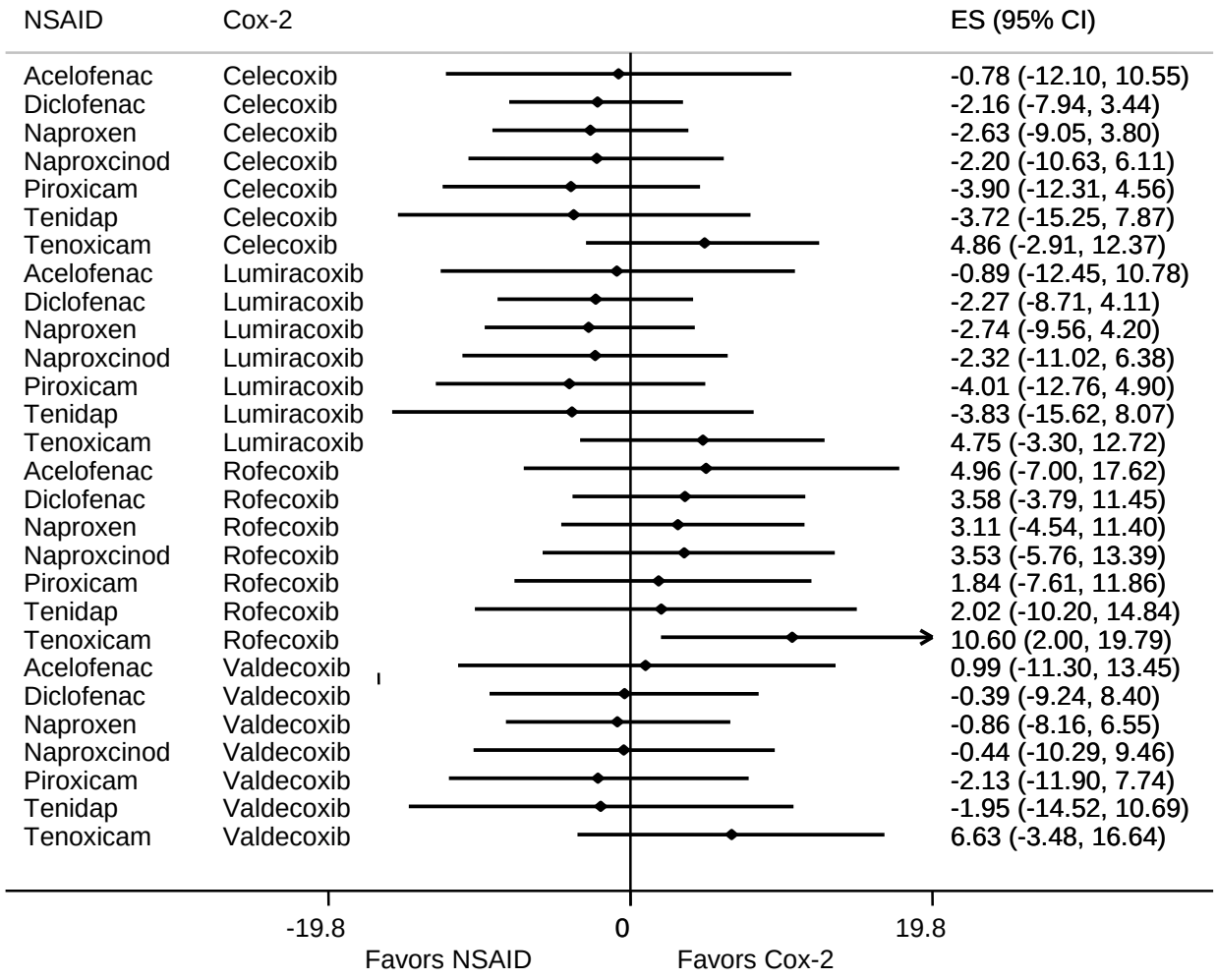


Figure 49. Network Meta-Analysis: Cox-2 Versus Cox-2 (Pain)

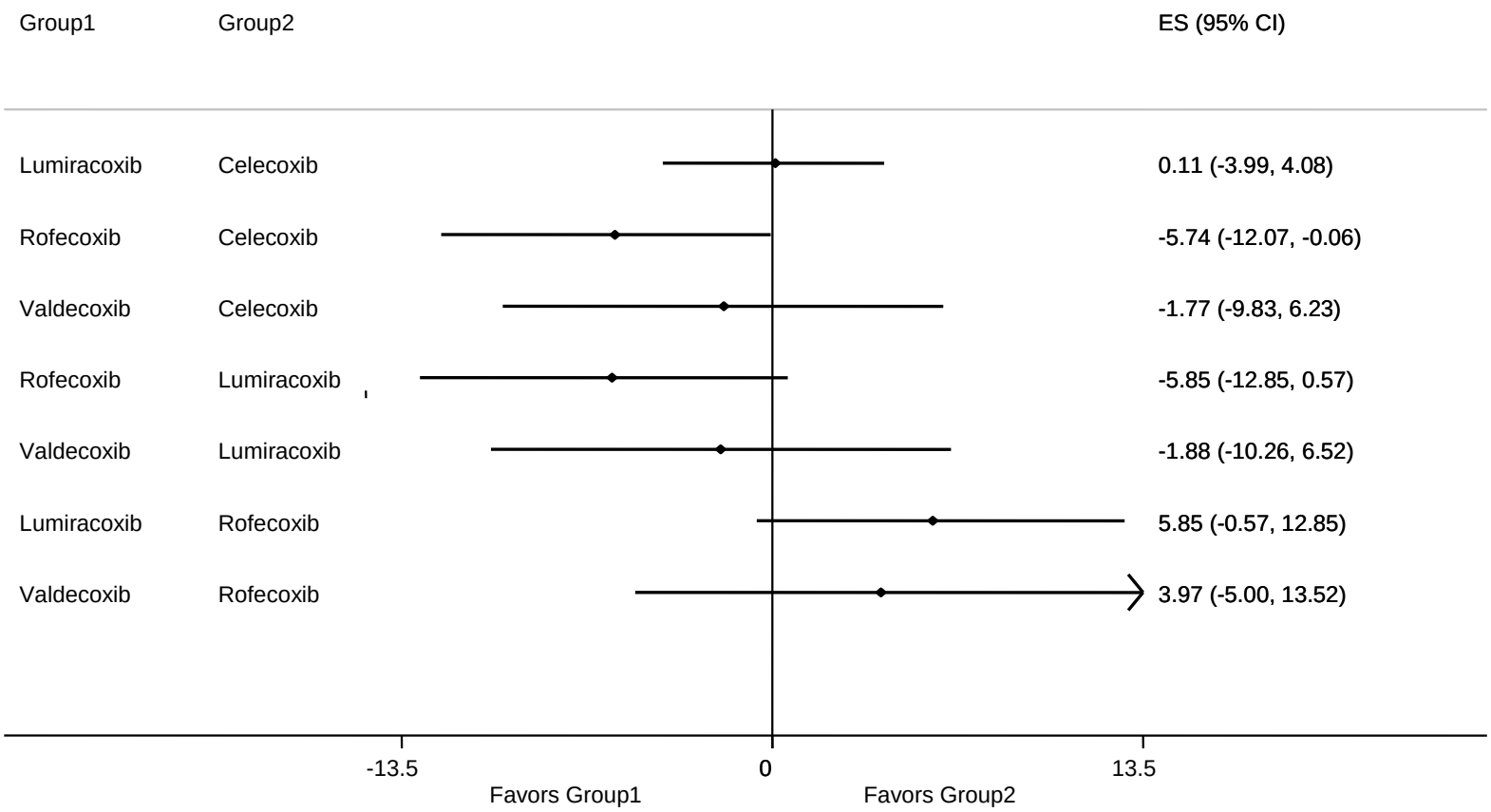


Figure 50. Network Meta-Analysis: NSAID Versus NSAID (Pain)

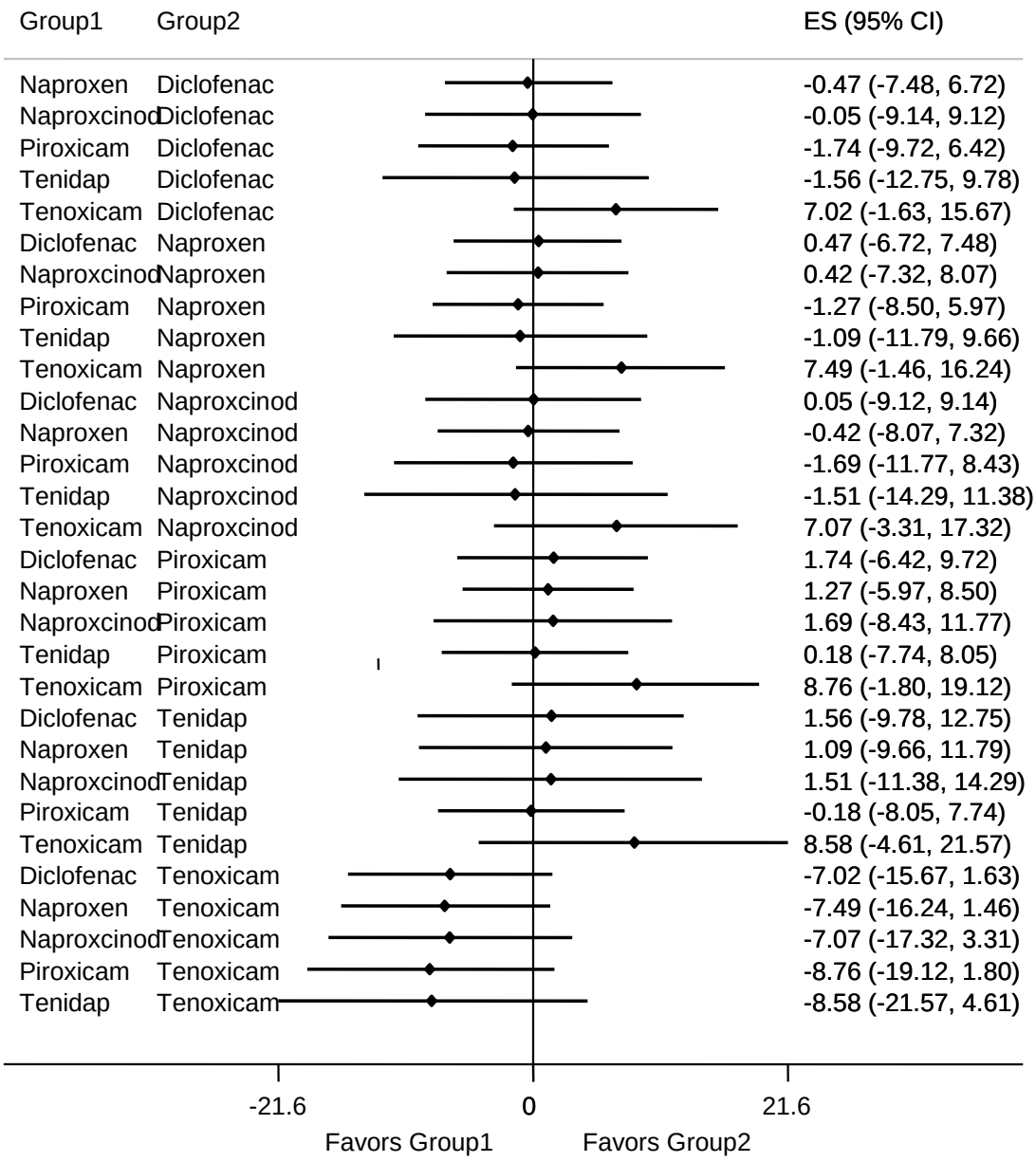


Figure 51. Network Meta-Analysis: Cox-2 and NSAIDS Versus Other Analgesics (Pain)

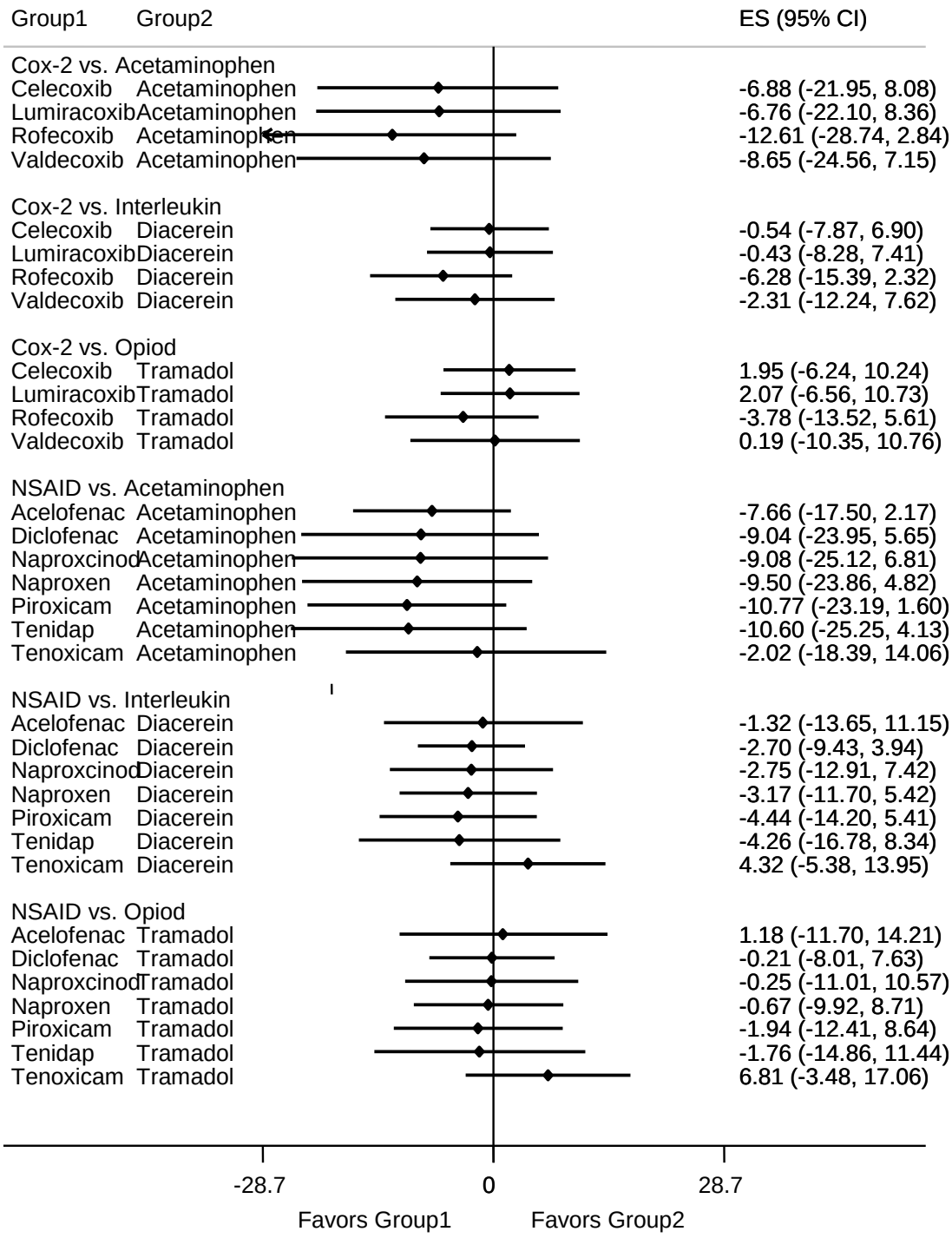


Figure 52. Network Meta-Analysis: Topical NSAIDS Versus Oral Analgesics (Pain)

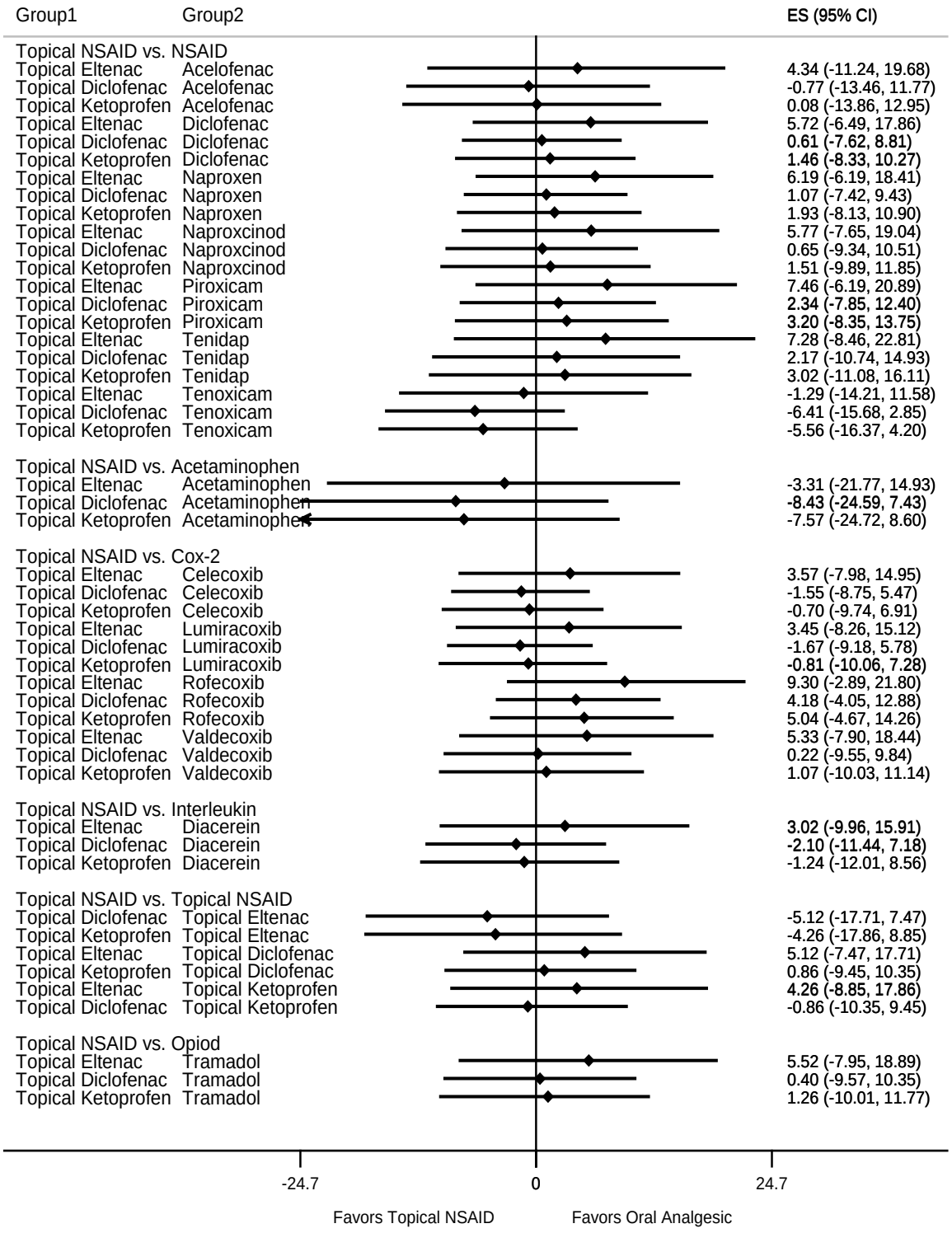
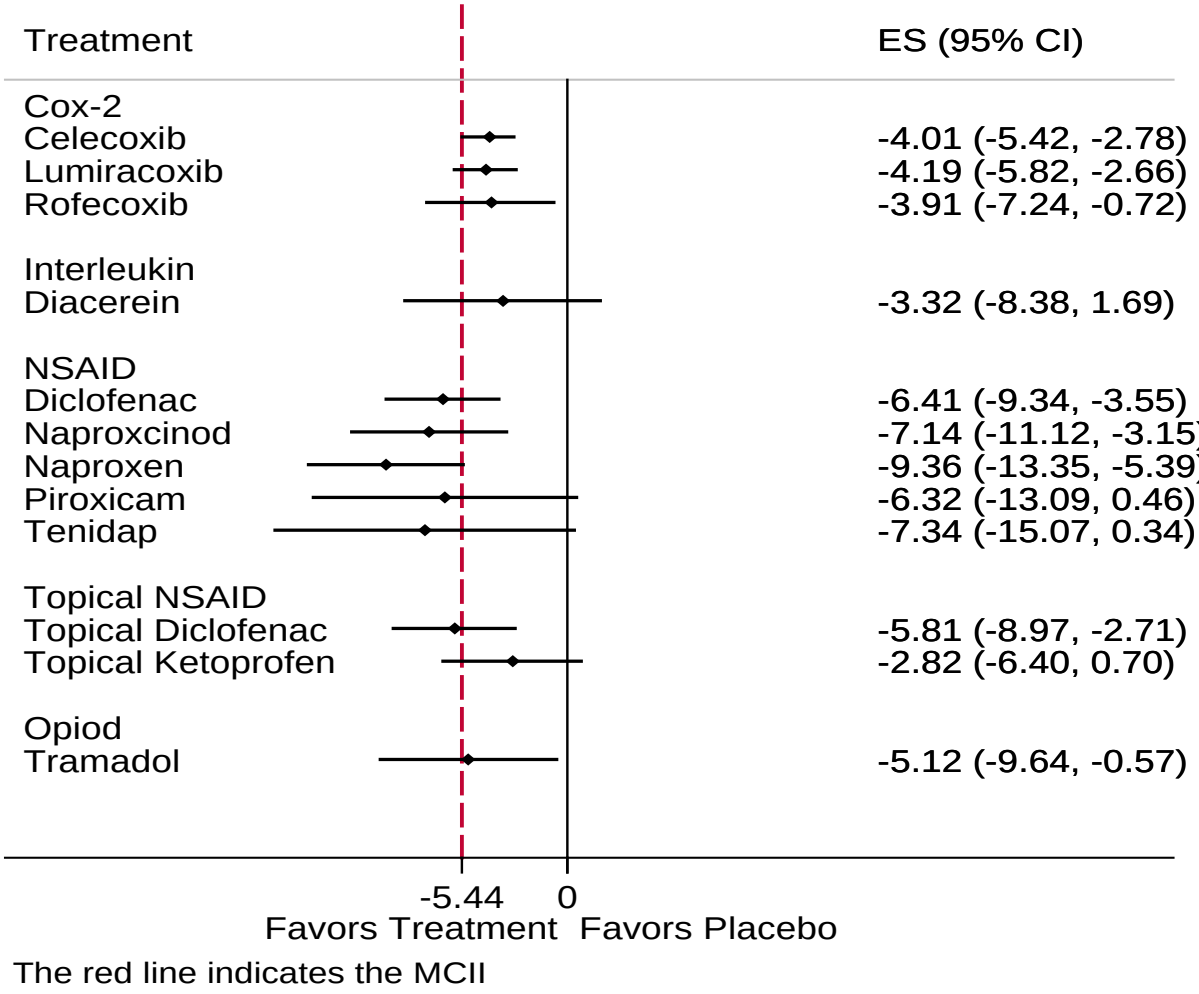
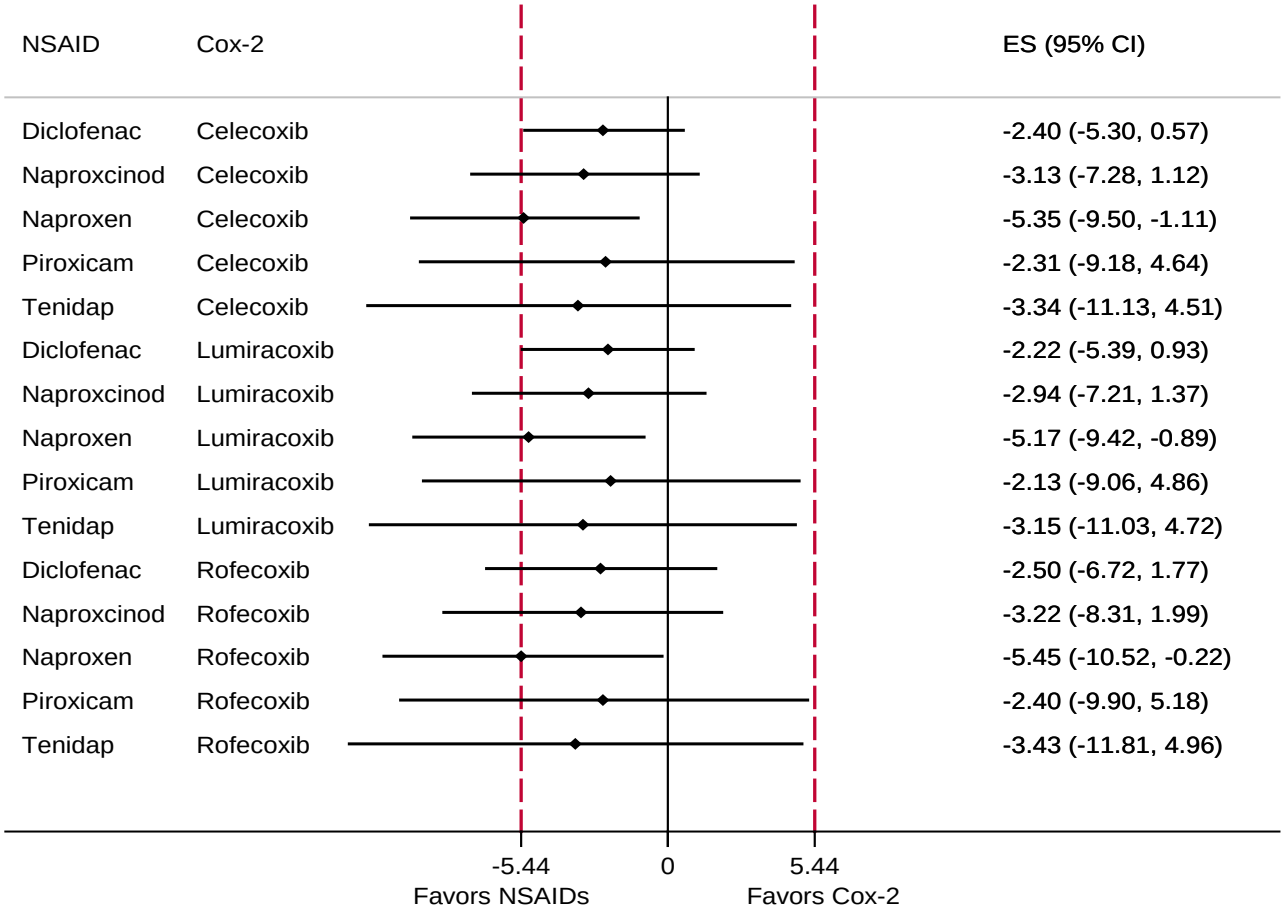


Figure 53. Network Meta-Analysis: Analgesics Versus Placebo (WOMAC Function)



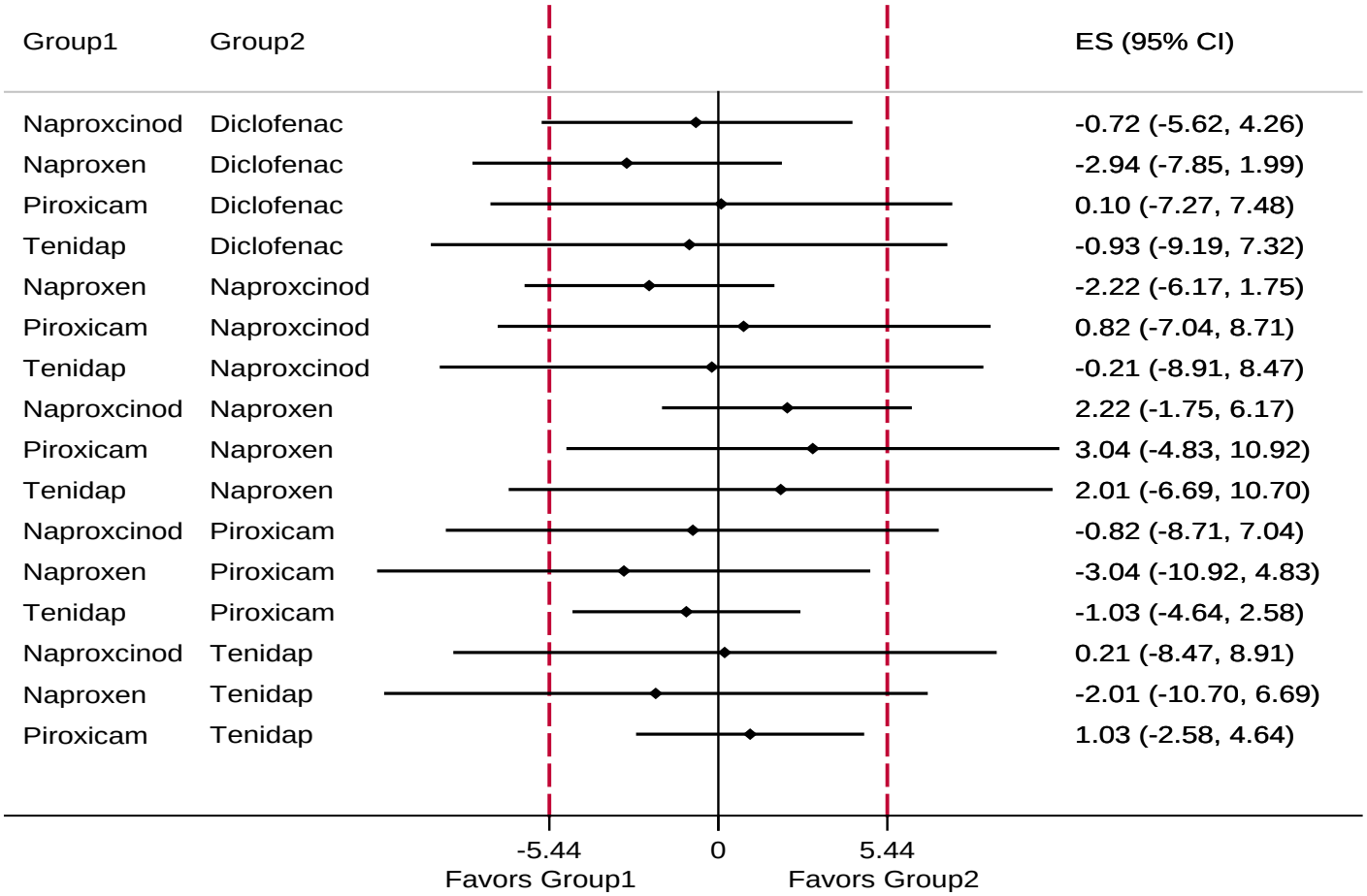
The red line indicates the MCII

Figure 54. Network Meta-Analysis: Cox-2 Versus NSAIDS (WOMAC Function)



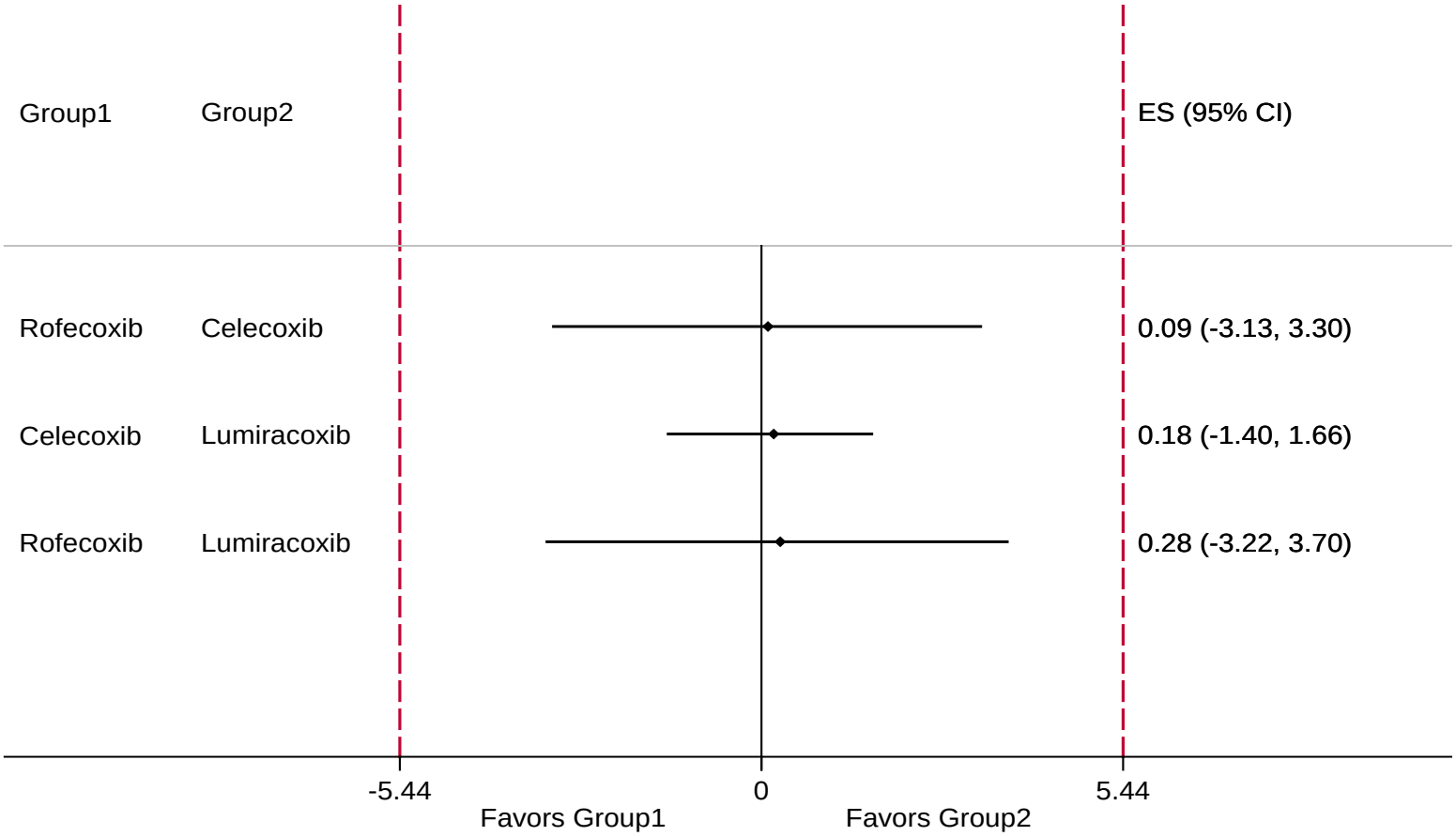
The red line indicates the MCII

Figure 55. Network Meta-Analysis: NSAID Versus NSAID (WOMAC Function)



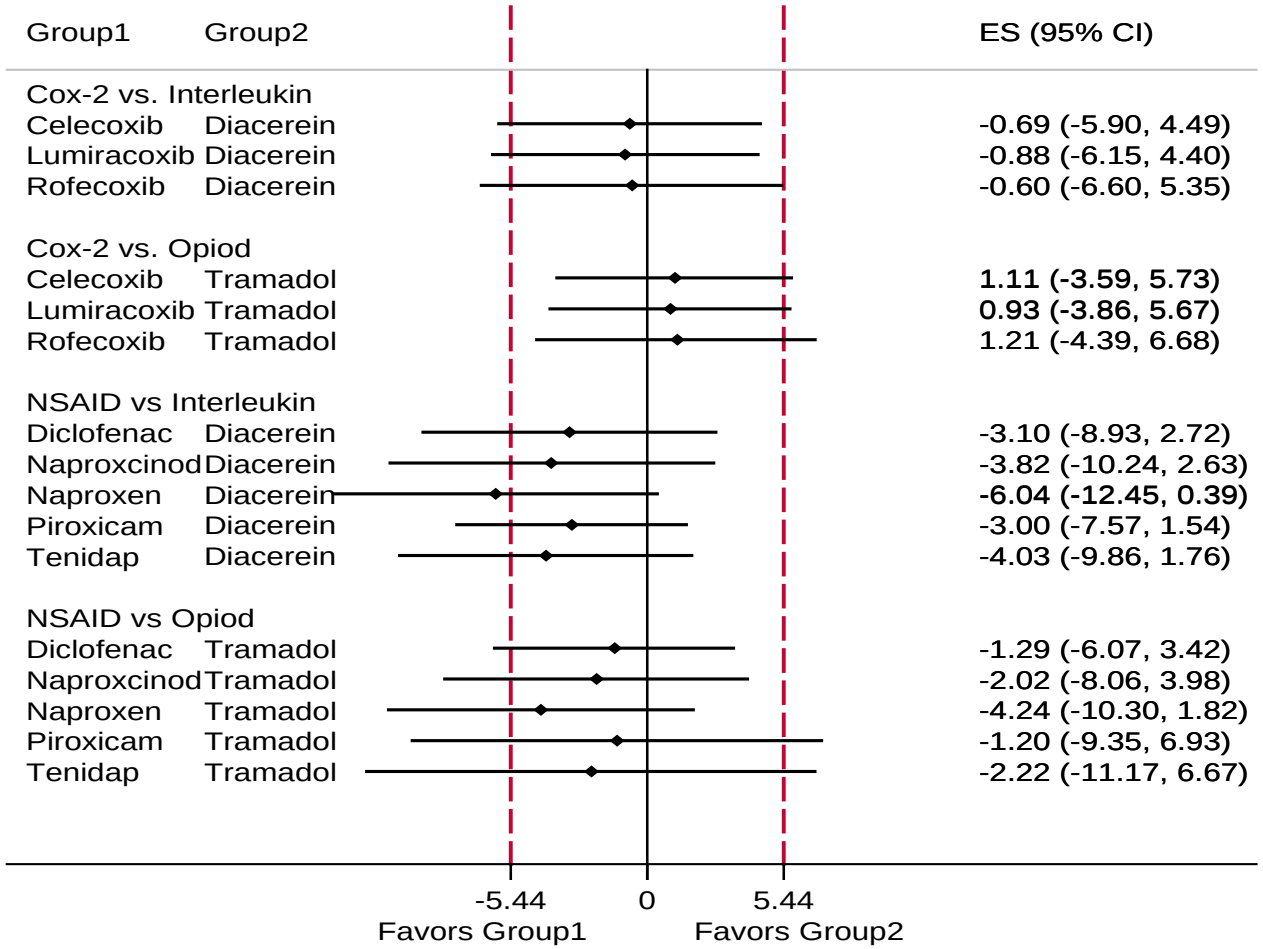
The red line indicates the MCII

Figure 56. Network Meta-Analysis: Cox-2 Versus Cox-2 (WOMAC Function)



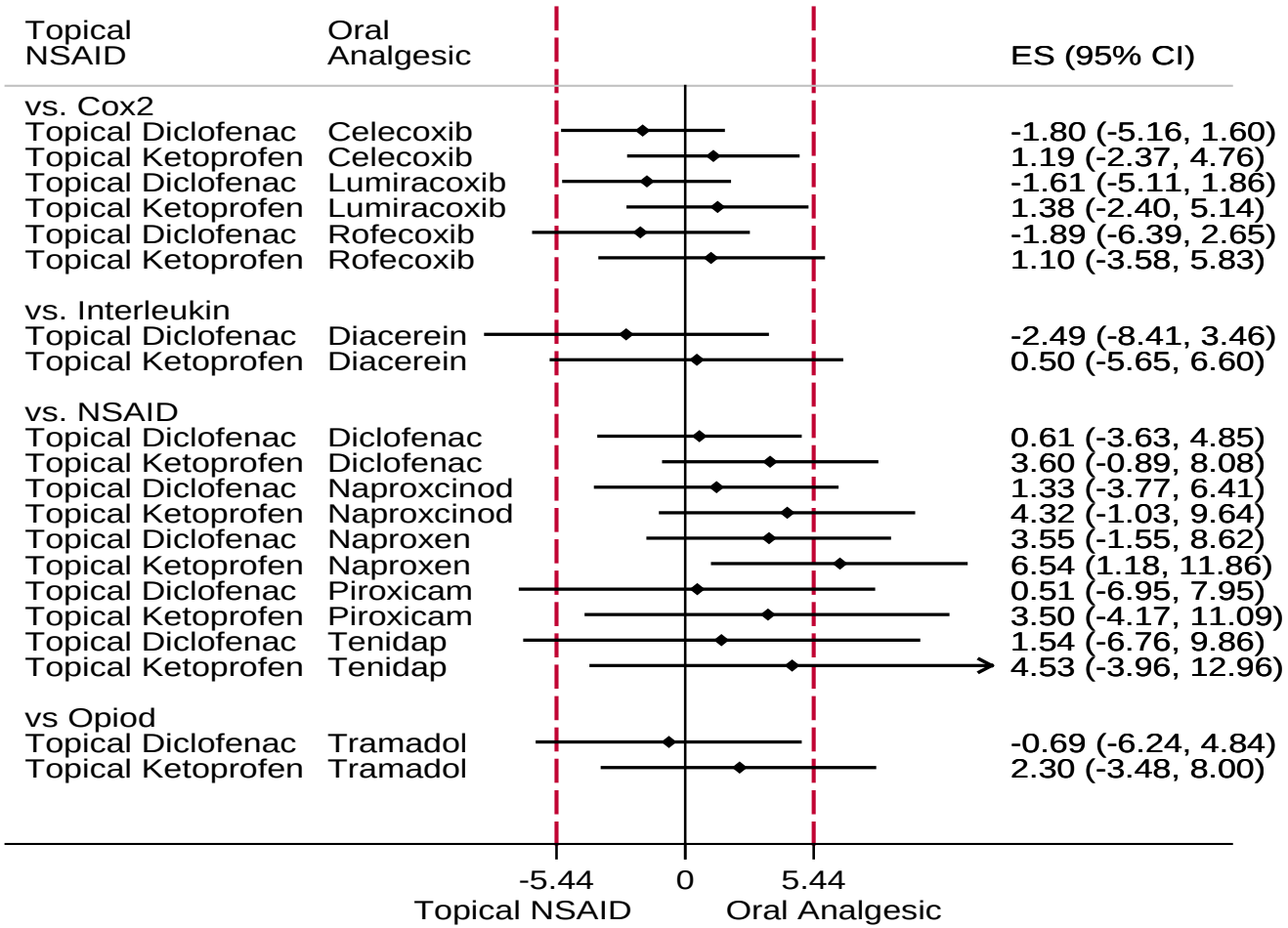
The red line indicates the MCII

Figure 57. Network Meta-Analysis: Cox-2 and NSAIDS Versus Other Analgesics (WOMAC Function)



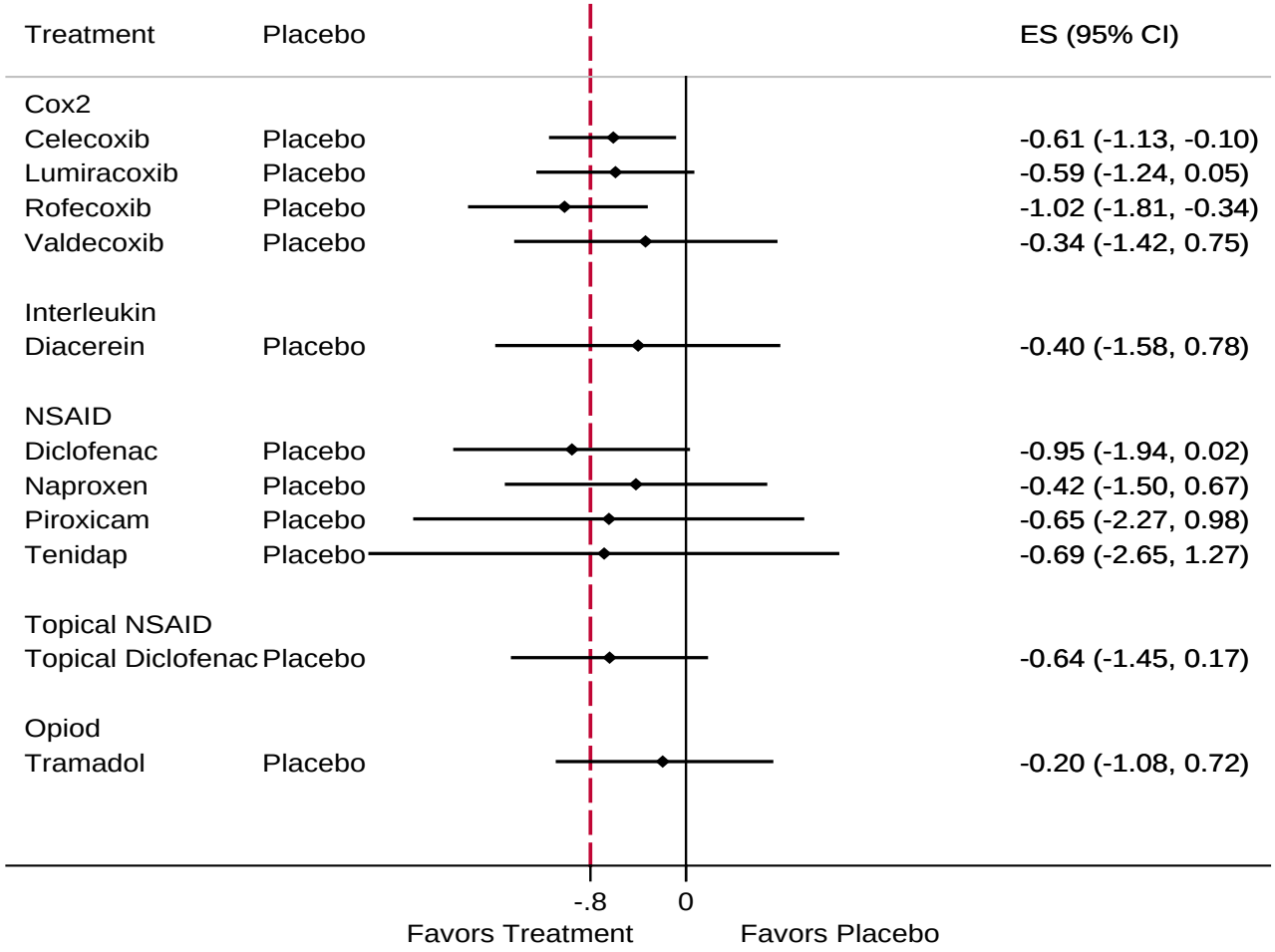
The red line indicates the MCII

Figure 58. Network Meta-Analysis: Topical NSAIDS Versus Other Analgesics (WOMAC Function)



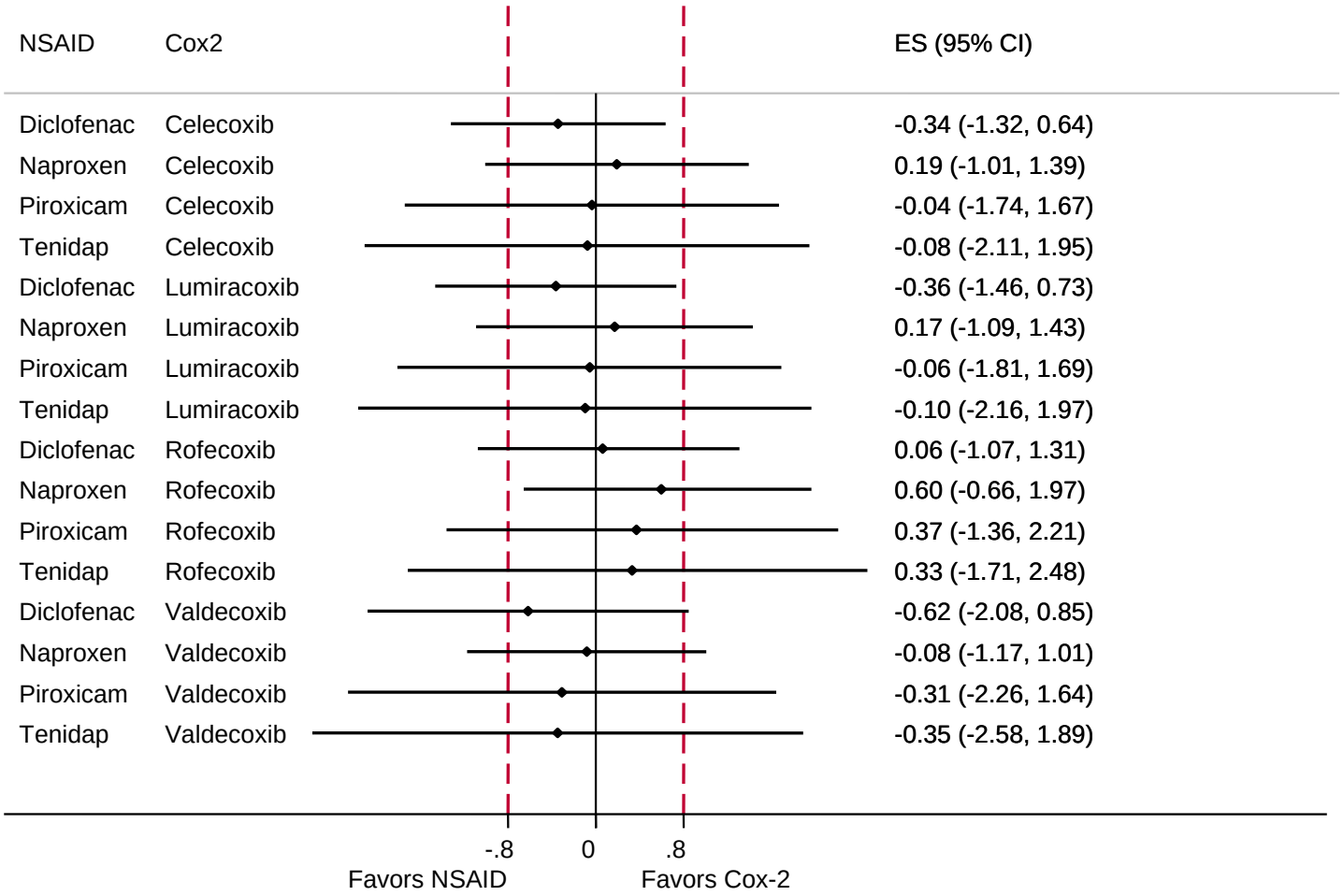
The red line indicates the MCII

Figure 59. Network Meta-Analysis: Analgesics Versus Placebo (WOMAC Stiffness)



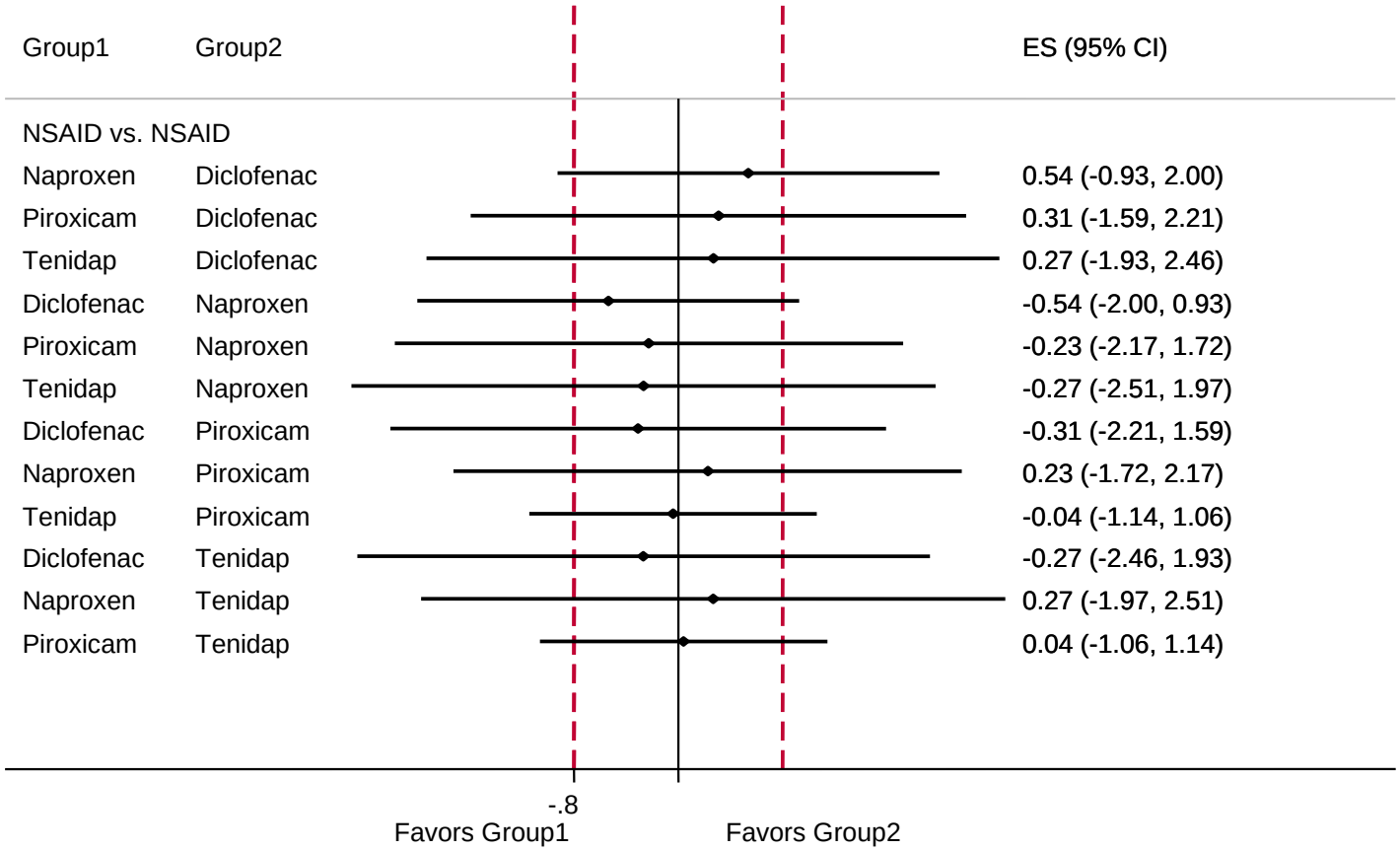
The red line indicates the MCII

Figure 60. Network Meta-Analysis: Cox-2 Versus NSAIDS (WOMAC Stiffness)



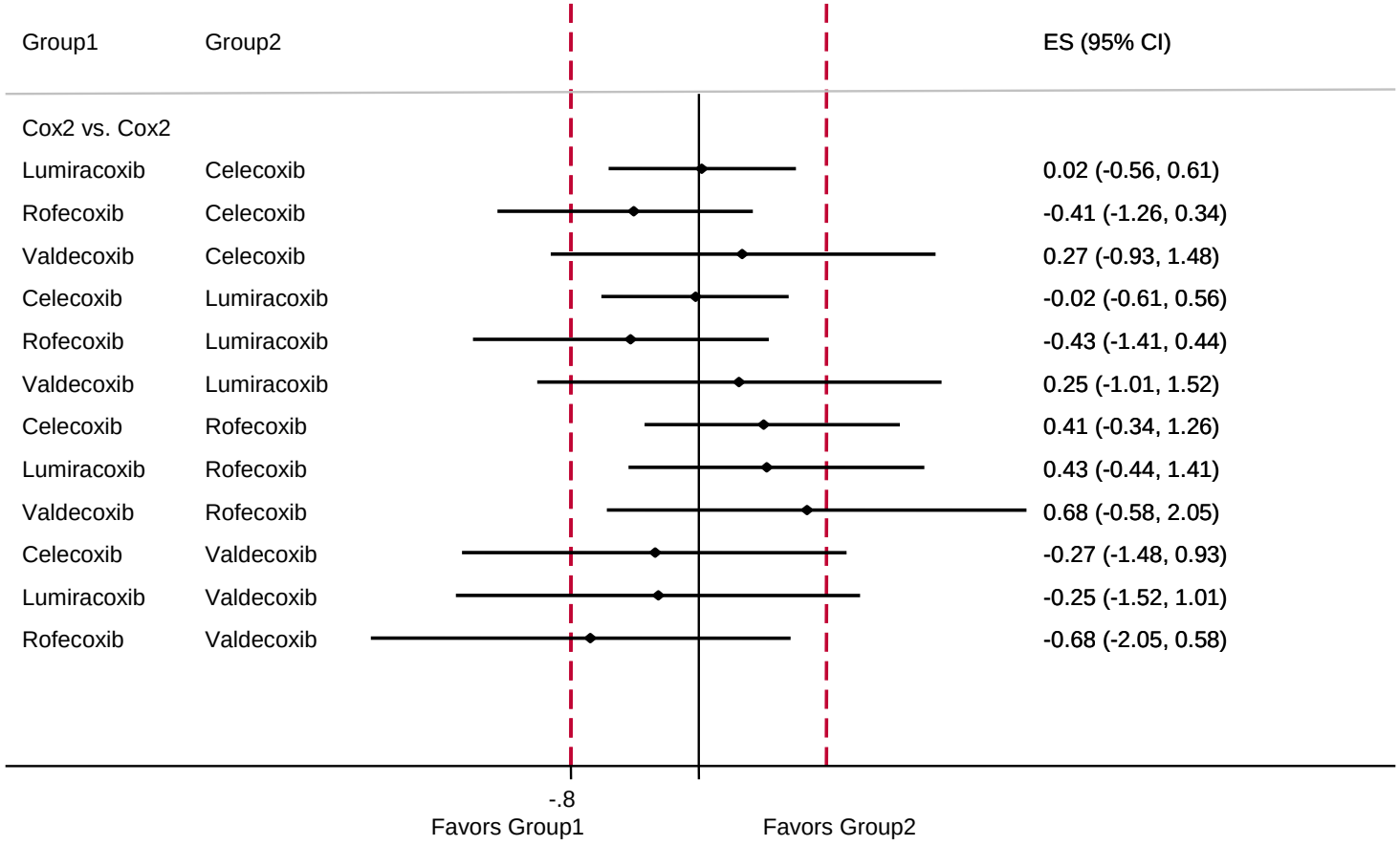
The red line indicates the MCII

Figure 61. Network Meta-Analysis: NSAIDS Versus NSAIDS (WOMAC Stiffness)



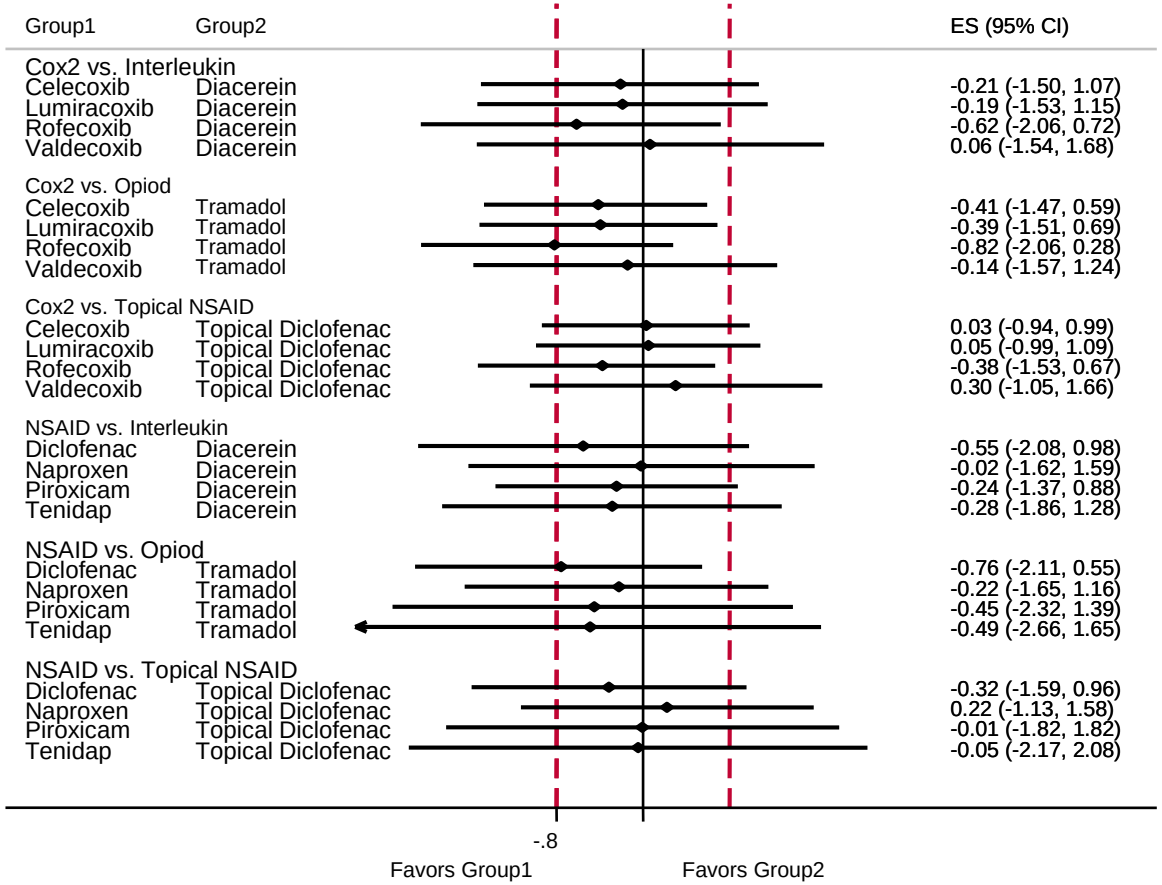
The red line indicates the MCII

Figure 62. Network Meta-Analysis: Cox-2 Versus Cox-2 (WOMAC Stiffness)



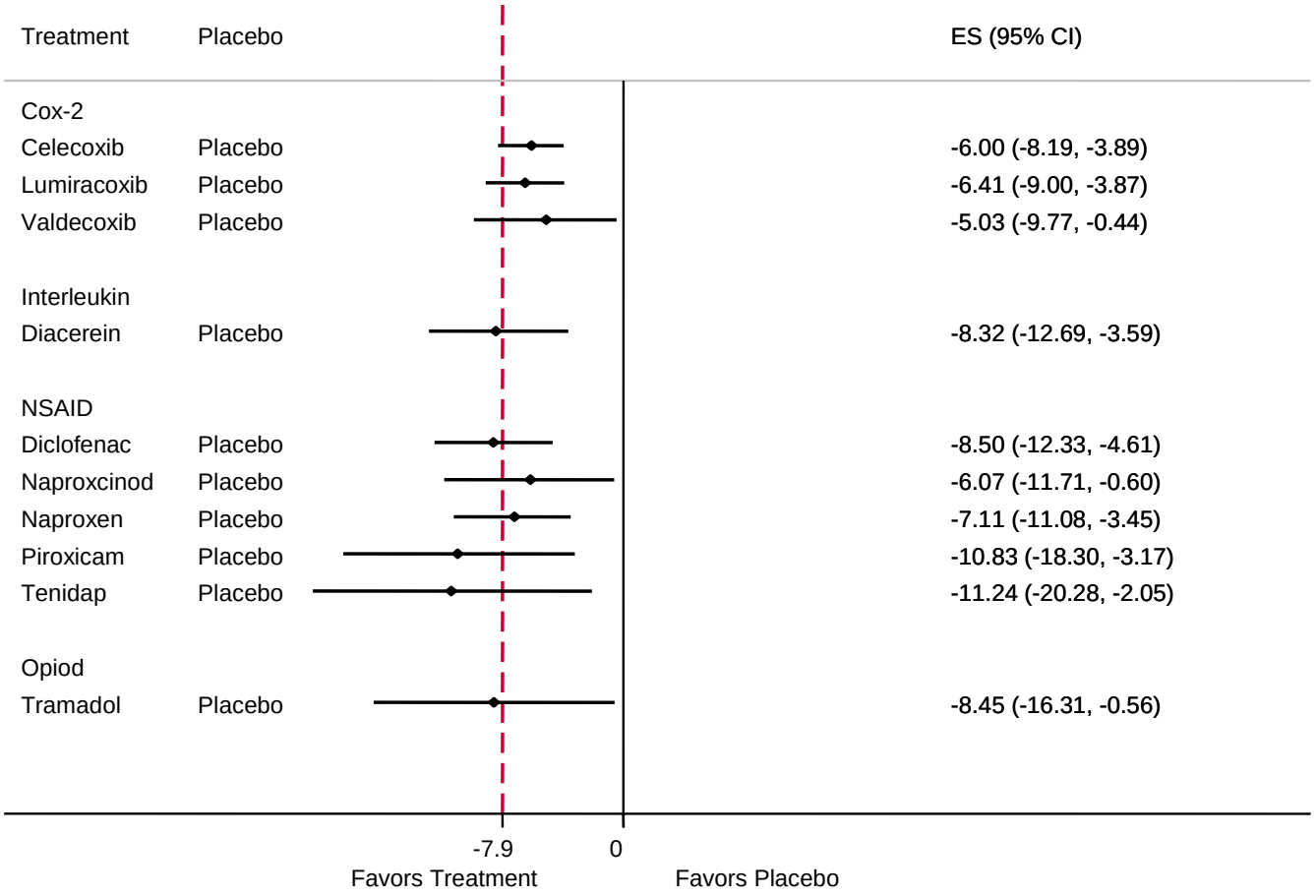
The red line indicates the MCII

Figure 63. Network Meta-Analysis: Cox-2 and NSAIDS Versus Other Analgesics (WOMAC Stiffness)



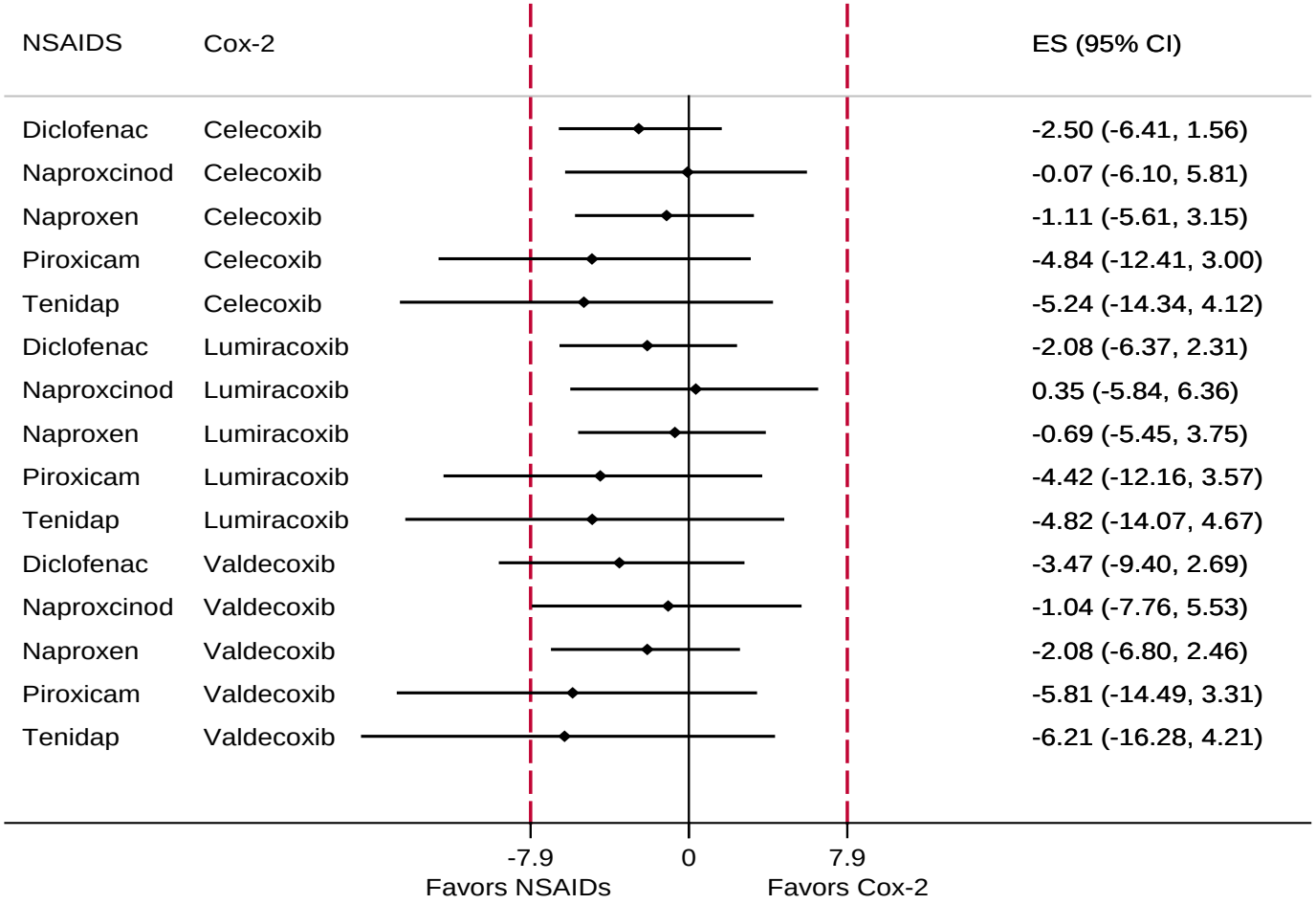
The red line indicates the MCII

Figure 64. Network Meta-Analysis: Analgesics Versus Placebo (WOMAC Total)



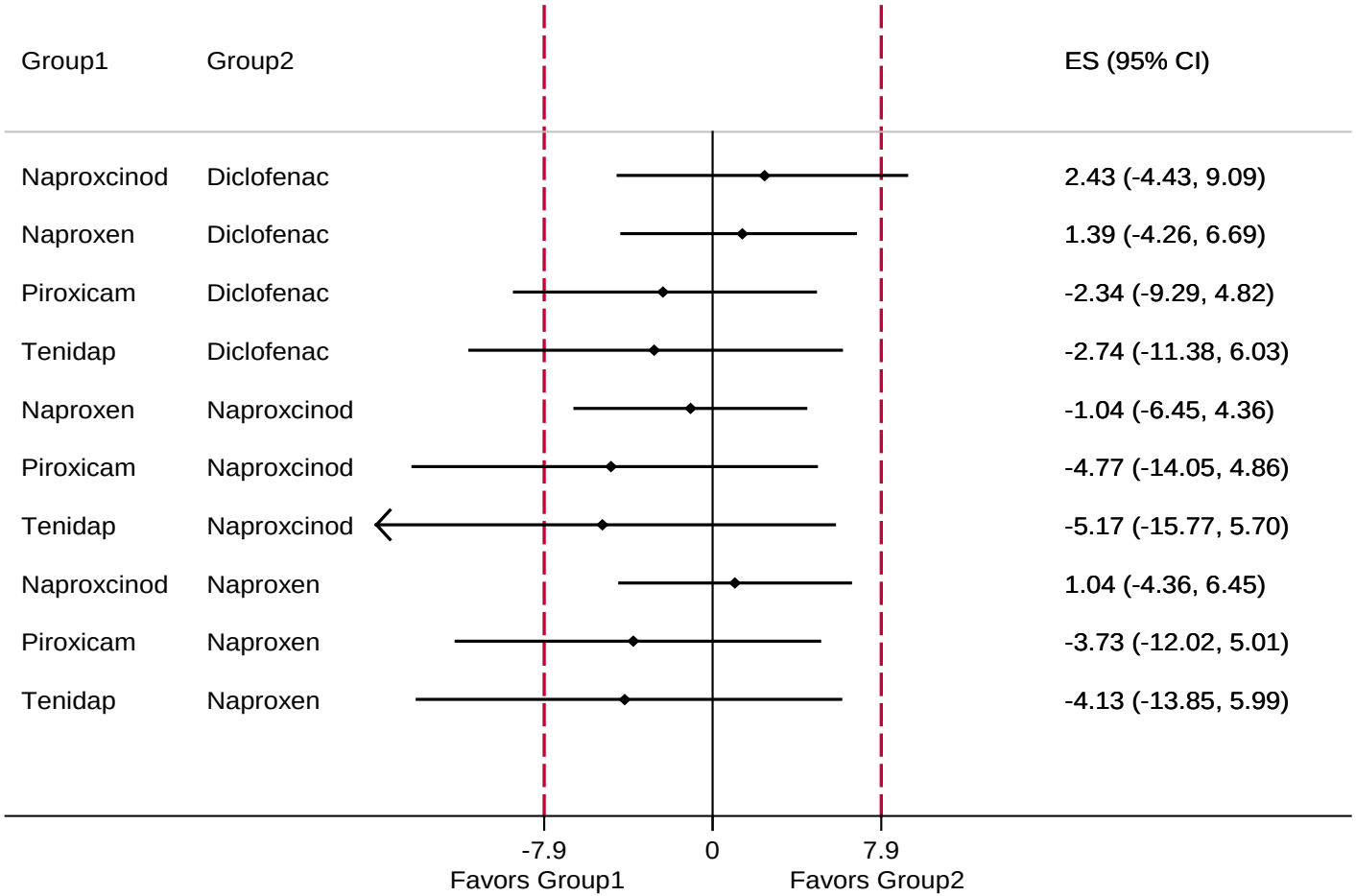
The red line indicates the MCII

Figure 65. Network Meta-Analysis: NSAIDS Versus Cox-2 (WOMAC Total)



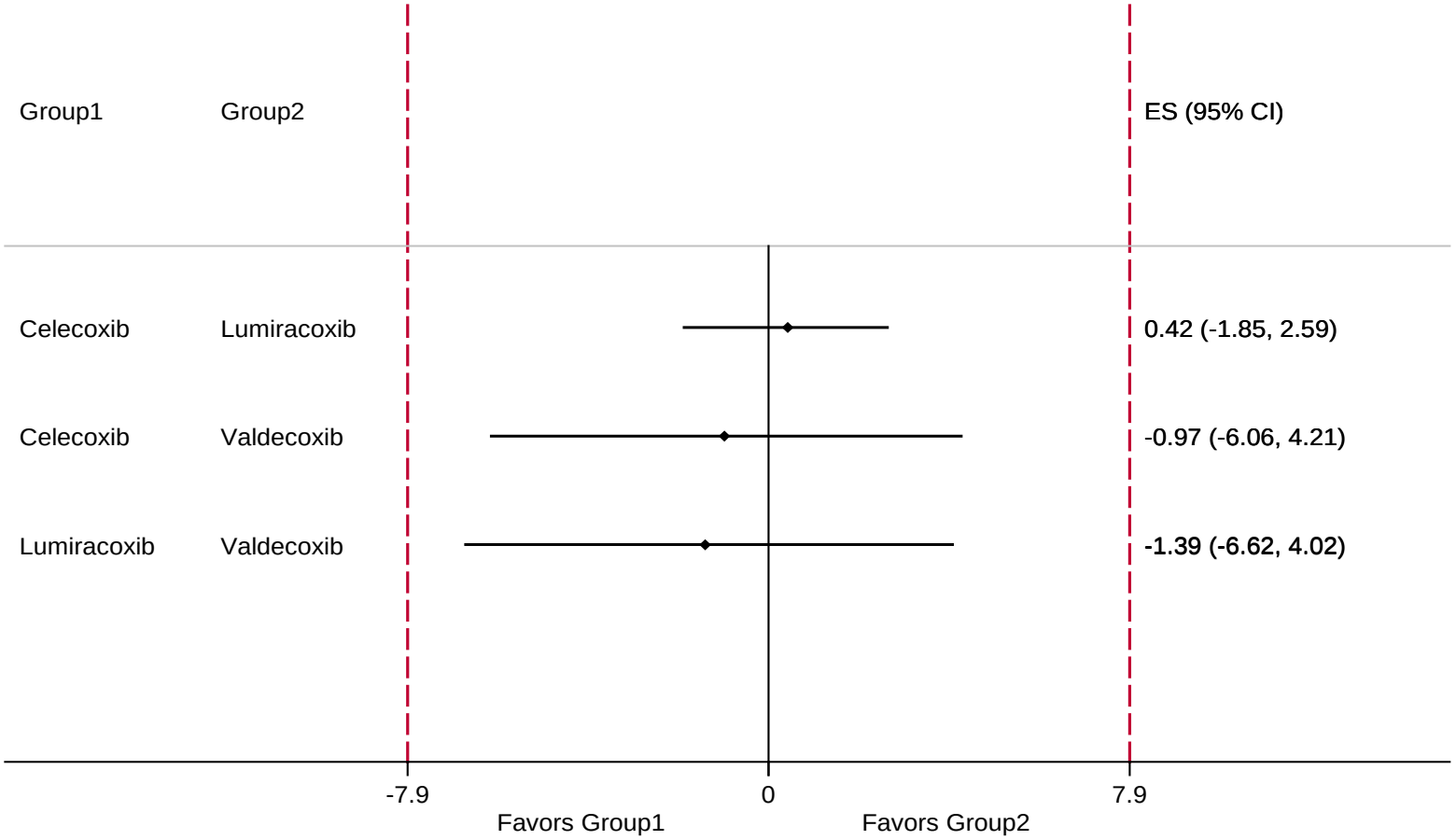
The red line indicates the MCII

Figure 66. Network Meta-Analysis: NSAIDS Versus NSAIDS (WOMAC Total)



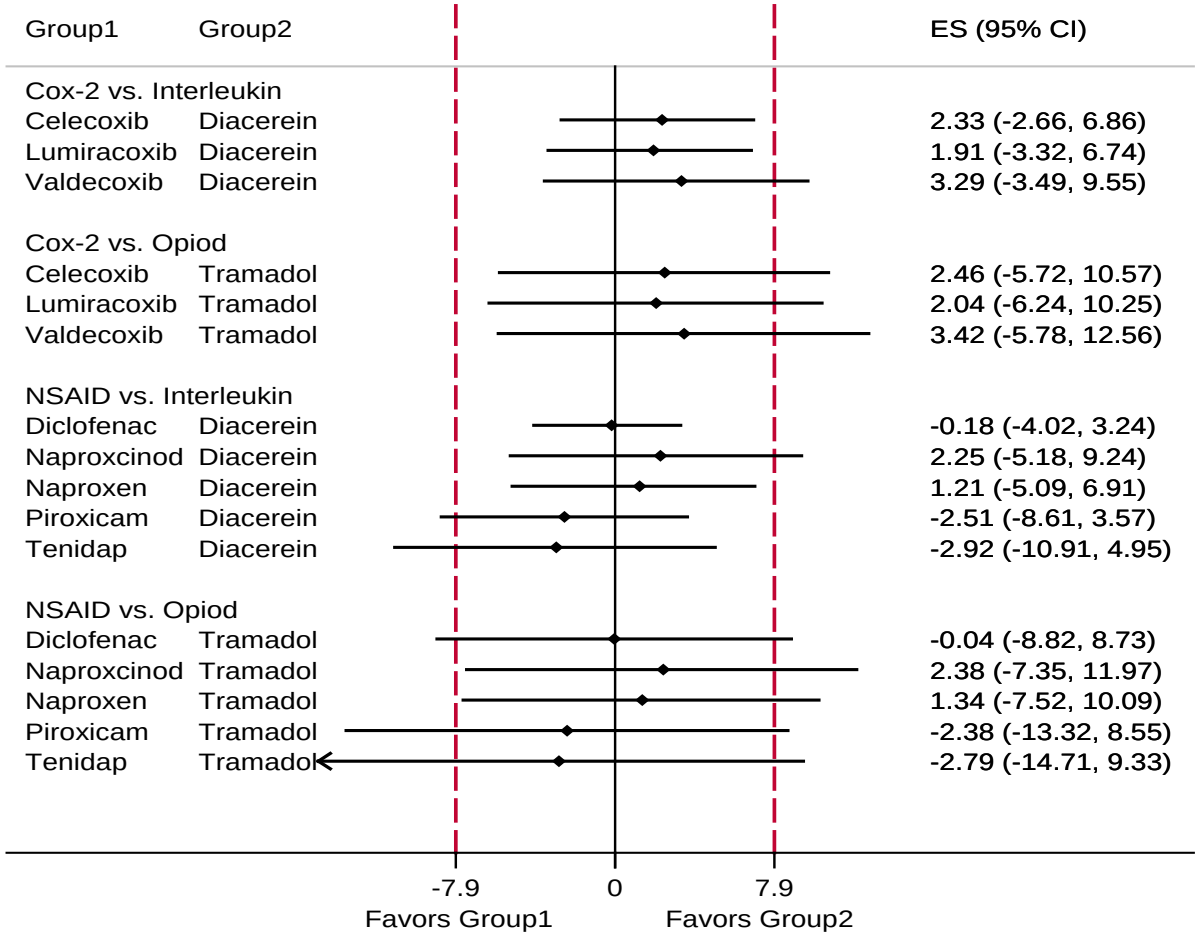
The red line indicates the MCII

Figure 67. Network Meta-Analysis: Cox-2 Versus Cox-2 (WOMAC Total)



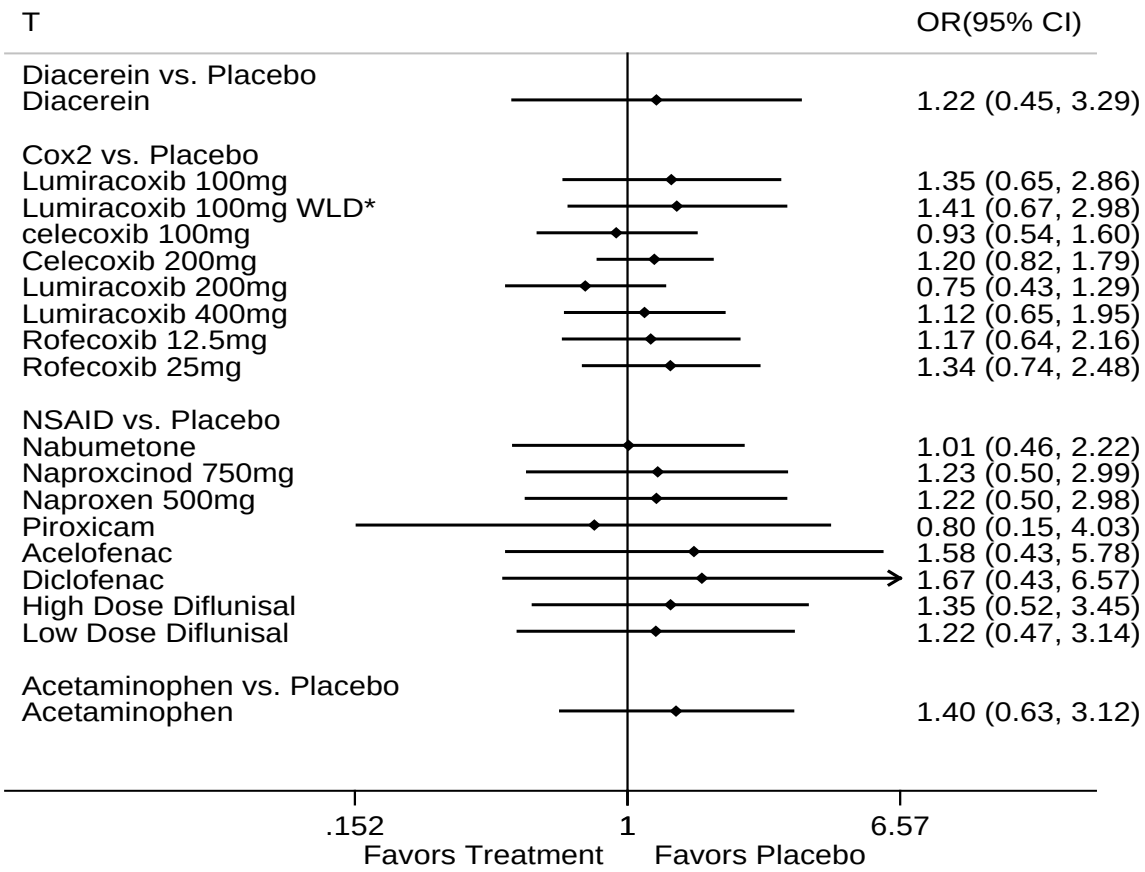
The red line indicates the MCII

Figure 68. Network Meta-Analysis: Cox-2 and NSAIDS Versus Other Analgesics (WOMAC Total)



The red line indicates the MCII

Figure 69. Network Meta-Analysis: Analgesics Versus Placebo (Adverse Events)



WLD=With Loading Dose

Figure 70. Network Meta-Analysis: Cox-2 Versus Cox-2 (Adverse Events)

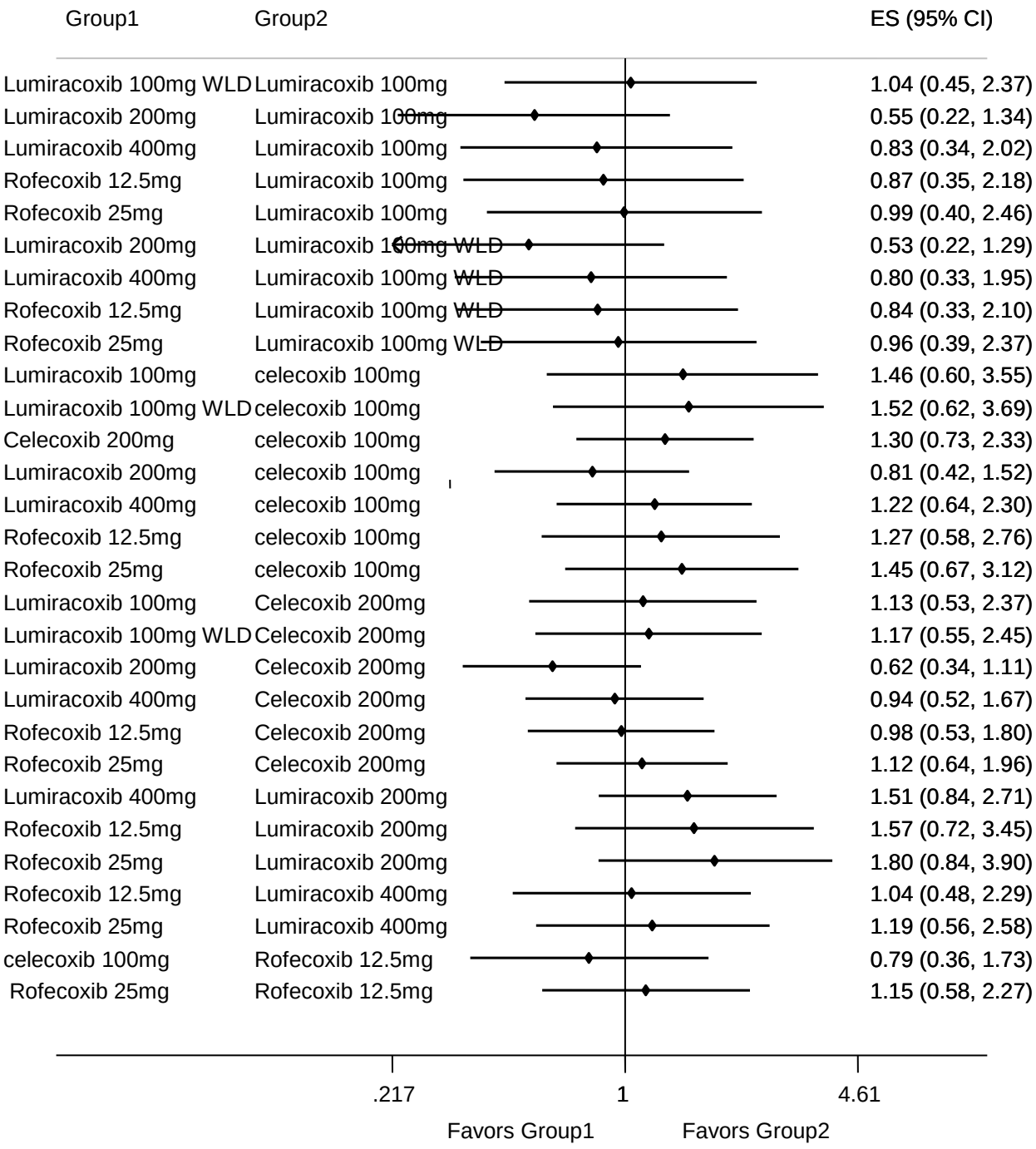


Figure 71. Network Meta-Analysis: NSAID Versus NSAID (Adverse Events)

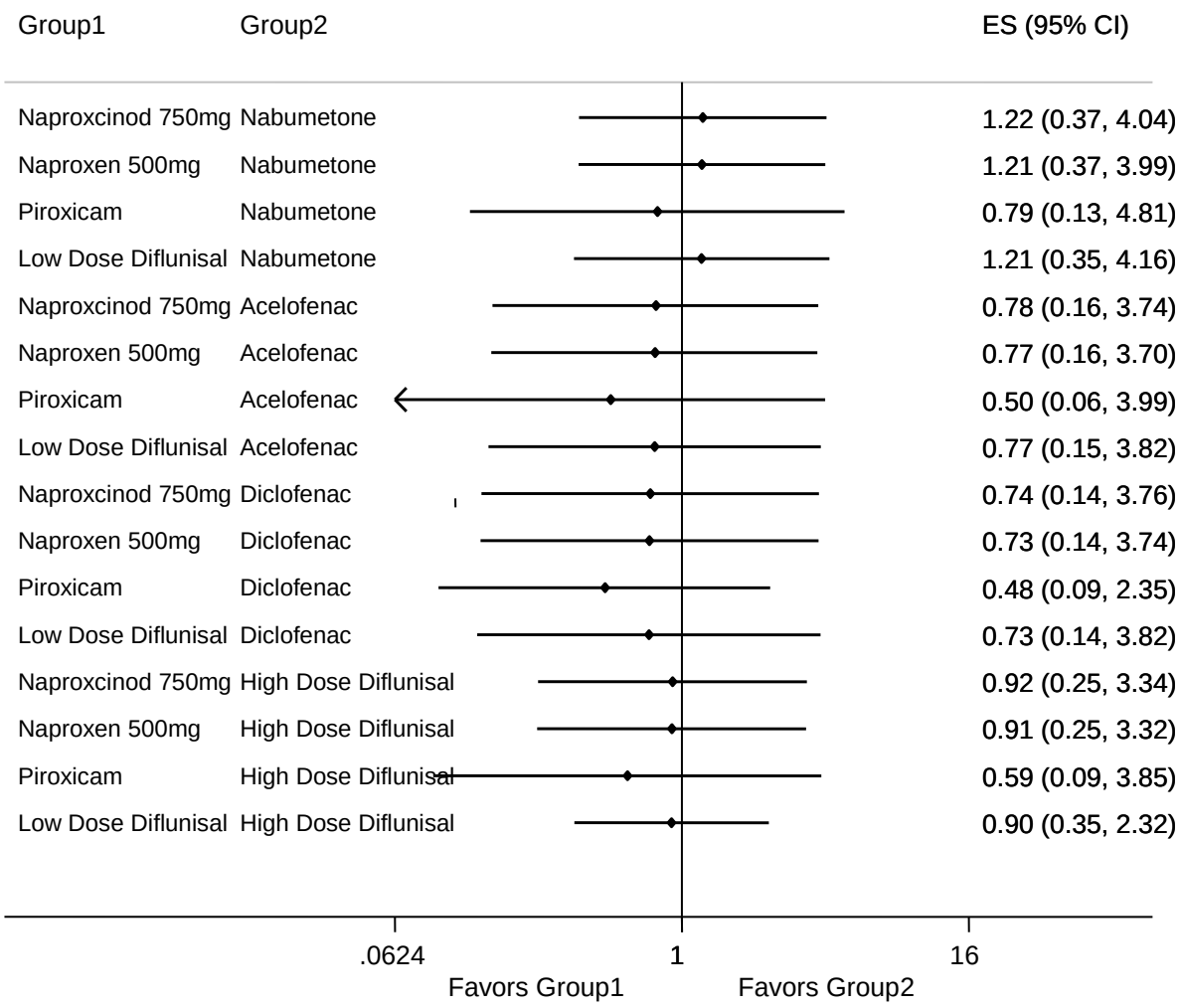
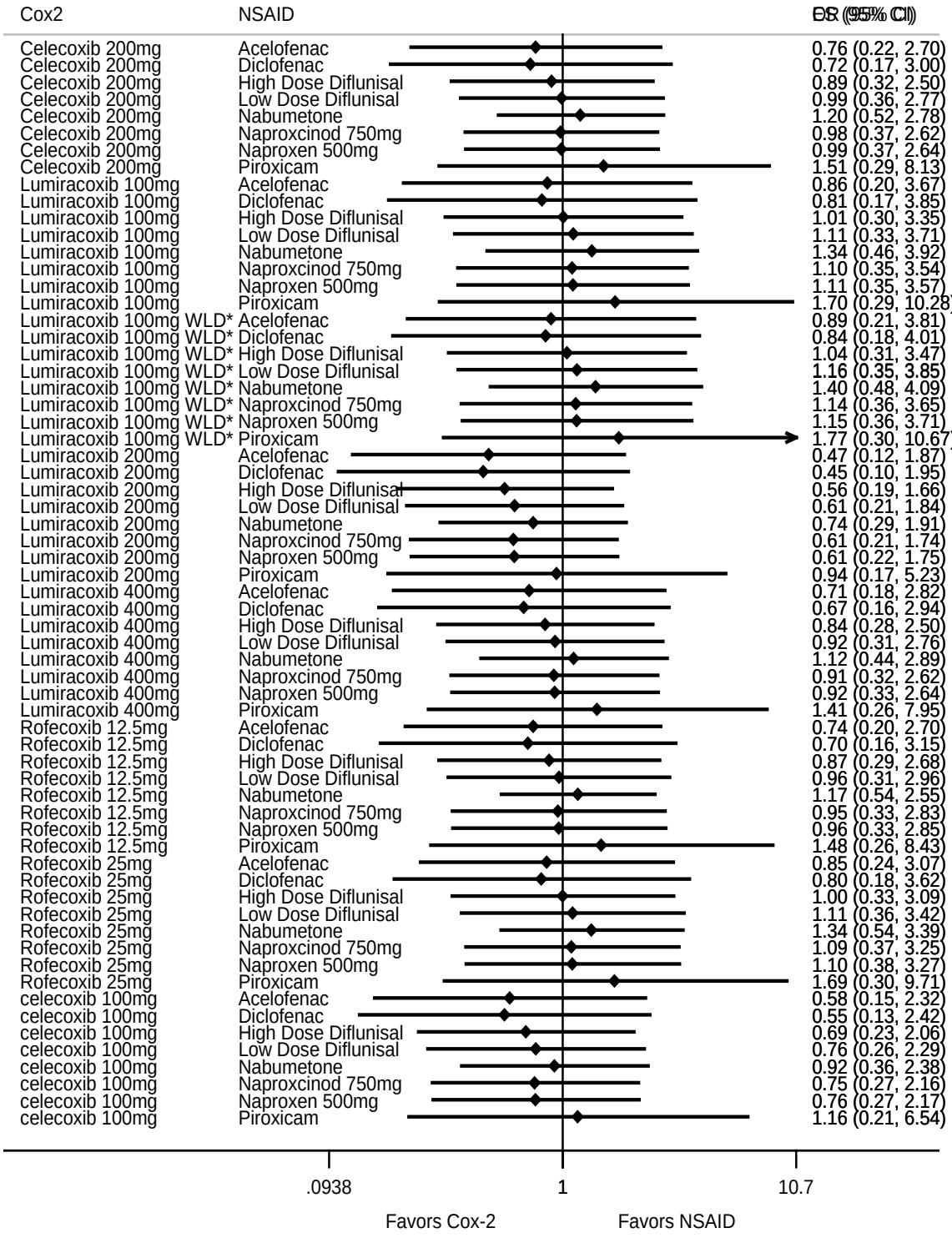


Figure 72. Network Meta-Analysis: Cox-2 Versus NSAID (Adverse Events)



*WLD= With Loading Dose

Figure 73. Network Meta-Analysis: Acetaminophen Versus Cox-2 and NSAIDS (Adverse Events)

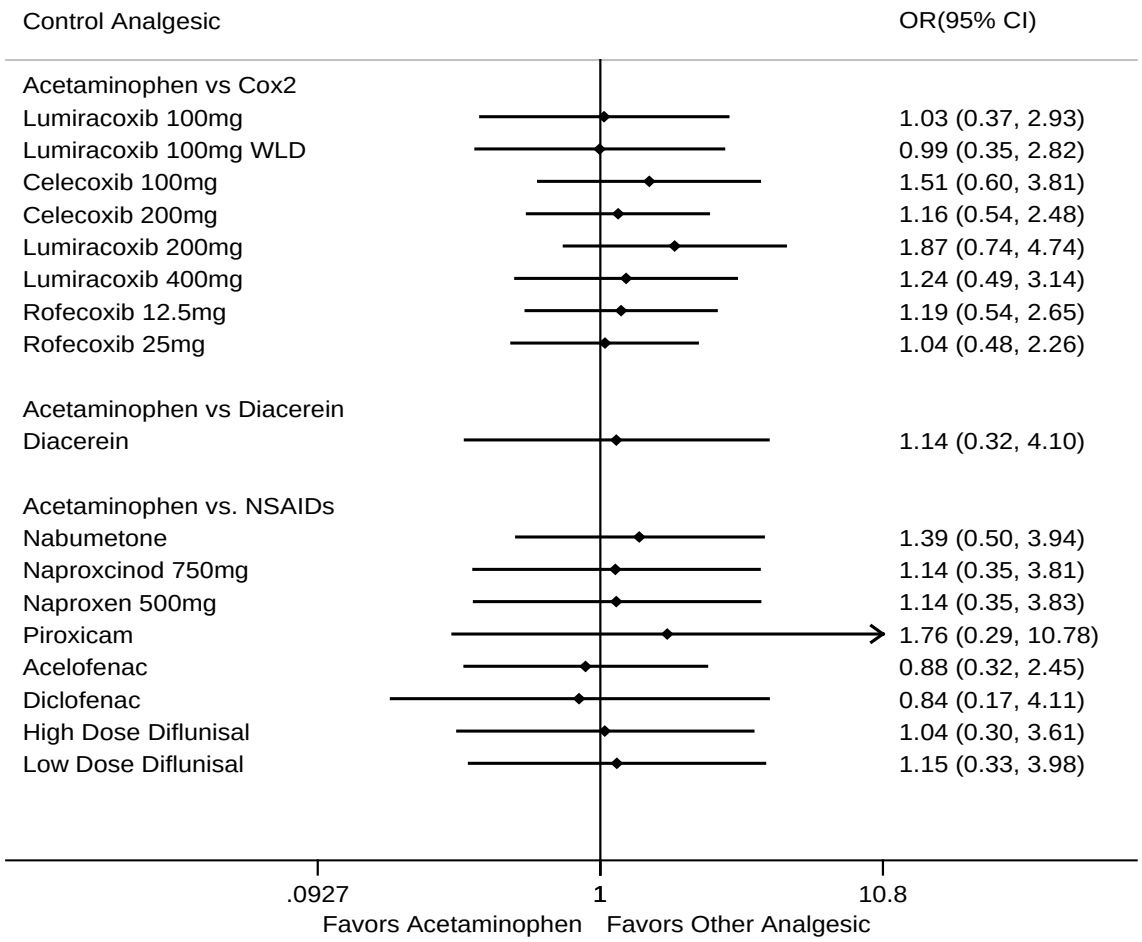
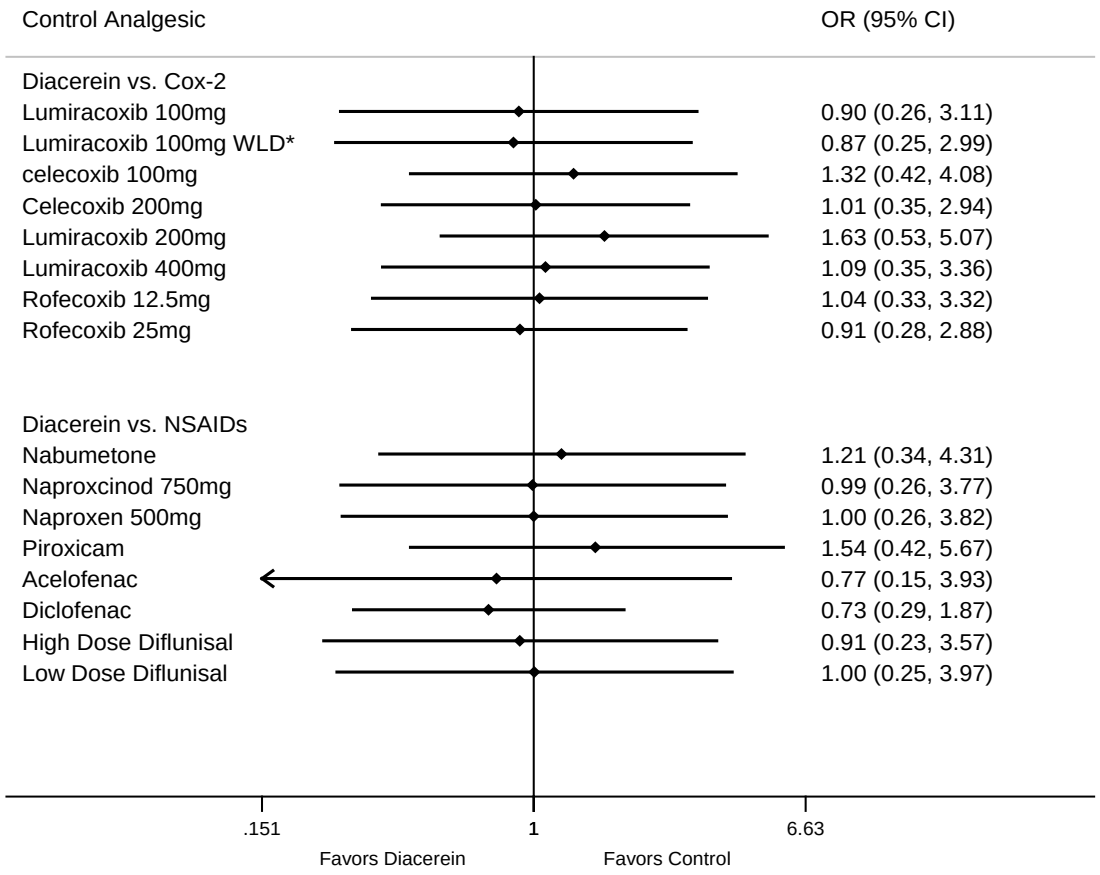


Figure 74. Network Meta-Analysis: Diacerein (Interleukin) Versus Cox-2 Inhibitors and NSAIDS (Adverse Events)



*WLD = With Loading Dose

Figure 75. Network Meta-Analysis: Gastrointestinal Cox-2 Versus NSAIDS (Adverse Events)

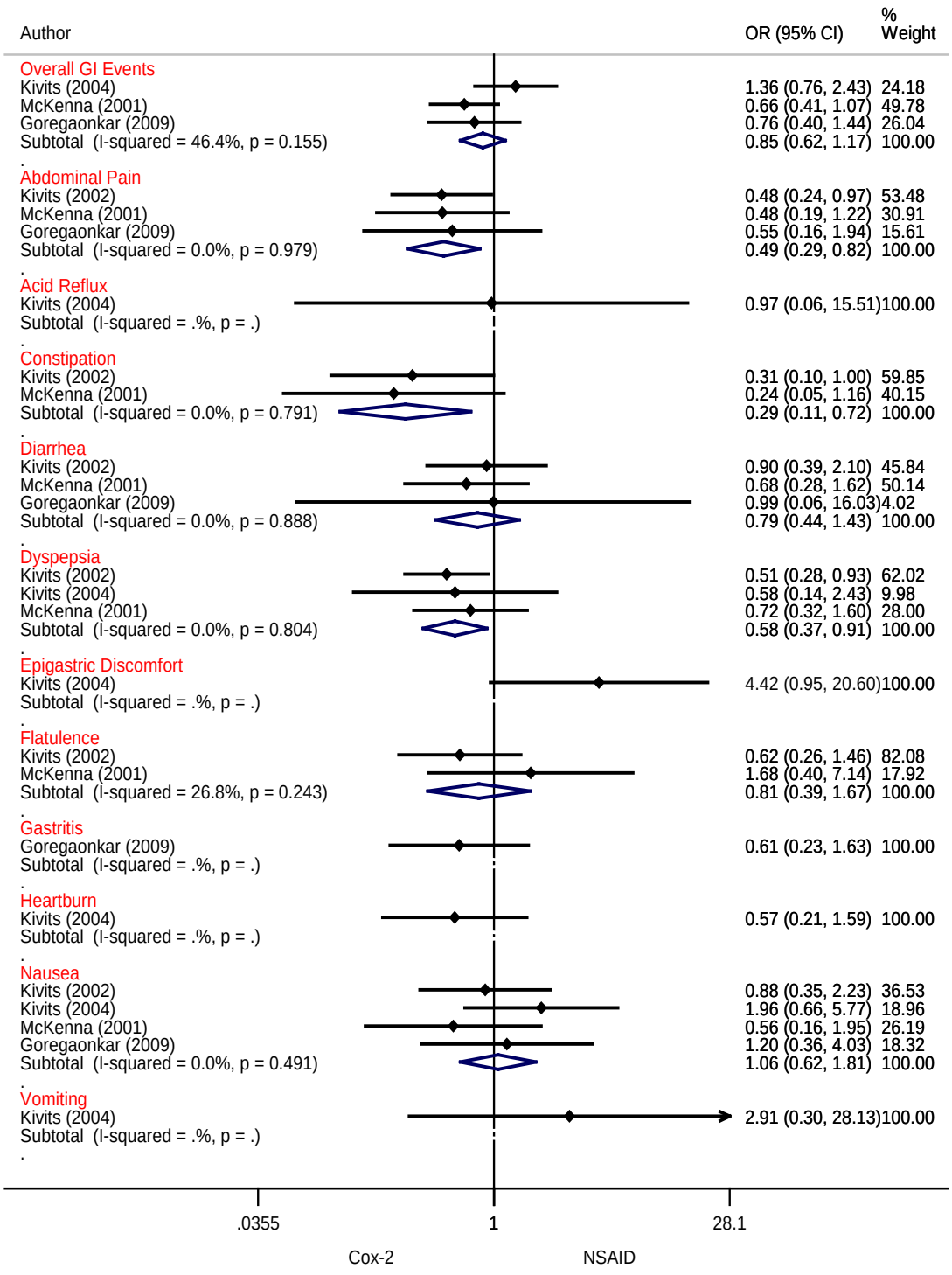


Figure 76. Network Meta-Analysis: Cox-2 Versus NSAID Non-Gastrointestinal (Adverse Events)

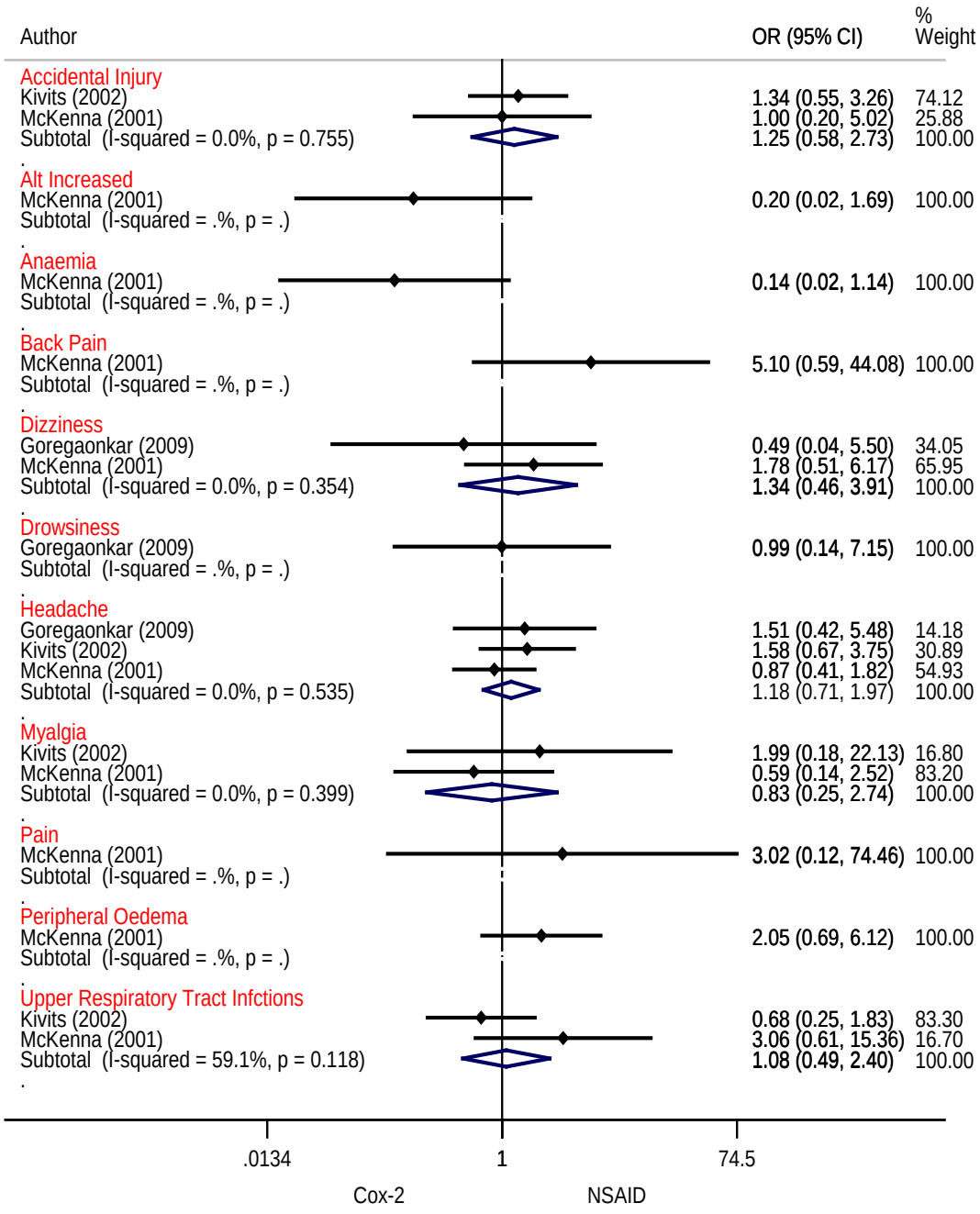


Figure 77. Network Meta-Analysis: Acetaminophen Versus Celecoxib (Adverse Events)

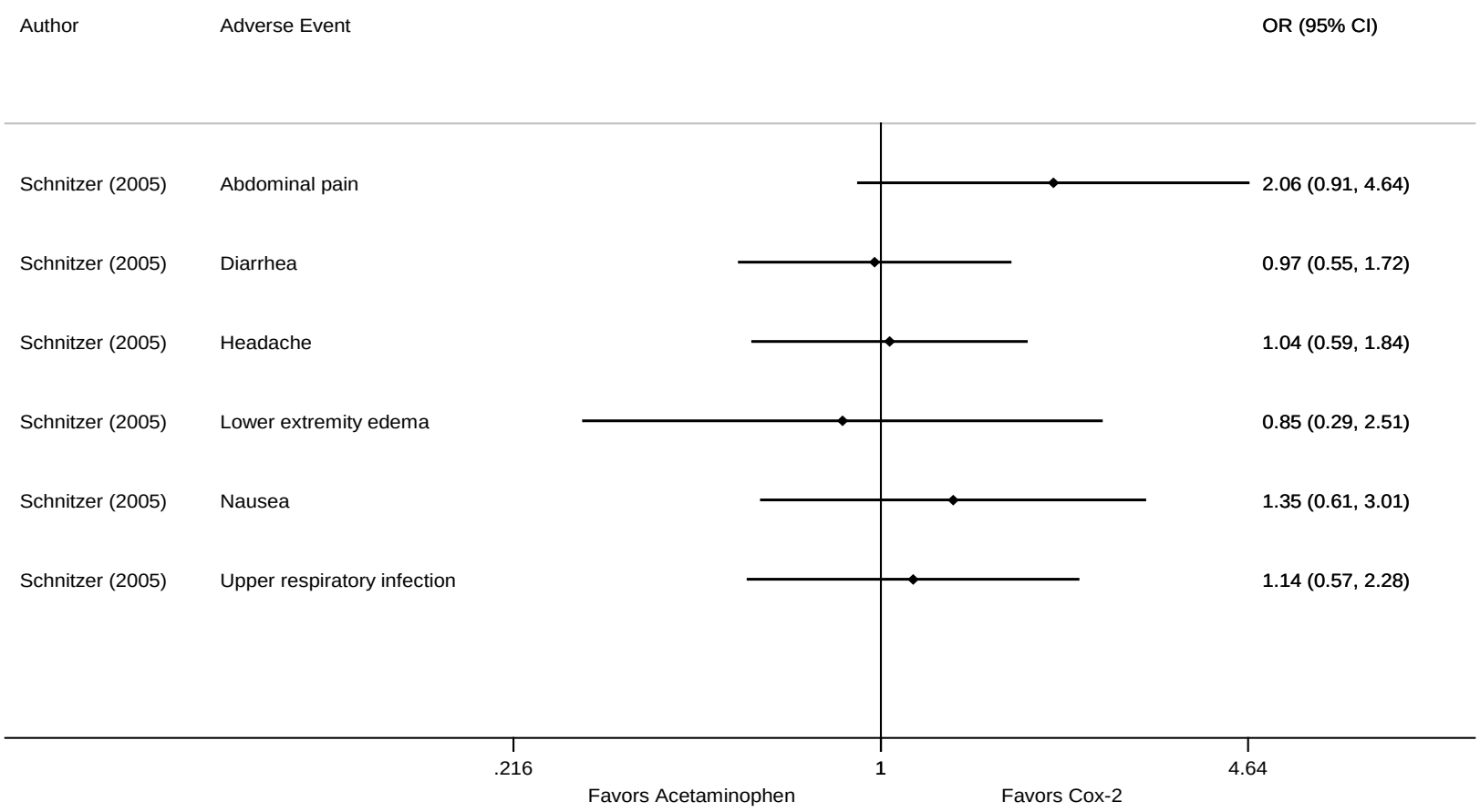


Figure 78. Network Meta-Analysis: Acetaminophen Versus Rofecoxib 12.5 mg (Adverse Events)

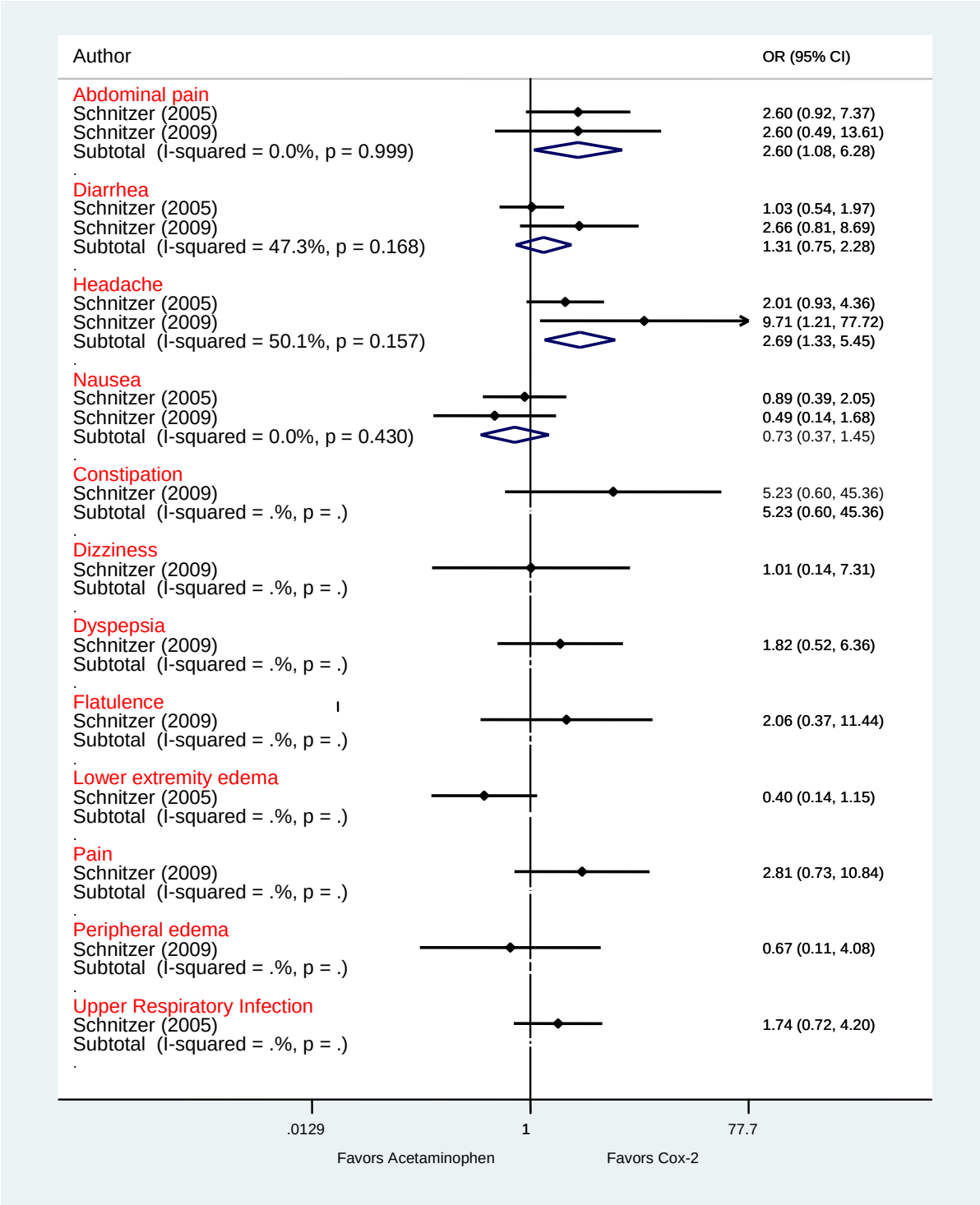


Figure 79. Network Meta-Analysis: Acetaminophen Versus Rofecoxib 25mg (Adverse Events)

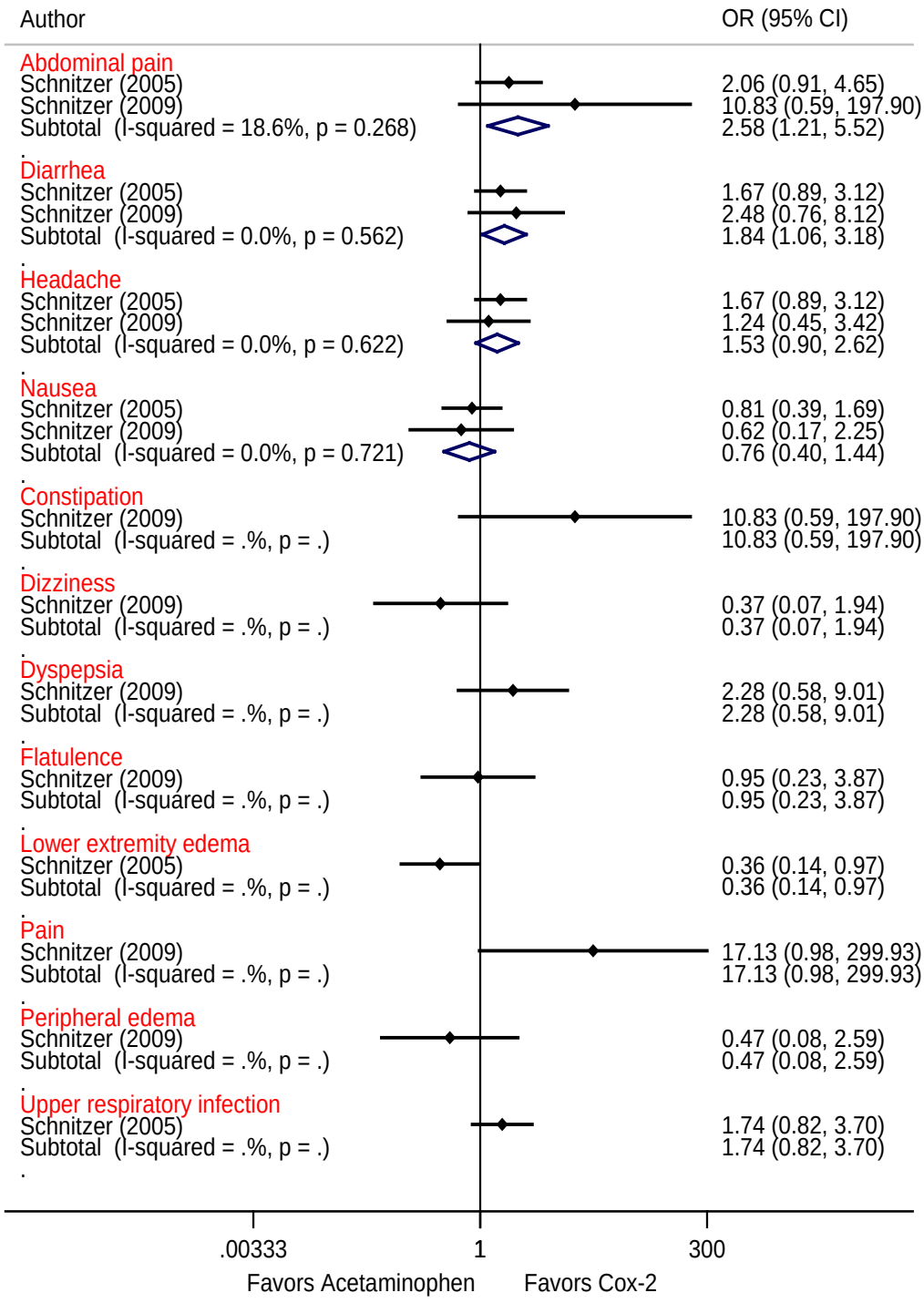
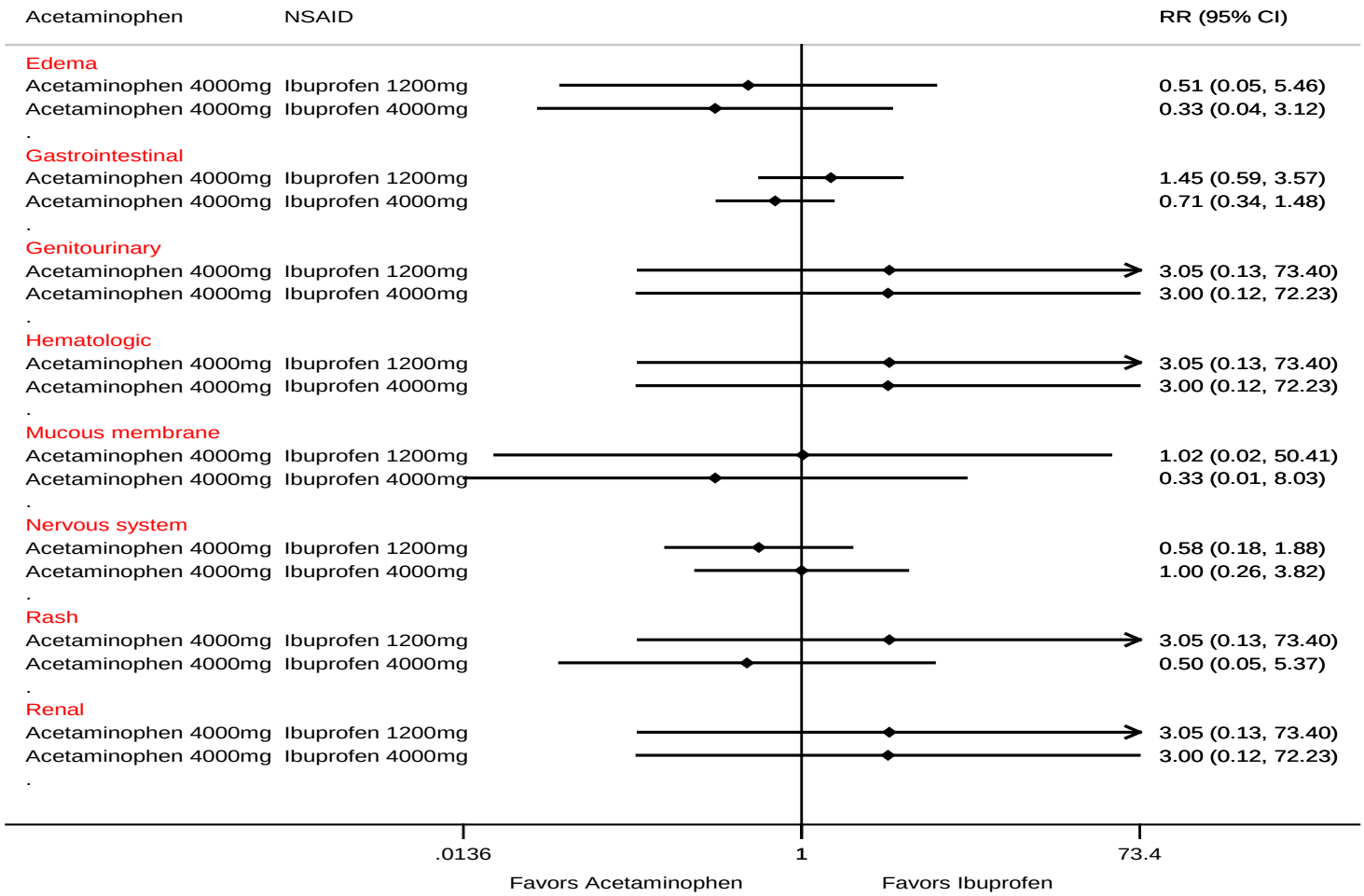


Figure 80. Network Meta-Analysis: Acetaminophen Versus Ibuprofen-Adverse Events (Bradley 1991)



RECOMMENDATION 8

We are unable to recommend for or against the use of intraarticular (IA) corticosteroids for patients with symptomatic osteoarthritis of the knee.

Strength of Recommendation: Inconclusive

Description: Evidence from a single low quality study or conflicting findings that do not allow a recommendation for or against the intervention. An **Inconclusive** recommendation means that there is a lack of compelling evidence that has resulted in an unclear balance between benefits and potential harm.

Implications: Practitioners should feel little constraint in following a recommendation labeled as **Inconclusive,** exercise clinical judgment, and be alert for emerging evidence that clarifies or helps to determine the balance between benefits and potential harm. Patient preference should have a substantial influencing role.

RATIONALE

Our search found only four placebo comparison studies that met criteria and evaluated pain relief for a minimum treatment period of four weeks.[102-105] One study found IA corticosteroids to be superior to placebo on WOMAC total subscale scores at four weeks.[102] However, another study found IA corticosteroid injections inferior to hyaluronic acid injections[106] and a third study found IA corticosteroids inferior to needle lavage (tidal irrigation).[107]Since the evidence in the guideline did not support the use of hyaluronic acid or needle lavage, the work group interpreted the evidence to be inconclusive as to the benefit of IA corticosteroids.

SUPPORTING EVIDENCE

QUALITY

Relevant Tables: Table 166-Table168, Table 169-Table 171

There were four moderate quality studies that compared intraarticular (IA) corticosteroids to placebo. None were flawed in the hypothesis, blinding, treatment integrity or measurement domains. All four studies were flawed in the group assignment domain, and three studies were flawed in the group comparability and investigator bias domains.

One additional moderate quality study compared IA corticosteroids to Hylan G-F 20 injections based on 10 outcomes.[106] None were flawed in the hypothesis, blinding, treatment integrity or measurement domains. They were all flawed in the group assignment, group comparability and investigator bias domains.

Another moderate quality study compared corticosteroids to tidal irrigation.[107]There was uncertainty about the comparability of the groups at baseline. Also, there was potential for investigator bias in the study.

APPLICABILITY

Relevant Tables: Table 166-Table168, Table 169-Table 171

In all but one included studies, the participants may not have been representative of those seen in clinical practice. Also, it was unclear if any of the studies administered treatment similarly provided in clinical settings. Compliance and adherence for all included studies were similar to what is seen in clinical practice. Finally, all but one study included all enrolled patients in the final analysis.

FINAL STRENGTH OF EVIDENCE

Four out of five studies comparing IA corticosteroids to placebo had moderate quality and moderate applicability resulting in a moderate strength of evidence rating. One study had high quality and moderate applicability so its strength of evidence was high.

Table 166. Quality and Applicability Summary: IA Corticosteroids Versus Placebo

Study	Outcome	Duration	Quality	Applicability	Strength of Evidence
Chao (2010)	WOMAC Pain	4 weeks	Moderate	Moderate	Moderate
Chao (2010)	WOMAC Total	4 weeks	Moderate	Moderate	Moderate
Gaffney (1995)	VAS Pain	6 weeks	Moderate	Moderate	Moderate
Gaffney (1995)	Health Assessment Questionnaire	6 weeks	Moderate	Moderate	Moderate
Gaffney (1995)	Walk Distance (1 minute)	6 weeks	Moderate	Moderate	Moderate
Raynauld (2003)	VAS Patient Pain Assessment at Night	1 year	Moderate	Moderate	Moderate
Raynauld (2003)	VAS Patient Pain at Night	2 years	Moderate	Moderate	Moderate
Raynauld (2003)	WOMAC Pain	1 year	Moderate	Moderate	Moderate
Raynauld (2003)	WOMAC Pain	2 years	Moderate	Moderate	Moderate
Raynauld (2003)	WOMAC Function	1 year	Moderate	Moderate	Moderate
Raynauld (2003)	WOMAC Function	2 years	Moderate	Moderate	Moderate

Study	Outcome	Duration	Quality	Applicability	Strength of Evidence
Raynauld (2003)	50-foot walking time (seconds)	1 year	Moderate	Moderate	Moderate
Raynauld (2003)	50-foot walking time (seconds)	2 years	Moderate	Moderate	Moderate
Raynauld (2003)	WOMAC Stiffness	1 year	Moderate	Moderate	Moderate
Raynauld (2003)	WOMAC Stiffness	2 years	Moderate	Moderate	Moderate
Raynauld (2003)	WOMAC Total	1 year	Moderate	Moderate	Moderate
Raynauld (2003)	WOMAC Total	2 years	Moderate	Moderate	Moderate
Raynauld (2003)	Physician Global Assessment	1 year	Moderate	Moderate	Moderate
Raynauld (2003)	Patient Global Assessment	1 year	Moderate	Moderate	Moderate
Raynauld (2003)	Physician Global Assessment	2 years	Moderate	Moderate	Moderate
Raynauld (2003)	Patient Global Assessment	3 years	High	Moderate	High
Smith (2003)	OARSI Responders	4 weeks	High	Moderate	High
Smith (2003)	OARSI Responders	8 weeks	High	Moderate	High
Smith (2003)	OARSI Responders	12 weeks	High	Moderate	High
Smith (2003)	OARSI Responders	24 weeks	High	Moderate	High

Table 167. Quality and Applicability Summary: IA Corticosteroids Versus Hyaluronic Acid

Study	Outcome	Duration	Quality	Applicability	Strength of Evidence
Carbon (2004)	WOMAC Pain on walking	12 weeks	Moderate	Moderate	Moderate
Carbon (2004)	WOMAC Pain on walking	26 weeks	Moderate	Moderate	Moderate
Carbon (2004)	WOMAC total	12 weeks	Moderate	Moderate	Moderate
Carbon (2004)	WOMAC total	26 weeks	Moderate	Moderate	Moderate
Carbon (2004)	WOMAC Function	12 weeks	Moderate	Moderate	Moderate
Carbon (2004)	WOMAC Function	26 weeks	Moderate	Moderate	Moderate
Carbon (2004)	Patient overall assessment (VAS)	12 weeks	Moderate	Moderate	Moderate
Carbon (2004)	Patient Global Assessment	26 weeks	Moderate	Moderate	Moderate
Carbon (2004)	Physician Global Assessment	12 weeks	Moderate	Moderate	Moderate
Carbon (2004)	Physician Global Assessment	26 weeks	Moderate	Moderate	Moderate
Carbon (2004)	WOMAC Pain on walking	12 weeks	Moderate	Moderate	Moderate
Carbon (2004)	WOMAC Pain on walking	26 weeks	Moderate	Moderate	Moderate
Carbon (2004)	WOMAC total	12 weeks	Moderate	Moderate	Moderate
Carbon (2004)	WOMAC total	26 weeks	Moderate	Moderate	Moderate
Carbon (2004)	WOMAC Function	12 weeks	Moderate	Moderate	Moderate
Carbon (2004)	WOMAC Function	26 weeks	Moderate	Moderate	Moderate
Carbon (2004)	Patient overall assessment (VAS)	12 weeks	Moderate	Moderate	Moderate

Table 168. Quality and Applicability Summary: IA Corticosteroids Versus Needle Lavage

Arden (2008)	WOMAC pain	4	Moderate	Moderate	Moderate
Arden (2008)	WOMAC pain	12	Moderate	Moderate	Moderate
Arden (2008)	WOMAC Total function	12	Moderate	Moderate	Moderate
Arden (2008)	WOMAC Total stiffness	12	Moderate	Moderate	Moderate
Arden (2008)	WOMAC pain	26	Moderate	Moderate	Moderate
Arden (2008)	WOMAC Total function	26	Moderate	Moderate	Moderate
Arden (2008)	WOMAC Total stiffness	26	Moderate	Moderate	Moderate

RESULTS

Relevant Tables: Figure 81-Figure 82, Table 172-Table 174

There were seven studies included in this recommendation. None provided enough information to determine whether or not the patient population had acute or chronic osteoarthritis of the knee. However, the average symptom duration was several years for six of the studies (the seventh study did not provide average symptom duration), so a majority of the patient population was likely suffering from chronic osteoarthritis. Also, excluding Raynauld et al., all studies included patients with a full range of osteoarthritis severity levels.

Five studies with 19 outcomes compared IA corticosteroid injections to the placebo assignment. Four of the outcomes were statistically significant in favor of the treatment. Pain and function were the two critical outcomes. There were five pain outcomes and one self reported functional outcome.

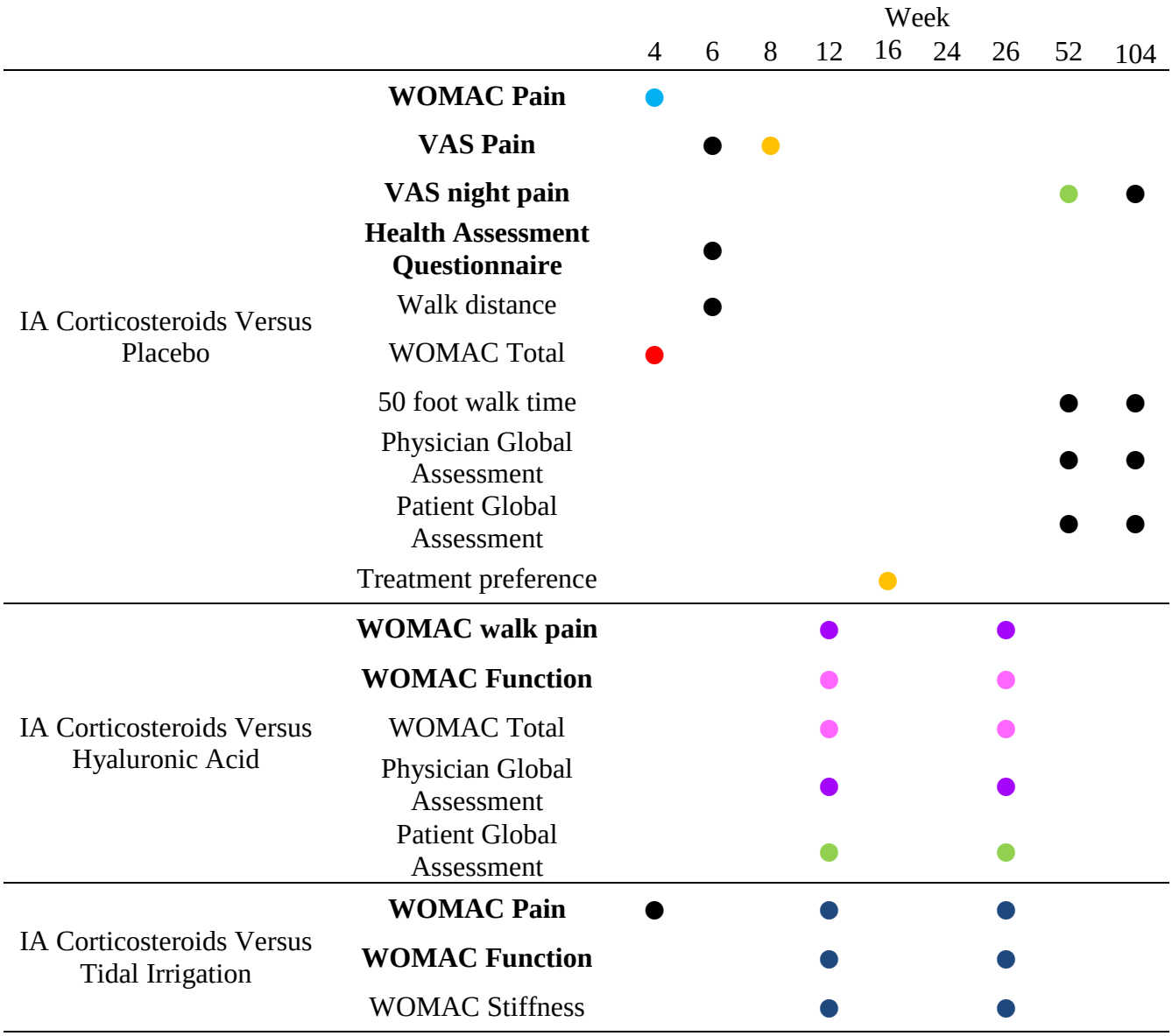
Of the five pain outcomes, three were statistically significant in favor of IA corticosteroids. However, one of them was not clinically important. The one other outcome, WOMAC Pain (Raynauld et al.[104]) was underpowered. The findings were included in a meta-analysis comparing pain in the corticosteroid and placebo groups. Chao et al.[102] and Raynauld et al.[104] used the visual analogue versions of WOMAC Pain, and Gaffney et al.[103] used the traditional VAS pain scale (both were 100mm long). Results showed that the treatment group had a lower weighted mean of 8.8mm on the VAS scale, which was statistically significant. Since WOMAC pain and VAS pain were combined, the clinical importance of IA corticosteroids could not be determined.

There were four functional outcomes included. One was the Health Assessment Questionnaire (HAQ) and the other three were functional task outcomes. Since the HAQ is a self reported measure of function, it was a critical outcome. All four functional outcomes were not statistically significant.

Carborn et al.[106] compared IA corticosteroids to Hylan G-F 20 at 12 and 26 weeks. Ten of 10 outcomes were statistically significant in favor of hyaluronic acid. WOMAC walking pain and WOMAC function were the critical outcomes presented in this study. (See Figure 81 for the results summary.)

Arden et al.[107] compared IA corticosteroids to tidal irrigation. Clinically significant results were found in favor of corticosteroids for six of 7 outcomes of which WOMAC function and pain were the critical variables. Four of five critical outcomes were significant in favor of the IA corticosteroid group (see Figure 81).

Figure 81. Results Summary: IA Corticosteroids



Key 1 ●=Not Significant; ●=Not Clinically Significant ●=Statistically Significant; ●=Possibly Clinically Significant; ●=Clinically Significant. ●=Favors HA; ●= Possibly Clinically Significant in Favor of HA. ●= Possibly Clinically Significant in Favor of Tidal Irrigation. Bold lettering indicates a critical outcome.

EVIDENCE TABLES AND FIGURES

QUALITY AND APPLICABILITY

Table 169. Quality and Applicability: IA Corticosteroids Versus Placebo

●*: Domain free of flaws*

○*: Domain flaws present*

◐*: Moderate power*

Study	***Outcome***	**Prospective**	**Power**	**Group Assignment**	**Blinding**	**Group Comparability**	**Treatment Integrity**	**Measurement**	**Investigator Bias**	***Quality***	**Participants**	**Intervention and Expertise**	**Compliance and Adherence**	**Analysis**	***Applicability Study***
Jones (1996)	15% improvement in VAS Pain	●	●	○	●	○	●	●	○	**Moderate**	○	○	●	●	**Moderate**
Jones (1996)	Treatment preference	●	●	○	●	○	●	●	○	**Moderate**	○	○	●	●	**Moderate**
Chao (2010)	WOMAC Pain	●	●	○	●	●	●	●	○	**Moderate**	○	○	●	○	**Moderate**
Chao (2010)	WOMAC Total	●	●	○	●	●	●	●	○	**Moderate**	○	○	●	○	**Moderate**
Gaffney (1995)	VAS Pain	●	●	○	●	○	●	●	○	**Moderate**	●	○	●	●	**Moderate**

●: *Domain free of flaws*

○: *Domain flaws present*

◐: *Moderate power*

Study	***Outcome***	**Prospective**	**Power**	**Group Assignment**	**Blinding**	**Group Comparability**	**Treatment Integrity**	**Measurement**	**Investigator Bias**	***Quality***	**Participants**	**Intervention and Expertise**	**Compliance and Adherence**	**Analysis**	***Applicability Study***
Gaffney (1995)	Health Assessment Questionnaire	●	◐	○	●	○	●	●	○	**Moderate**	●	○	●	●	**Moderate**
Gaffney (1995)	Walk Distance (1 minute)	●	◐	○	●	○	●	●	○	**Moderate**	●	○	●	●	**Moderate**
Raynauld (2003)	VAS Patient Pain Assessment at Night Week 52	●	●	○	●	○	●	●	●	**Moderate**	○	○	●	●	**Moderate**
Raynauld (2003)	VAS Patient Pain at Night 104 weeks	●	●	○	●	○	●	●	●	**Moderate**	○	○	●	●	**Moderate**
Raynauld (2003)	WOMAC Pain Week 52	●	○	○	●	○	●	●	●	**Moderate**	○	○	●	●	**Moderate**
Raynauld (2003)	WOMAC Pain 104 weeks	●	○	○	●	○	●	●	●	**Moderate**	○	○	●	●	**Moderate**
Raynauld (2003)	WOMAC Function Week 52	●	○	○	●	○	●	●	●	**Moderate**	○	○	●	●	**Moderate**

●: *Domain free of flaws*

○: *Domain flaws present*

◐: *Moderate power*

Study	***Outcome***	**Prospective**	**Power**	**Group Assignment**	**Blinding**	**Group Comparability**	**Treatment Integrity**	**Measurement**	**Investigator Bias**	***Quality***	**Participants**	**Intervention and Expertise**	**Compliance and Adherence**	**Analysis**	***Applicability Study***
Raynauld (2003)	WOMAC Function 104 weeks	●	○	○	●	○	●	●	●	**Moderate**	○	○	●	●	**Moderate**
Raynauld (2003)	50-foot walking time (seconds) Week 52	●	◐	○	●	○	●	●	●	**Moderate**	○	○	●	●	**Moderate**
Raynauld (2003)	50-foot walking time (seconds) 104 weeks	●	◐	○	●	○	●	●	●	**Moderate**	○	○	●	●	**Moderate**
Raynauld (2003)	WOMAC Stiffness Week 52	●	○	○	●	○	●	●	●	**Moderate**	○	○	●	●	**Moderate**
Raynauld (2003)	WOMAC Stiffness 104 weeks	●	○	○	●	○	●	●	●	**Moderate**	○	○	●	●	**Moderate**
Raynauld (2003)	WOMAC Total Week 52	●	○	○	●	○	●	●	●	**Moderate**	○	○	●	●	**Moderate**
Raynauld (2003)	WOMAC Total 104 weeks	●	○	○	●	○	●	●	●	**Moderate**	○	○	●	●	**Moderate**

●: *Domain free of flaws*

○: *Domain flaws present*

◐: *Moderate power*

Study	***Outcome***	**Prospective**	**Power**	**Group Assignment**	**Blinding**	**Group Comparability**	**Treatment Integrity**	**Measurement**	**Investigator Bias**	***Quality***	**Participants**	**Intervention and Expertise**	**Compliance and Adherence**	**Analysis**	***Applicability Study***
Raynauld (2003)	Physician Global Assessment Week 52	●	◐	○	●	○	●	●	●	**Moderate**	○	○	●	●	**Moderate**
Raynauld (2003)	Patient Global Assessment 52 weeks	●	●	○	●	○	●	●	●	**Moderate**	○	○	●	●	**Moderate**
Raynauld (2003)	Physician Global Assessment 104 weeks	●	◐	○	●	○	●	●	●	**Moderate**	○	○	●	●	**Moderate**
Raynauld (2003)	Patient Global Assessment 104 weeks	●	●	○	●	○	●	●	●	**Moderate**	○	○	●	●	**Moderate**
Chao (2010)	WOMAC Pain	●	●	○	●	●	●	●	○	**Moderate**	○	○	●	○	**Moderate**

Table 170. Quality and Applicability: IA Corticosteroids Versus Hyaluronic Acid

●: Domain free of flaws
○: Domain flaws present
◐: Moderate power

Study	*Outcome*	Prospective	Power	Group Assignment	Blinding	Group Comparability	Treatment Integrity	Measurement	Investigator Bias	*Quality*	Participants	Intervention and Expertise	Compliance and Adherence	Analysis	*Applicability Study*
Caborn (2004)	WOMAC Pain on walking week 12	●	●	○	●	○	●	●	○	**Moderate**	○	○	●	●	**Moderate**
Caborn (2004)	WOMAC Pain on walking week 26	●	●	○	●	○	●	●	○	**Moderate**	○	○	●	●	**Moderate**
Caborn (2004)	WOMAC Total week 12	●	●	○	●	○	●	●	○	**Moderate**	○	○	●	●	**Moderate**
Caborn (2004)	WOMAC Total week 26	●	●	○	●	○	●	●	○	**Moderate**	○	○	●	●	**Moderate**
Caborn (2004)	WOMAC Function week 12	●	●	○	●	○	●	●	○	**Moderate**	○	○	●	●	**Moderate**
Caborn (2004)	WOMAC Function week 26	●	●	○	●	○	●	●	○	**Moderate**	○	○	●	●	**Moderate**
Caborn (2004)	Patient Overall Assessment (VAS)	●	●	○	●	○	●	●	○	**Moderate**	○	○	●	●	**Moderate**

●: Domain free of flaws

○: Domain flaws present

◐: Moderate power

Study	*Outcome*	**Prospective**	**Power**	**Group Assignment**	**Blinding**	**Group Comparability**	**Treatment Integrity**	**Measurement**	**Investigator Bias**	*Quality*	**Participants**	**Intervention and Expertise**	**Compliance and Adherence**	**Analysis**	*Applicability Study*
	week 12														
Caborn (2004)	Patient Global Assessment week 26	●	●	○	●	○	●	●	○	**Moderate**	○	○	●	●	**Moderate**
Caborn (2004)	Physician Global Assessment week 12	●	●	○	●	○	●	●	○	**Moderate**	○	○	●	●	**Moderate**
Caborn (2004)	Physician Global Assessment week 26	●	●	○	●	○	●	●	○	**Moderate**	○	○	●	●	**Moderate**
Caborn (2004)	WOMAC Pain on walking week 12	●	●	○	●	○	●	●	○	**Moderate**	○	○	●	●	**Moderate**
Caborn (2004)	WOMAC Pain on walking week 26	●	●	○	●	○	●	●	○	**Moderate**	○	○	●	●	**Moderate**
Caborn (2004)	WOMAC Total week 12	●	●	○	●	○	●	●	○	**Moderate**	○	○	●	●	**Moderate**
Caborn (2004)	WOMAC Total week 26	●	●	○	●	○	●	●	○	**Moderate**	○	○	●	●	**Moderate**

●: Domain free of flaws

○: Domain flaws present

◐: Moderate power

Study	*Outcome*	**Prospective**	**Power**	**Group Assignment**	**Blinding**	**Group Comparability**	**Treatment Integrity**	**Measurement**	**Investigator Bias**	*Quality*	**Participants**	**Intervention and Expertise**	**Compliance and Adherence**	**Analysis**	*Applicability Study*
Caborn (2004)	WOMAC Function week 12	●	●	○	●	○	●	●	○	**Moderate**	○	○	●	●	**Moderate**
Caborn (2004)	WOMAC Function week 26	●	●	○	●	○	●	●	○	**Moderate**	○	○	●	●	**Moderate**
Caborn (2004)	Patient overall assessment (VAS) week 12	●	●	○	●	○	●	●	○	**Moderate**	○	○	●	●	**Moderate**

Table 171. Quality and Applicability: Needle Lavage Versus IA Corticosteroids

●: Domain free of flaws
○: Domain flaws present
◐: Moderate power

Study	*Outcome*	*Week*	Prospective	Power	Group Assignment	Blinding	Group Comparability	Treatment Integrity	Measurement	Investigator Bias	*Quality*	Participants	Intervention and Expertise	Compliance and Adherence	Analysis	*Applicability Study*
Arden (2008)	WOMAC Pain	4	●	●	●	●	○	●	●	○	**Moderate**	○	○	●	●	**Moderate**
Arden (2008)	WOMAC Pain	12	●	●	●	●	○	●	●	○	**Moderate**	○	○	●	●	**Moderate**
Arden (2008)	WOMAC Function	12	●	●	●	●	○	●	●	○	**Moderate**	○	○	●	●	**Moderate**
Arden (2008)	WOMAC Stiffness	12	●	●	●	●	○	●	●	○	**Moderate**	○	○	●	●	**Moderate**
Arden (2008)	WOMAC Pain	26	●	●	●	●	○	●	●	○	**Moderate**	○	○	●	●	**Moderate**
Arden (2008)	WOMAC Function	26	●	●	●	●	○	●	●	○	**Moderate**	○	○	●	●	**Moderate**
Arden (2008)	WOMAC Stiffness	26	●	●	●	●	○	●	●	○	**Moderate**	○	○	●	●	**Moderate**

FINDINGS

Table 172. IA Corticosteroids Versus Placebo

Type	Study	Outcome	N	Power	Week	Avg. Disease Length (Years)	Severity	Group 1	Group 2	SMD (Odds Ratio or Raw Mean Difference When Indicated)	Sig	Clinical Importance	Strength of Evidence
Pain	Gaffney (1995)	VAS Pain	84	Yes	6	6.9	Leding-Ham Scale 0 to 3	Triamcinolone	Placebo	-0.27 (-0.70, 0.16)	No	True negative	Moderate
	Raynauld (2003)	VAS Patient Pain Assessment at Night	66	Yes	52	9.25	K-L 2 to 3	Corticosteroid injections	Placebo	-0.66 (-1.16, -0.17)	Favors IA Corticosteroids	Not clinically Important	Moderate
	Raynauld (2003)	VAS Patient Pain at Night	66	Yes	104	9.25	K-L 2 to 3	Corticosteroid injections	Placebo	-0.08 (-0.56, 0.40)	No	True negative	Moderate

Type	Study	Outcome	N	Power	Week	Avg. Disease Length (Years)	Severity	Group 1	Group 2	SMD (Odds Ratio or Raw Mean Difference When Indicated)	Sig	Clinical Importance	Strength of Evidence
	Chao (2010)	WOMAC Pain	67	Yes	4	14	Altman All Grades	Corticosteroid injections	Placebo	-0.87 (-1.37, -0.36)	Favors IA Corticosteroids	Possibly clinically significant	Moderate
	Jones (1996)	15% improvement in VAS Pain	59 (Cross-over Study)	Yes	8	NR	NR	Corticosteroid injections	Placebo	OR=5.02 (2.09, 12.03)	Favors IA cortico-steroids	N/A	Moderate
Function	Gaffney (1995)	Health Assessment Questionnaire	84	Unclear	6	6.9	Leding-ham Scale 0 to 3	Triamcinolone	Placebo	0.30 (-0.13, 0.73)	No	N/A	Moderate
	Gaffney (1995)	Walk Distance (1 minute)	84	Unclear	6	6.9	Leding-ham Scale 0 to 3	Triamcinolone	Placebo	-0.05 (-0.48, 0.37)	No	N/A	Moderate

Type	Study	Outcome	N	Power	Week	Avg. Disease Length (Years)	Severity	Group 1	Group 2	SMD (Odds Ratio or Raw Mean Difference When Indicated)	Sig	Clinical Importance	Strength of Evidence
	Raynauld (2003)	50-foot walking time (seconds)	66	Unclear	52	9.25	K-L 2 to 3	Corticosteroid injections	Placebo	-0.06 (-0.55, 0.42)	No	N/A	Moderate
	Raynauld (2003)	50-foot walking time (seconds)	66	Unclear	104	9.25	K-L 2 to 3	Corticosteroid injections	Placebo	-0.14 (-0.62, 0.34)	No	N/A	Moderate
WOMAC Total	Chao (2010)	WOMAC Total	61	Yes	4	14	Altman All Grades	Corticosteroid injections	Placebo	-0.96 (-1.49, -0.43)	Favors IA Corticosteroids	Clinically significant	Moderate
Global Assessment	Raynauld (2003)	Physician Global Assessment	66	Unclear	52	9.25	K-L 2 to 3	Corticosteroid injections	Placebo	0.18 (-0.30, 0.66)	No	N/A	Moderate
	Raynauld (2003)	Patient Global Assessment	66	Yes	52	9.25	K-L 2 to 3	Corticosteroid injections	Placebo	0.01 (-0.47, 0.49)	No	True negative	Moderate

Type	Study	Outcome	N	Power	Week	Avg. Disease Length (Years)	Severity	Group 1	Group 2	SMD (Odds Ratio or Raw Mean Difference When Indicated)	Sig	Clinical Importance	Strength of Evidence
	Raynauld (2003)	Physician Global Assessment	66	Unclear	104	9.25	K-L 2 to 3	Corticosteroid injections	Placebo	0.01 (-0.47, 0.49)	No	N/A	Moderate
	Raynauld (2003)	Patient Global Assessment	66	Yes	104	9.25	K-L 2 to 3	Corticosteroid injections	Placebo	-0.02 (-0.50, 0.46)	No	True negative	Moderate
Preferred Treatment	Jones (1996)	Preferred Treatment	59 (Cross-over Study)	Yes	16	NR	NR	Corticosteroid injections	Placebo	OR=3.33 (1.51, 7.31)	Favors IA cortico-steroids	N/A	Moderate

Table 173. IA Corticosteroids Versus Hyaluronic Acid (Caborn et al., 2004)

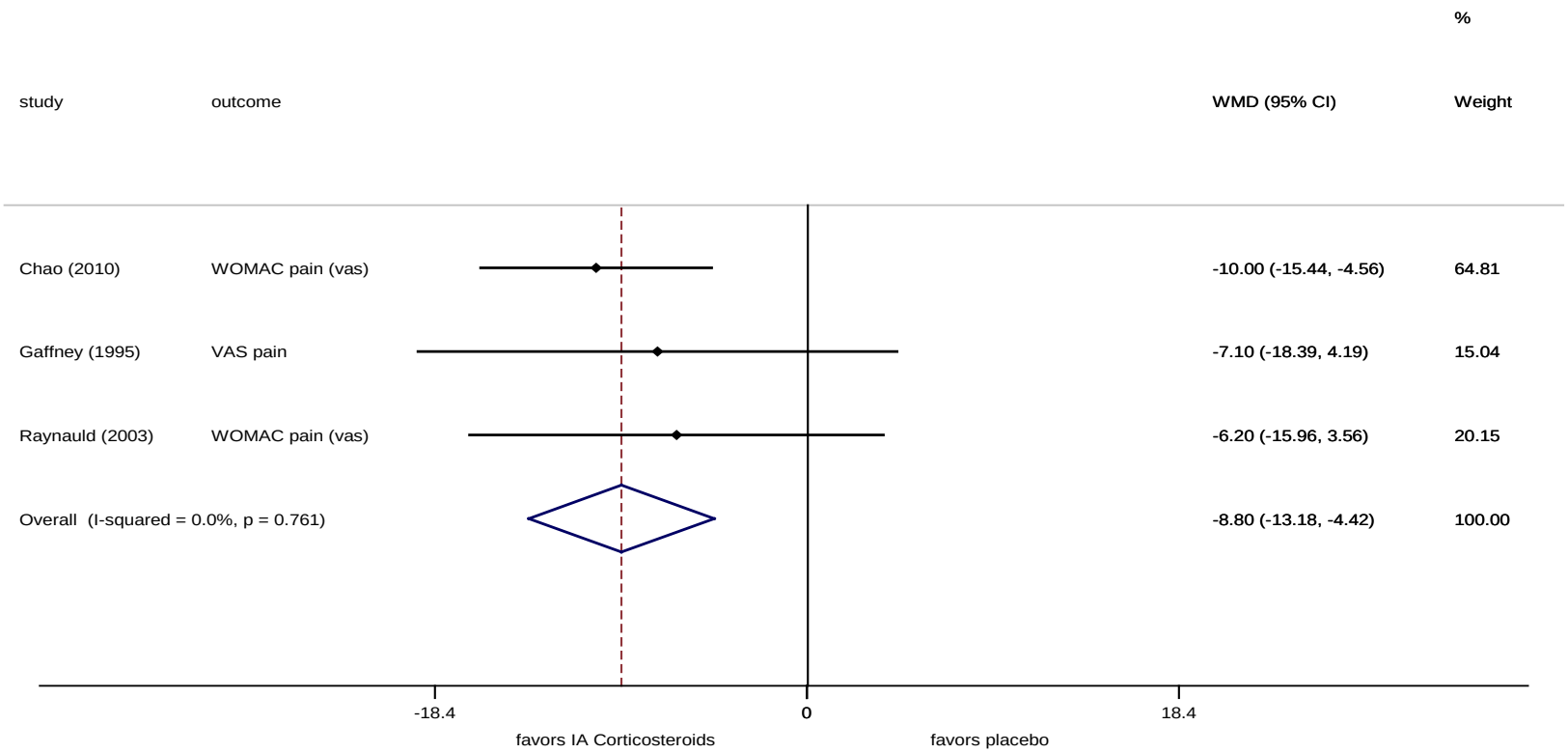
Outcome	N	Sufficient Power	Week	Symptom Duration	Severity	Group 1	Group 2	SMD (Odds Ratio or Raw Mean Difference When Indicated)	Sig	Clinical Importance	Strength of Evidence
WOMAC Pain on walking	215	Yes	12	Minimum of 2 months	NR	IA Corticosteroid	Hylan GF-20	0.38 (0.11, 0.65)	Favors HA	Unclear	Moderate
WOMAC Pain on walking	215	Yes	26	Minimum of 2 months	NR	IA Corticosteroid	Hylan GF-20	0.29 (0.02, 0.56)	Favors HA	Unclear	Moderate
WOMAC Total	215	Yes	12	Minimum of 2 months	NR	IA Corticosteroid	Hylan GF-20	0.47 (0.2, 0.74)	Favors HA	Possibly clinically significant	Moderate
WOMAC Total	215	Yes	26	Minimum of 2 months	NR	IA Corticosteroid	Hylan GF-20	0.44 (0.17, 0.71)	Favors HA	Possibly clinically significant	Moderate
WOMAC Function	215	Yes	12	Minimum of 2 months	NR	IA Corticosteroid	Hylan GF-20	0.46 (0.19, 0.73)	Favors HA	Possibly clinically significant	Moderate
WOMAC Function	215	yes	26	Minimum of 2 months	NR	IA Corticosteroid	Hylan GF-20	0.44 (0.17, 0.71)	Favors HA	Possibly clinically significant	Moderate

Outcome	N	Sufficient Power	Week	Symptom Duration	Severity	Group 1	Group 2	SMD (Odds Ratio or Raw Mean Difference When Indicated)	Sig	Clinical Importance	Strength of Evidence
Patient Global Assessment	215	Yes	12	Minimum of 2 months	NR	IA Corticosteroid	Hylan GF-20	0.57 (0.3, 0.84)	Favors HA	Not clinically significant	Moderate
Patient Global Assessment	215	Yes	26	Minimum of 2 months	NR	IA Corticosteroid	Hylan GF-20	0.59 (0.32, 0.86)	Favors HA	Not clinically significant	Moderate
Physician Global Assessment	215	Yes	12	Minimum of 2 months	NR	IA Corticosteroid	Hylan GF-20	0.29 (0.02, 0.56)	Favors HA	N/A	Moderate
Physician Global Assessment	215	Yes	26	Minimum of 2 months	NR	IA Corticosteroid	Hylan GF-20	0.47 (0.2, 0.75)	Favors HA	N/A	Moderate

Table 174. Needle Lavage Versus Corticosteroids

Study	Outcome	N	Sufficient Power	Week	Avg. Disease Duration (years)	Severity	Group 1	Group 2	SMD (Odds Ratio or Raw Mean Difference When Indicated)	Sig	Clinical Importance	Strength of Evidence
Arden (2008)	WOMAC Pain	146	Yes	4	4.75	K-L 1-4	Needle Lavage	IA Corticosteroid	0.24(-0.09, 0.56)	No	Inconclusive	Moderate
Arden (2008)	WOMAC Pain	146	Yes	12	4.75	K-L 1-4	Needle Lavage	IA Corticosteroid	0.35(0.02, 0.67)	Favors Needle Lavage	Possibly clinically significant	Moderate
Arden (2008)	WOMAC Total function	145	Yes	12	4.75	K-L 1-4	Needle Lavage	IA Corticosteroid	0.34(0.01, 0.66)	Favors Needle Lavage	Possibly clinically significant	Moderate
Arden (2008)	WOMAC Total stiffness	138	Yes	12	4.75	K-L 1-4	Needle Lavage	IA Corticosteroid	0.4(0.06, 0.74)	Favors Needle Lavage	Possibly clinically significant	Moderate
Arden (2008)	WOMAC pain	146	Yes	26	4.75	K-L 1-4	Needle Lavage	IA Corticosteroid	0.52(0.19, 0.85)	Favors Needle Lavage	Possibly clinically significant	Moderate
Arden (2008)	WOMAC Total function	145	Yes	26	4.75	K-L 1-4	Needle Lavage	IA Corticosteroid	0.44(0.11, 0.77)	Favors Needle Lavage	Possibly clinically significant	Moderate
Arden (2008)	WOMAC Total stiffness	138	Yes	26	4.75	K-L 1-4	Needle Lavage	IA Corticosteroid	0.45(0.11, 0.79)	Favors Needle Lavage	Possibly clinically significant	Moderate

Figure 82. Network Meta-Analysis: IA Corticosteroids Versus Placebo (Pain)



RECOMMENDATION 9

We cannot recommend using hyaluronic acid for patients with symptomatic osteoarthritis of the knee.

Strength of Recommendation: Strong

Description: Evidence is based on two or more "High" strength studies with consistent findings for recommending for or against the intervention. A **Strong** recommendation means that the quality of the supporting evidence is high. A harms analysis on this recommendation was not performed.

Implications: Practitioners should follow a **Strong** recommendation unless a clear and compelling rationale for an alternative approach is present.

RATIONALE

Fourteen studies (three high-strength studies and 11 moderate-strength studies) assessed intraarticular hyaluronic acid (HA) injections. A comparison of the patients in these studies and the ones validating the MCIIs we used to judge clinical significance revealed that they were demographically comparable for WOMAC and VAS pain as well as WOMAC function on the basis of age, baseline pain scores, BMI, weight and gender. Meta-analysis in meaningfully important difference (MID) units showed that the over effect was less than 0.5 MID units, indicating a low likelihood that an appreciable number of patients achieved clinically important benefits in the outcomes (Guyatt et al.). Although meta-analyses of WOMAC pain, function, and stiffness subscales scores all found statistically significant treatment effects, none of the improvements met the minimum clinically important improvement thresholds. When we differentiated high- versus low- molecular weight viscosupplementation, our analyses did show that most of the statistically significant outcomes were associated with high-molecular cross linked hyaluronic acid but when compared to mid-range molecular weight, statistical significance was not maintained. Treatment comparisons between any weights higher than 750 kDa were not significantly different. The strength of this recommendation was based on lack of efficacy, not on potential harm.

The 2008 edition of this guideline where the benefits of viscosupplementation were found to be inconclusive rather than non-affirming used a systematic review from AHRQ that compared Hylan G-F 20 to placebo. Although there was a statistically significant treatment effect associated with the high molecular weight, different pain measurement outcomes (WOMAC and VAS pain) were combined so clinical significance could not be determined. Also, the work group found evidence of publication bias (publicizing of primarily favorable studies). We excluded the AHRQ systematic review because the selection criteria did not match ours. The primary difference was that in the current edition of the guideline clinical efficacy beyond a 4-week treatment period was required for studies to be included. This 2nd edition was based on meta-analyses that combined like measurement instruments, which made it possible to determine that the overall effect of hyaluronic acid did not provide minimum clinically important improvement to patients. Additionally, the AHRQ review included trials of varying research-design quality due in part to variations in sample sizes. In AAOS clinical practice guidelines, evidence of lower strength is excluded when there are at least two higher strength studies evaluating an outcome, and we excluded many of the lower strength studies

included in the AHRQ review since they did not meet our selection criterion of at least 30 patients in each treatment group. Noted in the AHRQ review was that "There is evidence consistent with potential publication bias. Pooled results from small trials (<100 patients) showed effects up to twice those of larger trials consistent with selective publication of underpowered positive trials" (page 64)." Future research using clinically relevant outcomes, sub-group analyses, and controls for bias are needed.

SUPPORTING EVIDENCE

QUALITY

Relevant Tables: Table 175-Table176, Table 177-Table 178

There were 94 outcomes from 14 studies that compared intraarticular hyaluronic acid (HA) injections to control treatments. Twelve compared HA to placebo; one compared the treatment to conventional care, and one compared 25mg sodium hyaluron to .25mg hyaluron. All studies were of moderate quality except Lundsgaard et al.,[108] Huang et al.[109] and Puhl et al.,[110] which were rated as high quality.

All included studies were prospective and had no problems with the way the outcomes were measured. Every one, except the studies by Lundsgaard et al.,[108] and Puhl et al.,[110] was flawed in the group assignment domain. Ten out of 14 studies had potential group comparability flaws. Investigator bias was problematic in 12 out of 14 studies. Also, excluding Day et al.,[111] every study was not flawed in the treatment integrity domain amd all but one study was sufficiently blinded.

There were seven studies with 43 outcomes that compared high versus low molecular weight HA. Four of seven studies were of moderate quality. Juni et al.[112] and Maheu et al.[113] were high quality studies, and Lee et al.[114] was a low quality study.

None of the molecular weight HA studies were flawed in the prospective hypothesis, blinding or measurement domains. Excluding the articles by Juni et al.[112] and Maheu et al.,[113] all studies were flawed in the group assignment domain. Three of seven studies were not flawed in group comparability. Juni et al.[112] and Raman et al.[115] were the only studies with limited potential for investigator bias. The Raman et al.[115] and Lee et al.[114] studies were flawed in the treatment integrity domain.

APPLICABILITY

Relevant Tables: Table 175-Table176, Table 177-Table 178

For all studies that compared HA to a control group, there was uncertainty if the treatments were applied in a manner reflecting clinical practice. In all but two studies, there was uncertainty about whether the patients were representative of the typical patient population. Karlsson et al.[116] were the only researchers who did not include all enrolled patients in the final analysis. No unusual steps were taken by investigators in any of the studies to ensure a level of patient compliance beyond what is typically found in clinical settings.

Five out of seven molecular weight studies had participants that may not have been representative of the general osteoarthritis of the knee population. Each molecular weight study was flawed since the intervention was not applied in a similar manner to clinical practice. Only the Karlsson et al.[116] molecular weight study did not include all patients in the final analysis. Finally, compliance and adherence were similar to typical clinical practice in every study.

FINAL STRENGTH OF EVIDENCE

Thirteen out of 18 studies were rated as having moderate strength of evidence. Four studies were rated as having high evidence strength, and one low strength. Due to the moderate applicability ratings for all outcomes, every strength of evidence rating was the same as the quality ratings.

Table 175. Quality and Applicability Summary: Hyaluronic Acid Versus Control

Study	Outcome	Duration	Quality	Applicability	Strength of Evidence
Altman (2004)	WOMAC Pain	6 weeks	Moderate	Moderate	Moderate
Altman (2004)	WOMAC Pain	3 months	Moderate	Moderate	Moderate
Altman (2004)	WOMAC Pain	6 months	Moderate	Moderate	Moderate
Altman (2004)	WOMAC Function	6 weeks	Moderate	Moderate	Moderate
Altman (2004)	WOMAC Function	3 months	Moderate	Moderate	Moderate
Altman (2004)	WOMAC Function	6 months	Moderate	Moderate	Moderate
Altman (2004)	WOMAC Stiffness	6 weeks	Moderate	Moderate	Moderate
Altman (2004)	WOMAC Stiffness	3 months	Moderate	Moderate	Moderate
Altman (2004)	WOMAC Stiffness	6 months	Moderate	Moderate	Moderate
Altman (2009)	Change in 50 foot walk pain score	6 months	Moderate	Moderate	Moderate
Altman (2009)	SF-36 physical Function	6 months	Moderate	Moderate	Moderate
Altman (2009)	WOMAC Function	6 months	Moderate	Moderate	Moderate
Altman (2009)	WOMAC Pain	6 months	Moderate	Moderate	Moderate
Altman (2009)	WOMAC Stiffness	6 months	Moderate	Moderate	Moderate

Study	Outcome	Duration	Quality	Applicability	Strength of Evidence
Day (2004)	WOMAC Function	18 weeks	Moderate	Moderate	Moderate
Day (2004)	WOMAC Pain	18 weeks	Moderate	Moderate	Moderate
Huang (2011)	VAS pain on walking change from W0 to W5	5 weeks	High	Moderate	High
Huang (2011)	VAS pain on walking change from W0 to W13	12 weeks	High	Moderate	High
Huang (2011)	VAS pain on walking change from W0 to W25	25 weeks	High	Moderate	High
Huang (2011)	WOMAC Pain	25 weeks	High	Moderate	High
Huang (2011)	WOMAC Stiffness	25 weeks	High	Moderate	High
Huang (2011)	WOMAC Function	25 weeks	High	Moderate	High
Day (2004)	WOMAC Stiffness	18 weeks	Moderate	Moderate	Moderate
Jorgensen (2010)	Lequesne index difference between groups	13 weeks	Moderate	Moderate	Moderate
Jorgensen (2010)	Lequesne index difference between groups	6 months	Moderate	Moderate	Moderate
Jorgensen (2010)	Lequesne index difference between groups s	1 year	Moderate	Moderate	Moderate

Study	Outcome	Duration	Quality	Applicability	Strength of Evidence
Jorgensen (2010)	VAS Pain difference between groups	13 weeks	Moderate	Moderate	Moderate
Jorgensen (2010)	VAS Pain difference between groups	52 weeks	Moderate	Moderate	Moderate
Jorgensen (2010)	VAS Pain difference between groups 26 weeks	6 months	Moderate	Moderate	Moderate
Kahan (2003)	Change in Pain on Walking	9 months	Moderate	Moderate	Moderate
Kahan (2003)	Lequesne index	9 months	Moderate	Moderate	Moderate
Kahan (2003)	WOMAC Pain	9 months	Moderate	Moderate	Moderate
Kahan (2003)	WOMAC Stiffness	9 months	Moderate	Moderate	Moderate
Kahan (2003)	WOMAC Total	9 months	Moderate	Moderate	Moderate
Kahan (2003)	WOMAC Function	9 months	Moderate	Moderate	Moderate
Karlsson (2002)	VAS weight bearing pain week 12 (high molecular weight)	12 weeks	Moderate	Moderate	Moderate
Karlsson (2002)	VAS weight bearing pain week 12 (low molecular weight)	12 weeks	Moderate	Moderate	Moderate
Karlsson (2002)	VAS weight bearing pain week 20 (high molecular weight)	20 weeks	Moderate	Moderate	Moderate

Study	Outcome	Duration	Quality	Applicability	Strength of Evidence
Karlsson (2002)	VAS weight bearing pain week 20 (low molecular weight)	20 weeks	Moderate	Moderate	Moderate
Karlsson (2002)	VAS weight bearing pain week 26	6 months	Moderate	Moderate	Moderate
Karlsson (2002)	VAS weight bearing pain week 26	6 months	Moderate	Moderate	Moderate
Karlsson (2002)	Lequesne index week 20 (High Molecular Weight)	20 weeks	Moderate	Moderate	Moderate
Karlsson (2002)	Lequesne index week 20 (low molecular weight)	20 weeks	Moderate	Moderate	Moderate
Karlsson (2002)	Lequesne index week 26 (High Molecular Weight)	26 weeks	Moderate	Moderate	Moderate
Karlsson (2002)	Lequesne index week 26 (low molecular weight)	6 months	Moderate	Moderate	Moderate
Lohmander (1996)	Lequesne index	6 months	Moderate	Moderate	Moderate
Lundsgaard (2008)	KOOS Activities	6 months	High	Moderate	High
Lundsgaard (2008)	KOOS Pain	6 months	High	Moderate	High
Lundsgaard (2008)	KOOS Sports	6 months	High	Moderate	High
Lundsgaard (2008)	VAS Pain at movement	6 months	High	Moderate	High
Lundsgaard (2008)	VAS Pain at night	6 months	High	Moderate	High

Study	Outcome	Duration	Quality	Applicability	Strength of Evidence
Lundsgaard (2008)	VAS Pain at rest	6 months	High	Moderate	High
Navarro-Sarabia (2011)	OARSI Responders last follow-up	40 months	Moderate	Moderate	Moderate
Navarro-Sarabia (2011)	OARSI Responders	7 months	Moderate	Moderate	Moderate
Navarro-Sarabia (2011)	OARSI Responders	14 months	Moderate	Moderate	Moderate
Navarro-Sarabia (2011)	OARSI Responders	21 months	Moderate	Moderate	Moderate
Navarro-Sarabia (2011)	OARSI Responders	27 months	Moderate	Moderate	Moderate
Navarro-Sarabia (2011)	OARSI Responders	34 months	Moderate	Moderate	Moderate
Navarro-Sarabia (2011)	Pain or function reduction 50%	40 months	Moderate	Moderate	Moderate
Navarro-Sarabia (2011)	Overall pain reduction 20%	40 months	Moderate	Moderate	Moderate
Navarro-Sarabia (2011)	Function improvement 20%	40 months	Moderate	Moderate	Moderate

Study	Outcome	Duration	Quality	Applicability	Strength of Evidence
Navarro-Sarabia (2011)	Patient Global Assessment reduction 20% (10 mm), n (%)	40 months	Moderate	Moderate	Moderate
Navarro-Sarabia (2011)	Mean consumption of Paracetamol mg/day	40 months	Moderate	Moderate	Moderate
Petrella (2006)	Change in VAS stepping Pain 13 weeks	13 weeks	Moderate	Moderate	Moderate
Petrella (2006)	Change in VAS stepping Pain 6 weeks	6 weeks	Moderate	Moderate	Moderate
Petrella (2006)	Change in VAS Walking Pain	6 weeks	Moderate	Moderate	Moderate
Petrella (2006)	Change in VAS Walking Pain	13 weeks	Moderate	Moderate	Moderate
Petrella (2006)	SF-36 Physical 13 weeks	13 weeks	Moderate	Moderate	Moderate
Petrella (2006)	SF-36 Physical Function 6 weeks	6 weeks	Moderate	Moderate	Moderate
Petrella (2006)	WOMAC Function	13 weeks	Moderate	Moderate	Moderate
Petrella (2006)	WOMAC Pain	13 weeks	Moderate	Moderate	Moderate
Petrella (2006)	WOMAC Stiffness	13 weeks	Moderate	Moderate	Moderate

Study	Outcome	Duration	Quality	Applicability	Strength of Evidence
Wobig (1998)	Evaluator assessment of VAS night pain-number symptom free	26 weeks	Moderate	Moderate	Moderate
Wobig (1998)	Evaluator assessment of weight bearing pain	26 weeks	Moderate	Moderate	Moderate
Wobig (1998)	Evaluator VAS assessment of night pain-number symptom free	12 weeks	Moderate	Moderate	Moderate
Wobig (1998)	Evaluator VAS Assessment of Weight bearing pain-number symptom free	12 weeks	Moderate	Moderate	Moderate
Wobig (1998)	Patient VAS Assessment of night pain-number symptom free	12weeks	Moderate	Moderate	Moderate
Wobig (1998)	Patient VAS assessment of pain during most painful knee movement-number symptom free	12 weeks	Moderate	Moderate	Moderate
Wobig (1998)	Patient VAS Assessment of Weight bearing pain-number symptom free	12 weeks	Moderate	Moderate	Moderate

Study	Outcome	Duration	Quality	Applicability	Strength of Evidence
Wobig (1998)	Evaluator Assessment of Loss of Activities (symptom free)	12 weeks	Moderate	Moderate	Moderate
Wobig (1998)	Evaluator Assessment of Loss of Activities (symptom free)	26 weeks	Moderate	Moderate	Moderate
Chevalier (2010)	WOMAC Pain	26 weeks	Moderate	Moderate	Moderate
Chevalier (2010)	WOMAC Function	26 weeks	Moderate	Moderate	Moderate
Chevalier (2010)	OARSI Responders	26 weeks	Moderate	Moderate	Moderate
Chevalier (2010)	Any treatment-emergent target knee AE	26 weeks	Moderate	Moderate	Moderate
Chevalier (2010)	Any treatment and/or procedure-related target knee AE	26 weeks	Moderate	Moderate	Moderate
Chevalier (2010)	Arthralgia	26 weeks	Moderate	Moderate	Moderate
Chevalier (2010)	Joint effusion	26 weeks	Moderate	Moderate	Moderate
Chevalier (2010)	Arthropathy	26 weeks	Moderate	Moderate	Moderate
Chevalier (2010)	Injection site pain	26 weeks	Moderate	Moderate	Moderate
Chevalier (2010)	Any treatment-related target knee AE	26 weeks	Moderate	Moderate	Moderate

Study	Outcome	Duration	Quality	Applicability	Strength of Evidence
Chevalier (2010)	Any procedure-related target knee AE	26 weeks	Moderate	Moderate	Moderate
Puhl (1993)	Lequesne index week 10	10 weeks	High	Moderate	High
Puhl (1993)	Lequesne index week 14	14 weeks	High	Moderate	High

Table 176. Quality and Applicability Summary: High Versus Low Molecular Weight Hyaluronic Acid

Study	Outcome	Duration	Quality	Applicability	Strength of Evidence
Juni (2007)	WOMAC Function	6 months	High	Moderate	High
Juni (2007)	WOMAC Pain	12 weeks	High	Moderate	High
Juni (2007)	WOMAC Pain	6 months	High	Moderate	High
Juni (2007)	WOMAC Stiffness	6 months	High	Moderate	High
Juni (2007)	WOMAC Total	6 months	High	Moderate	High
Karlsson (2002)	Lequesne index week 20	20 weeks	Moderate	Moderate	Moderate
Karlsson (2002)	Lequesne index week 26	6 months	Moderate	Moderate	Moderate
Karlsson (2002)	VAS weight bearing pain	12 weeks	Moderate	Moderate	Moderate
Karlsson (2002)	VAS weight bearing pain week 20	20 weeks	Moderate	Moderate	Moderate
Karlsson (2002)	VAS weight bearing pain week 26	6 months	Moderate	Moderate	Moderate
Lee (2006)	VAS weight bearing pain	12 weeks	Low	Moderate	Low

Study	Outcome	Duration	Quality	Applicability	Strength of Evidence
Maheu (2011)	LFI score	24	Moderate	Moderate	Moderate
Maheu (2011)	Global pain	24	Moderate	Moderate	Moderate
Maheu (2011)	Investigator's assessment	24	Moderate	Moderate	Moderate
Maheu (2011)	SF-12 Physical component	24	Moderate	Moderate	Moderate
Maheu (2011)	SF-12 Mental component	24	Moderate	Moderate	Moderate
Maheu (2011)	OARSI OMERACT Responders	24	Moderate	Moderate	Moderate
Maheu (2011)	OARSI OMERACT Responders	24	Moderate	Moderate	Moderate
Maheu (2011)	Rescue medication: Patients who did NOT take Paracetamol during the study period	24	Moderate	Moderate	Moderate
Maheu (2011)	Rescue medication: Patients who did NOT	24	Moderate	Moderate	Moderate
Maheu (2011)	Patients with one or more AE	24	Moderate	Moderate	Moderate

Study	Outcome	Duration	Quality	Applicability	Strength of Evidence
Maheu (2011)	Patients with treatment emergent AE	24	Moderate	Moderate	Moderate
Maheu (2011)	Patients with serious AE	24	Moderate	Moderate	Moderate
Pavelka (2011)	WOMAC Pain	26	Moderate	Moderate	Moderate
Pavelka (2011)	WOMAC Pain	4	Moderate	Moderate	Moderate
Pavelka (2011)	WOMAC Pain	12	Moderate	Moderate	Moderate
Pavelka (2011)	WOMAC Function	26	Moderate	Moderate	Moderate
Pavelka (2011)	WOMAC Stiffness	26	Moderate	Moderate	Moderate
Pavelka (2011)	WOMAC Total	26	Moderate	Moderate	Moderate
Pavelka (2011)	Lequesne index	4	Moderate	Moderate	Moderate
Pavelka (2011)	Lequesne index	12	Moderate	Moderate	Moderate
Pavelka (2011)	Lequesne index	26	Moderate	Moderate	Moderate
Pavelka (2011)	Percent using rescue medication	4 weeks	Moderate	Moderate	Moderate
Pavelka (2011)	Percent using rescue medication	4 to 12 weeks	Moderate	Moderate	Moderate
Pavelka (2011)	Percent using rescue medication	12-26 weeks	Moderate	Moderate	Moderate

Study	Outcome	Duration	Quality	Applicability	Strength of Evidence
Pavelka (2011)	Percent using rescue medication	Baseline to 26 weeks	Moderate	Moderate	Moderate
Raman (2008)	WOMAC Pain	6 weeks	Moderate	Moderate	Moderate
Raman (2008)	WOMAC Pain	13 weeks	Moderate	Moderate	Moderate
Raman (2008)	WOMAC Pain	6 months	Moderate	Moderate	Moderate
Raman (2008)	WOMAC Pain	1 year	Moderate	Moderate	Moderate
Wobig (1999)	Evaluator VAS overall condition improvement	12 weeks	Moderate	Moderate	Moderate
Wobig (1999)	Patient VAS improvement in most painful knee	12 weeks	Moderate	Moderate	Moderate
Wobig (1999)	VAS Pain	12 weeks	Moderate	Moderate	Moderate

RESULTS

Relevant Tables: Figure 83-Figure 91, Table 179-Table189

Out of 37 total pain outcomes comparing HA to placebo, twelve were statistically improved in the treatment group. Figure 88 shows the pooled weighted mean differences between HA and placebo for WOMAC pain. The meta-analysis excludes the studies by Kahan et al.[117] and Altman et al.[118] because they were both significant causes of heterogeneity in the model. Kahan et al.[117] did not blind the patients or investigators. The lack of blinding caused a much larger treatment effect than was found in the other studies, which is where the heterogeneity originated. The Altman et al.[118] study enrolled significantly more women in the placebo group than in the treatment group. The authors note that the statistically insignificant results of the primary analysis may have been confounded by the inclusion of patients whose osteoarthritis was not confined to the knee. When they analyzed a subgroup of patients with osteoarthritis localized to the knee, they found that responder rates (40% reduction in WOMAC pain with a minimum improvement of five points) were significantly higher in the treatment group

When the Kahan et al.[117] and Altman et al.[118] studies were removed from the analysis, the HA group reported significantly lower pain scores than the control group. This difference was not clinically significant since the lower bound of the confidence interval was higher than the MCII (Figure 88).

Figure 89 shows the meta-analysis results for pain on weight bearing/movement. Each outcome was measured by the Visual Analogue Scale. Again the results were statistically significant but not clinically important.

Seven of 16 function outcomes were statistically significant in favor of HA over the control treatments. Figure 90 contains the results for a meta-analysis of the difference in function scores between the HA and placebo groups. Each study used WOMAC function (scaled to 100mm VAS) as an outcome. Altman et al.[118] and Kahan et al.[117] were again excluded from the analysis to reduce the heterogeneity to an acceptable level. The final results indicate that HA did produce statistically significant improvement in function but the effect was not clinically important.

One of eight WOMAC stiffness outcomes was statistically significant in favor of HA over the control assignment. Results of the meta-analysis for this outcome can be found in Figure 91. Again, Altman et al.[118] and Kahan et al.[117] were excluded. The results showed that WOMAC stiffness scores were significantly lower in patients receiving HA than those in the control group but the difference was not clinically important.

Kahan et al.[117] compared WOMAC total scores between treatment and control groups. They found that patients who received HA plus conventional treatment reported significantly better scores than those who received only usual care and the difference was clinically important.

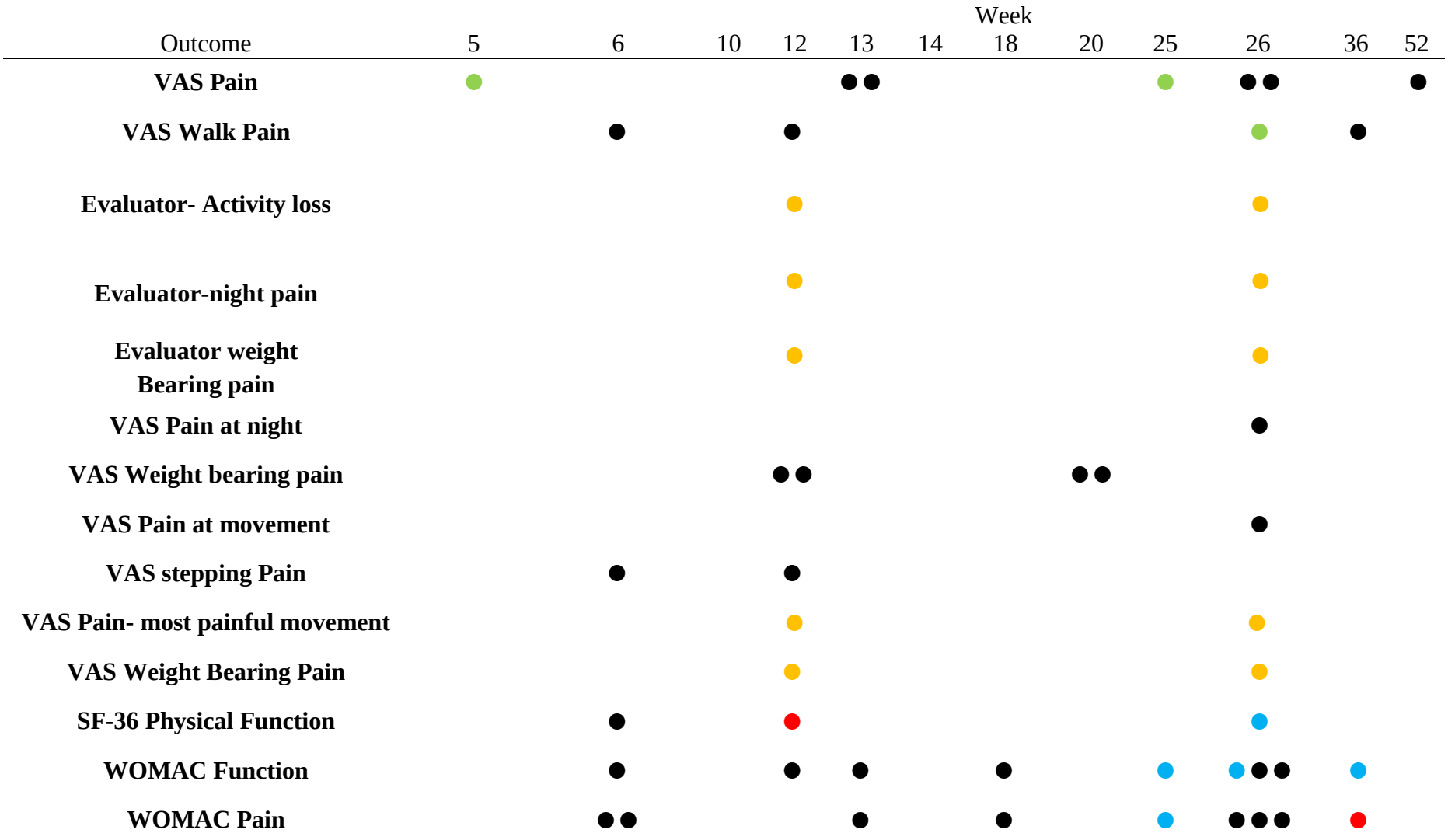
There were nine Lequesne index outcomes comparing HA and control treatments. Only one was statistically significant in favor of HA.

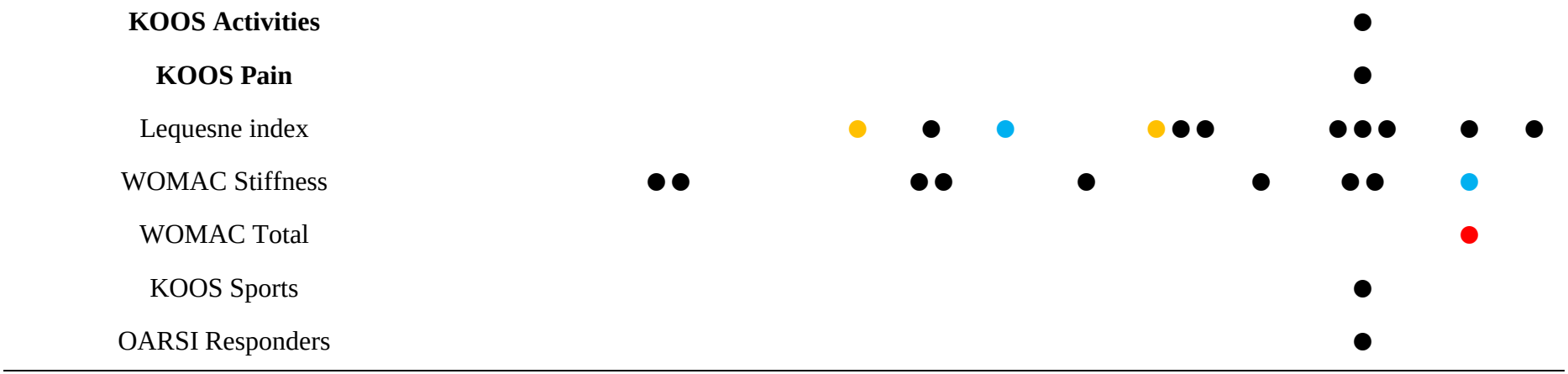
There was evidence to suggest that high molecular weight HAs were more effective than those with lower weights. Eight of 12 pain outcomes significantly favored Hylan G-F 20 (6 million Da) over placebo assignment. Nine of the 12 statistically significant placebo-compared pain outcomes were of HAs of at least 2.4 million Daltons.

Five of six placebo-compared functional outcomes that compared HA of at least 2.4 million Daltons to placebo were statistically significant in favor of the treatment group. Also, high molecular weight HA accounted for five of the seven significant pain outcomes. Out of eight WOMAC stiffness outcomes, the only one that was statistically significant compared to placebo was for Hylan G-F 20 (6 million Da).

Six of seven pain outcomes were statistically significant in favor of Hylan G-F 20 over HAs with a molecular weight of .5 to .75 Daltons. These treatments represented the highest and lowest molecular weight HAs, and the results suggested statistically and possibly clinically important differences in favor of Hylan G-F 20. Three outcomes were possibly clinically important, and the other three were indeterminable.There were not any statistically significant differences between high and medium molecular weight HAs, or between the medium and low molecular weights.

Figure 83. Results Summary: Intraarticular Hyaluronic Acid Versus Control





Key: ●=Not Significant; ●=Statistically Significant; ●=Possibly Clinically Significant; ●=Clinically Significant.
(Bold lettering indicates a critical outcome.)

Figure 84. Results Summary: High Versus Low Molecular Weight Hyaluronic Acid

		Weeks							
Molecular Weight Comparison	Outcome	4	6	12	13	20	24	26	52
Comparison 1: 6 million Da **versus** 1-2.9 million Da	WOMAC pain			●				●	
	WOMAC function								
	WOMAC stiffness								
	WOMAC total								
Comparison 2: 6 million Da **versus** 2.2-2.7 million Da	Lequesne index							●	
	Global pain							●	
	Investigator's assessment							●	
	SF12 : Physical component							●	
	SF12 : Mental component							●	
	OARSI OMERACT Responder			●				●	
	Rescue medication use							●	
	patientes with one or more AE							●	
	patients with treatment emergent AE							●	
	Patients with serious AE							●	
Comparison 3: 6 million Da **versus** 800kda-1200kda	WOMAC pain	●		●				●	
	WOMAC function							●	
	WOMAC stiffness							●	
	WOMAC total							●	
	Lequesne index	●		●				●	
	rescue medication use	●		●				●	
	Patients with treatment related adverse events							●	
	Patients with severe adverse events							●	
Comparison 4: 7 million Da **versus** 1 million Da	VAS Weight bearing pain			●		●		●	

		Weeks							
Molecular Weight Comparison	Outcome	4	6	12	13	20	24	26	52
Comparison 5: All molecular weights >.75kDa **versus** .5-.75 kDa	WOMAC pain		●		●			●	●
	VAS pain							●	
	ICOAP-total pain							●	
	ICOAP-constant pain							●	
	ICOAP-intermittent pain							●	
	significant pain improvement							●	
	VAS Weight bearing pain			●					
	evaluator assessment			●					
	patient assessment			●					
	WOMAC function							●	
	WOMAC total							●	
	lequesne index							●	
	adverse events			●					
	treatment related Adverse events								●

Key: ●=Not Significant; ●=Statistically Significant in Favor of High Molecular Weight: ●=Possibly Clinically Significant in Favor of High Molecular Weight Hyaluronic Acid

EVIDENCE TABLES AND FIGURES

QUALITY AND APPLICABILITY

Table 177. Quality and Applicability: Hyaluronic Acid Versus Control

●: Domain free of flaws

○: Domain flaws present

◐: Moderate power

Study	*Outcome*	Prospective	Power	Group Assignment	Blinding	Group Comparability	Treatment Integrity	Measurement	Investigator Bias	*Quality*	Participants	Intervention and Expertise	Compliance and Adherence	Analysis	*Applicability Study*
Heybeli (2008)	WOMAC Pain	●	●	○	●	●	●	●	○	**Moderate**	○	○	●	●	**Moderate**
Heybeli (2008)	WOMAC Function	●	●	○	●	●	●	●	○	**Moderate**	○	○	●	●	**Moderate**
Lundsgaard (2008)	KOOS Pain	●	◐	●	●	●	●	●	○	**High**	○	○	●	●	**Moderate**
Altman (2009)	Change in 50 foot walk pain score	●	●	○	●	○	●	●	○	**Moderate**	○	○	●	●	**Moderate**
Altman (2009)	WOMAC Pain	●	●	○	●	○	●	●	○	**Moderate**	○	○	●	●	**Moderate**

●: Domain free of flaws

○: Domain flaws present

◐: Moderate power

Study	*Outcome*	**Prospective**	**Power**	**Group Assignment**	**Blinding**	**Group Comparability**	**Treatment Integrity**	**Measurement**	**Investigator Bias**	*Quality*	**Participants**	**Intervention and Expertise**	**Compliance and Adherence**	**Analysis**	*Applicability Study*
Altman (2009)	SF-36 Physical Function	●	●	○	●	○	●	●	○	**Moderate**	○	○	●	●	**Moderate**
Altman (2009)	WOMAC Function	●	●	○	●	○	●	●	○	**Moderate**	○	○	●	●	**Moderate**
Altman (2009)	WOMAC Stiffness	●	●	○	●	○	●	●	○	**Moderate**	○	○	●	●	**Moderate**
Altman (2004)	WOMAC Pain 6 weeks	●	●	○	●	○	●	●	○	**Moderate**	○	○	●	●	**Moderate**
Altman (2004)	WOMAC Pain 13 weeks	●	●	○	●	○	●	●	○	**Moderate**	○	○	●	●	**Moderate**
Altman (2004)	WOMAC Pain 26 weeks	●	●	○	●	○	●	●	○	**Moderate**	○	○	●	●	**Moderate**

●: Domain free of flaws

○: Domain flaws present

◐: Moderate power

Study	*Outcome*	**Prospective**	**Power**	**Group Assignment**	**Blinding**	**Group Comparability**	**Treatment Integrity**	**Measurement**	**Investigator Bias**	*Quality*	**Participants**	**Intervention and Expertise**	**Compliance and Adherence**	**Analysis**	*Applicability Study*
Altman (2004)	WOMAC Function 6 weeks	●	●	○	●	○	●	●	○	**Moderate**	○	○	●	●	**Moderate**
Altman (2004)	WOMAC Function13 weeks	●	●	○	●	○	●	●	○	**Moderate**	○	○	●	●	**Moderate**
Altman (2004)	WOMAC Function 36 weeks	●	●	○	●	○	●	●	○	**Moderate**	○	○	●	●	**Moderate**
Altman (2004)	WOMAC Stiffness 6 weeks	●	●	○	●	○	●	●	○	**Moderate**	○	○	●	●	**Moderate**
Altman (2004)	WOMAC Stiffness 13 weeks	●	●	○	●	○	●	●	○	**Moderate**	○	○	●	●	**Moderate**
Altman (2004)	WOMAC Stiffness 26 weeks	●	●	○	●	○	●	●	○	**Moderate**	○	○	●	●	**Moderate**

●: Domain free of flaws

○: Domain flaws present

◐: Moderate power

Study	*Outcome*	**Prospective**	**Power**	**Group Assignment**	**Blinding**	**Group Comparability**	**Treatment Integrity**	**Measurement**	**Investigator Bias**	*Quality*	**Participants**	**Intervention and Expertise**	**Compliance and Adherence**	**Analysis**	*Applicability Study*
Day (2004)	WOMAC Pain	●	●	○	●	○	○	●	○	**Moderate**	○	○	●	●	**Moderate**
Day (2004)	WOMAC Function	●	●	○	●	○	○	●	○	**Moderate**	○	○	●	●	**Moderate**
Day (2004)	WOMAC Stiffness	●	●	○	●	○	○	●	○	**Moderate**	○	○	●	●	**Moderate**
Jorgensen (2010)	VAS Pain difference between groups 13 weeks	●	●	○	●	○	●	●	●	**Moderate**	○	○	●	●	**Moderate**
Jorgensen (2010)	VAS Pain difference between groups 26 weeks	●	◐	○	●	○	●	●	●	**Moderate**	○	○	●	●	**Moderate**
Jorgensen (2010)	VAS Pain difference between groups 52 weeks	●	◐	○	●	○	●	●	●	**Moderate**	○	○	●	●	**Moderate**

●: Domain free of flaws

○: Domain flaws present

◐: Moderate power

Study	*Outcome*	**Prospective**	**Power**	**Group Assignment**	**Blinding**	**Group Comparability**	**Treatment Integrity**	**Measurement**	**Investigator Bias**	*Quality*	**Participants**	**Intervention and Expertise**	**Compliance and Adherence**	**Analysis**	*Applicability Study*
Jorgensen (2010)	Lequesne index difference between groups 13 weeks	●	◐	○	●	○	●	●	●	**Moderate**	○	○	●	●	**Moderate**
Jorgensen (2010)	Lequesne index difference between groups 26 weeks	●	◐	○	●	○	●	●	●	**Moderate**	○	○	●	●	**Moderate**
Jorgensen (2010)	Lequesne index difference between groups 52weeks	●	◐	○	●	○	●	●	●	**Moderate**	○	○	●	●	**Moderate**
Kahan (2003)	Change in Pain on Walking	●	●	○	○	●	●	●	○	**Moderate**	●	○	●	●	**Moderate**
Kahan (2003)	WOMAC Pain	●	●	○	○	●	●	●	○	**Moderate**	●	○	●	●	**Moderate**

●: Domain free of flaws

○: Domain flaws present

◐: Moderate power

Study	*Outcome*	**Prospective**	**Power**	**Group Assignment**	**Blinding**	**Group Comparability**	**Treatment Integrity**	**Measurement**	**Investigator Bias**	*Quality*	**Participants**	**Intervention and Expertise**	**Compliance and Adherence**	**Analysis**	*Applicability Study*
Kahan (2003)	WOMAC Stiffness	●	●	○	○	●	●	●	○	**Moderate**	●	○	●	●	**Moderate**
Kahan (2003)	WOMAC Total	●	●	○	○	●	●	●	○	**Moderate**	●	○	●	●	**Moderate**
Kahan (2003)	Lequesne index	●	●	○	○	●	●	●	○	**Moderate**	●	○	●	●	**Moderate**
Kahan (2003)	WOMAC Function	●	●	○	○	●	●	●	○	**Moderate**	●	○	●	●	**Moderate**
Karlsson (2002)	VAS weight bearing pain week 12 (high molecular weight)	●	●	○	●	○	●	●	○	**Moderate**	○	○	●	○	**Moderate**
Karlsson (2002)	VAS weight bearing pain week 12 (low molecular weight)	●	●	○	●	○	●	●	○	**Moderate**	○	○	●	○	**Moderate**
Karlsson	VAS weight bearing pain week 20 (high	●	●	○	●	○	●	●	○	**Moderate**	○	○	●	○	**Moderate**

●: Domain free of flaws

○: Domain flaws present

◐: Moderate power

Study	*Outcome*	**Prospective**	**Power**	**Group Assignment**	**Blinding**	**Group Comparability**	**Treatment Integrity**	**Measurement**	**Investigator Bias**	*Quality*	**Participants**	**Intervention and Expertise**	**Compliance and Adherence**	**Analysis**	*Applicability Study*
(2002)	molecular weight)														
Karlsson (2002)	VAS weight bearing pain week 20 (low molecular weight)	●	●	○	●	○	●	●	○	**Moderate**	○	○	●	○	**Moderate**
Karlsson (2002)	VAS weight bearing pain week 26	●	●	○	●	○	●	●	○	**Moderate**	○	○	●	○	**Moderate**
Karlsson (2002)	VAS weight bearing pain week 26	●	●	○	●	○	●	●	○	**Moderate**	○	○	●	○	**Moderate**
Karlsson (2002)	Lequesne index week 20 (High Molecular Weight)	●	◐	○	●	○	●	●	○	**Moderate**	○	○	●	○	**Moderate**
Karlsson (2002)	Lequesne index week 20 (low molecular	●	◐	○	●	○	●	●	○	**Moderate**	○	○	●	○	**Moderate**

●: Domain free of flaws

○: Domain flaws present

◐: Moderate power

Study	*Outcome*	**Prospective**	**Power**	**Group Assignment**	**Blinding**	**Group Comparability**	**Treatment Integrity**	**Measurement**	**Investigator Bias**	*Quality*	**Participants**	**Intervention and Expertise**	**Compliance and Adherence**	**Analysis**	*Applicability Study*
	weight)														
Karlsson (2002)	Lequesne index week 26 (High Molecular Weight)	●	◐	○	●	○	●	●	○	**Moderate**	○	○	●	○	**Moderate**
Karlsson (2002)	Lequesne index week 26 (low molecular weight)	●	◐	○	●	○	●	●	○	**Moderate**	○	○	●	○	**Moderate**
Lohmander (1996)	Lequesne index	●	●	○	●	○	●	●	○	**Moderate**	○	○	●	●	**Moderate**
Lundsgaard (2008)	VAS Pain at movement	●	●	●	●	●	●	●	○	**High**	○	○	●	●	**Moderate**
Lundsgaard (2008)	VAS Pain at rest	●	●	●	●	●	●	●	○	**High**	○	○	●	●	**Moderate**

●: Domain free of flaws

○: Domain flaws present

◐: Moderate power

Study	*Outcome*	**Prospective**	**Power**	**Group Assignment**	**Blinding**	**Group Comparability**	**Treatment Integrity**	**Measurement**	**Investigator Bias**	*Quality*	**Participants**	**Intervention and Expertise**	**Compliance and Adherence**	**Analysis**	*Applicability Study*
Lundsgaard (2008)	VAS Pain at night	●	●	●	●	●	●	●	○	**High**	○	○	●	●	**Moderate**
Lundsgaard (2008)	KOOS Activities	●	◐	●	●	●	●	●	○	**High**	○	○	●	●	**Moderate**
Lundsgaard (2008)	KOOS Sports	●	◐	●	●	●	●	●	○	**High**	○	○	●	●	**Moderate**
Petrella (2006)	Change in VAS Walking Pain 6 weeks	●	◐	○	●	○	●	●	○	**Moderate**	○	○	●	●	**Moderate**
Petrella (2006)	Change in VAS Walking Pain 13 weeks	●	●	○	●	○	●	●	○	**Moderate**	○	○	●	●	**Moderate**
Petrella (2006)	Change in VAS stepping Pain 6 weeks	●	●	○	●	○	●	●	○	**Moderate**	○	○	●	●	**Moderate**

●: Domain free of flaws

○: Domain flaws present

◐: Moderate power

Study	*Outcome*	**Prospective**	**Power**	**Group Assignment**	**Blinding**	**Group Comparability**	**Treatment Integrity**	**Measurement**	**Investigator Bias**	*Quality*	**Participants**	**Intervention and Expertise**	**Compliance and Adherence**	**Analysis**	*Applicability Study*
Petrella (2006)	Change in VAS stepping Pain 13 weeks	●	●	○	●	○	●	●	○	**Moderate**	○	○	●	●	**Moderate**
Petrella (2006)	SF-36 Physical Function 6 weeks	●	●	○	●	○	●	●	○	**Moderate**	○	○	●	●	**Moderate**
Petrella (2006)	SF-36 Physical 13 weeks	●	●	○	●	○	●	●	○	**Moderate**	○	○	●	●	**Moderate**
Petrella (2006)	WOMAC Function	●	○	○	●	○	●	●	○	**Moderate**	○	○	●	●	**Moderate**
Petrella (2006)	WOMAC Stiffness	●	○	○	●	○	●	●	○	**Moderate**	○	○	●	●	**Moderate**
Petrella (2006)	WOMAC Pain	●	●	○	●	○	●	●	○	**Moderate**	○	○	●	●	**Moderate**

●: Domain free of flaws

○: Domain flaws present

◐: Moderate power

Study	*Outcome*	**Prospective**	**Power**	**Group Assignment**	**Blinding**	**Group Comparability**	**Treatment Integrity**	**Measurement**	**Investigator Bias**	*Quality*	**Participants**	**Intervention and Expertise**	**Compliance and Adherence**	**Analysis**	*Applicability Study*
Wobig (1998)	Patient VAS Assessment of Weight bearing pain-number symptom free	●	●	○	●	○	●	●	○	**Moderate**	●	○	●	●	**Moderate**
Wobig (1998)	Patient VAS Assessment of night pain- number symptom free	●	●	○	●	○	●	●	○	**Moderate**	●	○	●	●	**Moderate**
Wobig (1998)	Patient VAS assessment of pain during most painful knee movement-number symptom free	●	●	○	●	○	●	●	○	**Moderate**	●	○	●	●	**Moderate**
Wobig (1998)	Evaluator VAS Assessment of Weight	●	●	○	●	○	●	●	○	**Moderate**	●	○	●	●	**Moderate**

●: Domain free of flaws

○: Domain flaws present

◐: Moderate power

Study	*Outcome*	**Prospective**	**Power**	**Group Assignment**	**Blinding**	**Group Comparability**	**Treatment Integrity**	**Measurement**	**Investigator Bias**	*Quality*	**Participants**	**Intervention and Expertise**	**Compliance and Adherence**	**Analysis**	*Applicability Study*
	bearing pain-number symptom free														
Wobig (1998)	Evaluator VAS assessment of night pain-number symptom free	●	●	○	●	○	●	●	○	**Moderate**	●	○	●	●	**Moderate**
Wobig (1998)	Evaluator assessment of weight bearing pain	●	●	○	●	○	●	●	○	**Moderate**	●	○	●	●	**Moderate**
Wobig (1998)	Evaluator assessment of VAS night pain-number symptom free	●	●	○	●	○	●	●	○	**Moderate**	●	○	●	●	**Moderate**
Wobig (1998)	Evaluator Assessment of Loss of Activities (symptom free)	●	●	○	●	○	●	●	○	**Moderate**	●	○	●	●	**Moderate**

●: Domain free of flaws

○: Domain flaws present

◐: Moderate power

Study	*Outcome*	**Prospective**	**Power**	**Group Assignment**	**Blinding**	**Group Comparability**	**Treatment Integrity**	**Measurement**	**Investigator Bias**	*Quality*	**Participants**	**Intervention and Expertise**	**Compliance and Adherence**	**Analysis**	*Applicability Study*
Wobig (1998)	Evaluator Assessment of Loss of Activities (symptom free)	●	●	○	●	○	●	●	○	**Moderate**	●	○	●	●	**Moderate**
Navarro-Sarabia (2011)	OARSI Responders last follow-up, 40 months	●	◐	○	●	○	●	●	○	**Moderate**	○	○	●	●	**Moderate**
Navarro-Sarabia (2011)	OARSI Responders 7 months	●	◐	○	●	○	●	●	○	**Moderate**	○	○	●	●	**Moderate**
Navarro-Sarabia (2011)	OARSI Responders 14 months	●	◐	○	●	○	●	●	○	**Moderate**	○	○	●	●	**Moderate**
Navarro-Sarabia	OARSI Responders 21 months	●	◐	○	●	○	●	●	○	**Moderate**	○	○	●	●	**Moderate**

●: Domain free of flaws

○: Domain flaws present

◐: Moderate power

Study	*Outcome*	**Prospective**	**Power**	**Group Assignment**	**Blinding**	**Group Comparability**	**Treatment Integrity**	**Measurement**	**Investigator Bias**	*Quality*	**Participants**	**Intervention and Expertise**	**Compliance and Adherence**	**Analysis**	*Applicability Study*
(2011)															
Navarro-Sarabia (2011)	OARSI Responders 27 months	●	◐	○	●	○	●	●	○	**Moderate**	○	○	●	●	**Moderate**
Navarro-Sarabia (2011)	OARSI Responders 34 months	●	◐	○	●	○	●	●	○	**Moderate**	○	○	●	●	**Moderate**
Navarro-Sarabia (2011)	Pain or function reduction 50%	●	◐	○	●	○	●	●	○	**Moderate**	○	○	●	●	**Moderate**
Navarro-Sarabia (2011)	Overall pain reduction 20%	●	◐	○	●	○	●	●	○	**Moderate**	○	○	●	●	**Moderate**

●: Domain free of flaws

○: Domain flaws present

◐: Moderate power

Study	*Outcome*	**Prospective**	**Power**	**Group Assignment**	**Blinding**	**Group Comparability**	**Treatment Integrity**	**Measurement**	**Investigator Bias**	*Quality*	**Participants**	**Intervention and Expertise**	**Compliance and Adherence**	**Analysis**	*Applicability Study*
Navarro-Sarabia (2011)	Function improvement 20%	●	◐	○	●	○	●	●	○	**Moderate**	○	○	●	●	**Moderate**
Navarro-Sarabia (2011)	Patient Global Assessment reduction 20% (10 mm), n (%)	●	◐	○	●	○	●	●	○	**Moderate**	○	○	●	●	**Moderate**
Navarro-Sarabia (2011)	Mean consumption of Paracetamol mg/day	●	◐	○	●	○	●	●	○	**Moderate**	○	○	●	●	**Moderate**
Huang (2011)	VAS Pain on walking Change from W0 to W5	●	●	○	●	●	●	●	●	**High**	○	○	●	●	**Moderate**
Huang (2011)	VAS Pain on walking Change from W0 to W13	●	●	○	●	●	●	●	●	**High**	○	○	●	●	**Moderate**

●: Domain free of flaws

○: Domain flaws present

◐: Moderate power

Study	*Outcome*	**Prospective**	**Power**	**Group Assignment**	**Blinding**	**Group Comparability**	**Treatment Integrity**	**Measurement**	**Investigator Bias**	*Quality*	**Participants**	**Intervention and Expertise**	**Compliance and Adherence**	**Analysis**	*Applicability Study*
Huang (2011)	VAS Pain on walking Change from W0 to W25	●	●	○	●	●	●	●	●	**High**	○	○	●	●	**Moderate**
Huang (2011)	WOMAC Pain	●	●	○	●	●	●	●	●	**High**	○	○	●	●	**Moderate**
Huang (2011)	WOMAC Stiffness	●	●	○	●	●	●	●	●	**High**	○	○	●	●	**Moderate**
Huang (2011)	WOMAC Function	●	●	○	●	●	●	●	●	**High**	○	○	●	●	**Moderate**
Chevalier (2010)	WOMAC Pain	●	●	○	●	○	●	●	○	**Moderate**	○	○	●	●	**Moderate**
Chevalier (2010)	WOMAC Function	●	●	○	●	○	●	●	○	**Moderate**	○	○	●	●	**Moderate**
Chevalier (2010)	OARSI Responders	●	◐	○	●	○	●	●	○	**Moderate**	○	○	●	●	**Moderate**
Chevalier (2010)	Any treatment-emergent target knee AE	●	◐	○	●	○	●	●	○	**Moderate**	○	○	●	●	**Moderate**

●: Domain free of flaws

○: Domain flaws present

◐: Moderate power

Study	*Outcome*	**Prospective**	**Power**	**Group Assignment**	**Blinding**	**Group Comparability**	**Treatment Integrity**	**Measurement**	**Investigator Bias**	*Quality*	**Participants**	**Intervention and Expertise**	**Compliance and Adherence**	**Analysis**	*Applicability Study*
Chevalier (2010)	Any treatment and/or procedure-related target knee AE	●	◐	○	●	○	●	●	○	**Moderate**	○	○	●	●	**Moderate**
Chevalier (2010)	Arthralgia	●	◐	○	●	○	●	●	○	**Moderate**	○	○	●	●	**Moderate**
Chevalier (2010)	Joint effusion	●	◐	○	●	○	●	●	○	**Moderate**	○	○	●	●	**Moderate**
Chevalier (2010)	Arthropathy	●	◐	○	●	○	●	●	○	**Moderate**	○	○	●	●	**Moderate**
Chevalier (2010)	Injection site pain	●	◐	○	●	○	●	●	○	**Moderate**	○	○	●	●	**Moderate**
Chevalier (2010)	Any treatment-related target knee AE	●	◐	○	●	○	●	●	○	**Moderate**	○	○	●	●	**Moderate**
Chevalier (2010)	Any procedure-related target knee AE	●	◐	○	●	○	●	●	○	**Moderate**	○	○	●	●	**Moderate**
Puhl (1993)	Lequesne index week 10	●	◐	●	●	●	●	●	○	**High**	○	○	●	●	**Moderate**

●: Domain free of flaws

○: Domain flaws present

◐: Moderate power

Study	*Outcome*	**Prospective**	**Power**	**Group Assignment**	**Blinding**	**Group Comparability**	**Treatment Integrity**	**Measurement**	**Investigator Bias**	*Quality*	**Participants**	**Intervention and Expertise**	**Compliance and Adherence**	**Analysis**	*Applicability Study*
Puhl (1993)	Lequesne index week 14	●	◐	●	●	●	●	●	○	**High**	○	○	●	●	**Moderate**

Table 178. Quality and Applicability: High Versus Low Molecular Weight Hyaluronic Acid

●: Domain free of flaws
○: Domain flaws present

◐: Moderate power

Study	Outcome	Prospective	Power	Group Assignment	Blinding	Group Comparability	Treatment Integrity	Measurement	Investigator Bias	*Quality*	Participants	Intervention and Expertise	Compliance and Adherence	Analysis	*Applicability* Study
Karlsson (2002)	VAS weight bearing pain	●	●	○	●	○	●	●	○	**Moderate**	○	○	●	○	**Moderate**
Juni (2007)	WOMAC Pain	●	●	●	●	●	●	●	●	**High**	○	○	●	●	**Moderate**
Juni (2007)	WOMAC Pain	●	●	●	●	●	●	●	●	**High**	○	○	●	●	**Moderate**
Berenbaum (2012)	WOMAC Pain	●	●	●	●	○	●	●	○	**Moderate**	○	○	●	●	**Moderate**
Berenbaum (2012)	WOMAC Function	●	●	●	●	○	●	●	○	**Moderate**	○	○	●	●	**Moderate**
Berenbaum (2012)	WOMAC Stiffness	●	●	●	●	○	●	●	○	**Moderate**	○	○	●	●	**Moderate**
Berenbaum (2012)	WOMAC Total	●	●	●	●	○	●	●	○	**Moderate**	○	○	●	●	**Moderate**

Berenbaum (2012)	VAS Pain	●	●	●	●	○	●	●	○	**Moderate**	○	○	●	●	**Moderate**
Berenbaum (2012)	Lequesne index	●	●	●	●	○	●	●	○	**Moderate**	○	○	●	●	**Moderate**
Berenbaum (2012)	ICOAP-total pain	●	◐	●	●	○	●	●	○	**Moderate**	○	○	●	●	**Moderate**
Berenbaum (2012)	ICOAP-constant pain	●	●	●	●	○	●	●	○	**Moderate**	○	○	●	●	**Moderate**
Berenbaum (2012)	ICOAP-Intermittent pain	●	◐	●	●	○	●	●	○	**Moderate**	○	○	●	●	**Moderate**
Juni (2007)	WOMAC Function between groups difference	●	◐	●	●	●	●	●	●	**High**	○	○	●	●	**Moderate**
Juni (2007)	WOMAC Stiffness	●	◐	●	●	●	●	●	●	**High**	○	○	●	●	**Moderate**
Juni (2007)	WOMAC Total	●	◐	●	●	●	●	●	●	**High**	○	○	●	●	**Moderate**
Karlsson (2002)	VAS weight bearing pain week 20	●	●	○	●	○	●	●	○	**Moderate**	○	○	●	○	**Moderate**
Karlsson (2002)	VAS weight bearing pain week 26	●	●	○	●	○	●	●	○	**Moderate**	○	○	●	○	**Moderate**
Karlsson (2002)	Lequesne index week 20	●	◐	○	●	○	●	●	○	**Moderate**	○	○	●	○	**Moderate**
Karlsson (2002)	Lequesne index week 26	●	◐	○	●	○	●	●	○	**Moderate**	○	○	●	○	**Moderate**

Lee (2006)	VAS weight bearing pain	●	●	○	●	○	○	●	○	**Low**	○	○	●	●	**Moderate**
Raman (2008)	WOMAC Pain	●	●	○	●	○	○	●	●	**Moderate**	●	○	●	●	**Moderate**
Raman (2008)	WOMAC Pain	●	●	○	●	○	○	●	●	**Moderate**	●	○	●	●	**Moderate**
Raman (2008)	WOMAC Pain	●	●	○	●	○	○	●	●	**Moderate**	●	○	●	●	**Moderate**
Raman (2008)	WOMAC Pain	●	●	○	●	○	○	●	●	**Moderate**	●	○	●	●	**Moderate**
Wobig (1999)	VAS Pain	●	●	○	●	○	●	●	○	**Moderate**	●	○	●	●	**Moderate**
Wobig (1999)	Evaluator VAS overall condition improvement	●	●	○	●	○	●	●	○	**Moderate**	●	○	●	●	**Moderate**
Wobig (1999)	Patient VAS improvement in most painful knee	●	●	○	●	○	●	●	○	**Moderate**	●	○	●	●	**Moderate**
Maheu (2011)	LFI Score (change Baseline - W24)	●	◐	●	●	●	●	●	○	**High**	○	○	●	●	**Moderate**
Maheu (2011)	Global pain (change Baseline - W24)	●	●	●	●	●	●	●	○	**High**	○	○	●	●	**Moderate**

Maheu (2011)	Investigator's assessment (change Baseline - W24)	●	◐	●	●	●	●	●	○	**High**	○	○	●	●	**Moderate**
Maheu (2011)	SF-12 Physical component (change Baseline - W24)	●	◐	●	●	●	●	●	○	**High**	○	○	●	●	**Moderate**
Maheu (2011)	SF-12 Mental component (change Baseline - W24)	●	◐	●	●	●	●	●	○	**High**	○	○	●	●	**Moderate**
Maheu (2011)	OARSI OMERACT Responders rate at W 12	●	◐	●	●	●	●	●	○	**High**	○	○	●	●	**Moderate**
Maheu (2011)	OARSI OMERACT Responders rate at W24	●	◐	●	●	●	●	●	○	**High**	○	○	●	●	**Moderate**
Maheu (2011)	Rescue medication: Patients who did NOT take Paracetamol during the study period	●	◐	●	●	●	●	●	○	**High**	○	○	●	●	**Moderate**

Maheu (2011)	Rescue medication: Patients who did NOT	●	◐	●	●	●	●	●	○	**High**	○	○	●	●	**Moderate**
Maheu (2011)	Patients with one or more AE	●	◐	●	●	●	●	●	○	**High**	○	○	●	●	**Moderate**
Maheu (2011)	Patients with treatment emergent AE	●	◐	●	●	●	●	●	○	**High**	○	○	●	●	**Moderate**
Maheu (2011)	Patients with serious AE	●	◐	●	●	●	●	●	○	**High**	○	○	●	●	**Moderate**
Pavelka (2011)	WOMAC Pain week 26	●	◐	○	●	●	●	●	○	**Moderate**	○	○	●	●	**Moderate**
Pavelka (2011)	WOMAC Pain week 4	●	◐	○	●	●	●	●	○	**Moderate**	○	○	●	●	**Moderate**
Pavelka (2011)	WOMAC Pain week 12	●	◐	○	●	●	●	●	○	**Moderate**	○	○	●	●	**Moderate**
Pavelka (2011)	WOMAC Function week 26	●	◐	○	●	●	●	●	○	**Moderate**	○	○	●	●	**Moderate**
Pavelka (2011)	WOMAC Stiffness week 26	●	◐	○	●	●	●	●	○	**Moderate**	○	○	●	●	**Moderate**
Pavelka (2011)	WOMAC Total week 26	●	◐	○	●	●	●	●	○	**Moderate**	○	○	●	●	**Moderate**
Pavelka (2011)	Lequesne index week 4	●	◐	○	●	●	●	●	○	**Moderate**	○	○	●	●	**Moderate**
Pavelka (2011)	Lequesne index week 12	●	◐	○	●	●	●	●	○	**Moderate**	○	○	●	●	**Moderate**

Pavelka (2011)	Lequesne index week 26	●	◐	○	●	●	●	●	○	**Moderate**	○	○	●	●	**Moderate**
Pavelka (2011)	Percent using Rescue medication 4 weeks	●	◐	○	●	●	●	●	○	**Moderate**	○	○	●	●	**Moderate**
Pavelka (2011)	Percent using Rescue medication 4 to 12 weeks	●	◐	○	●	●	●	●	○	**Moderate**	○	○	●	●	**Moderate**
Pavelka (2011)	Percent using Rescue medication 12-26 weeks	●	◐	○	●	●	●	●	○	**Moderate**	○	○	●	●	**Moderate**
Pavelka (2011)	Percent using Rescue medication baseline to 26 weeks	●	◐	○	●	●	●	●	○	**Moderate**	○	○	●	●	**Moderate**

FINDINGS

Table 179. Hyaluronic Acid Versus Control: Pain

Study	Outcome	N	Powered	Week	Severity	# Of Injections	Weight	Group 1	Group 2	SMD (Odds Ratio or Raw Mean Difference When Indicated)	Sig	Clinical Importan
Huang (2011)	VAS Pain	198	Yes	5	K-L 2-3	5	500-730kda	Hyalgan	Placebo	-0.31 (-0.59, -0.03)	Favors HA	Not clinically significan
Huang (2011)	VAS Pain	198	Yes	13	K-L 2-3	5	500-730kda	Hyalgan	Placebo	-0.20 (-0.48, 0.08)	No	True negative
Huang (2011)	VAS Pain	198	Yes	25	K-L 2-3	5	500-730kda	Hyalgan	Placebo	-0.47 (-0.75, -0.19)	Favors HA	Not clinically significan
Huang (2011)	WOMAC Pain	198	Yes	25	K-L 2-3	5	500-730kda	Hyalgan	Placebo	-0.40 (-0.68, -0.12)	Favors HA	Possibly clinically importan
Karlsson (2002)	VAS weight bearing pain	133	Yes	12	Ahlback 1-2	3	10^6 Da	HA (Artzal)	Placebo	-.10(-.44, .24)	No	N/A
Karlsson (2002)	VAS weight bearing pain	133	Yes	20	Ahlback 1-2	3	10^6 Da	HA (Artzal)	Placebo	-.27(-.62, .07)	No	N/A

Study	Outcome	N	Powered	Week	Severity	# Of Injections	Weight	Group 1	Group 2	SMD (Odds Ratio or Raw Mean Difference When Indicated)	Sig	Clinical Importan
Karlsson (2002)	VAS weight bearing pain	133	Yes	26	Ahlback 1-2	3	10^6 Da	HA (Artzal)	Placebo	.03(-.31, .37)	No	N/A
Day (2004)	WOMAC Pain	116	Yes	18	NR	5	6.2-11.7 x 10^5 Da	HA	Placebo	-.24(-.49, .01)	No	True negative
Heybeli (2008)	WOMAC Pain	67	Yes	26	K-L 2-3	3	1-2.9 million Da	HA	Placebo	-0.20 (-0.68, 0.28)	No	Inconclusi
Altman (2009)	Change in 50 foot walk pain score	586	Yes	26	K-L 2-3	3	2.4-3.6 Million Daltons	HA	Placebo	-0.23 (-0.40, -0.07)	Favors HA	Not clinically significan
Altman (2009)	WOMAC Pain	586	Yes	26	K-L 2-3	3	2.4-3.6 Million Daltons	HA	Placebo	-0.11 (-0.27, 0.05)	No	True negative

Study	Outcome	N	Powered	Week	Severity	# Of Injections	Weight	Group 1	Group 2	SMD (Odds Ratio or Raw Mean Difference When Indicated)	Sig	Clinical Importan
Wobig (1998)	Patient VAS Assessment of Weight bearing pain-number symptom free	117	yes	12	Larsen Grade 1-4	3	6 million Daltons	Hylan G-F 20	Placebo	OR=9.69(3.763 24.960)	Favors HA	N/A
Wobig (1998)	Patient VAS Assessment of night pain-number symptom free	117	yes	12	Larsen Grade 1-4	3	6 million Daltons	Hylan G-F 20	Placebo	OR=4.11 (1.76, 9.63)	Favors HA	N/A

Study	Outcome	N	Powered	Week	Severity	# Of Injections	Weight	Group 1	Group 2	SMD (Odds Ratio or Raw Mean Difference When Indicated)	Sig	Clinical Importan
Wobig (1998)	Patient VAS assessment of pain during most painful knee movement-number symptom free	117	Yes	12	Larsen Grade 1-4	3	6 million Daltons	Hylan G-F 20	Placebo	OR=9.61(3.86, 23.95)	Favors HA	N/A
Wobig (1998)	Evaluator VAS Assessment of Weight bearing pain-number symptom free	117	Yes	12	Larsen Grade 1-4	3	6 million Daltons	Hylan G-F 20	Placebo	OR=9.90(3.45, 28.37)	Favors HA	N/A

Study	Outcome	N	Powered	Week	Severity	# Of Injections	Weight	Group 1	Group 2	SMD (Odds Ratio or Raw Mean Difference When Indicated)	Sig	Clinical Importan
Wobig (1998)	Evaluator VAS assessment of night pain-number symptom free	117	Yes	12	Larsen Grade 1-4	3	6 million Daltons	Hylan G-F 20	Placebo	OR=4.74(2.12, 10.59)	Favors HA	N/A
Wobig (1998)	Evaluator assessment of weight bearing pain	117	Yes	26	Larsen Grade 1-4	3	6 million Daltons	Hylan G-F 20	Placebo	OR=4.09(1.64, 10.21)	Favors HA	N/A
Wobig (1998)	Evaluator assessment of VAS night pain-number symptom free	117	Yes	26	Larsen Grade 1-4	3	6 million Daltons	Hylan G-F 20	Placebo	OR=2.88(1.34, 6.16)	Favors HA	N/A
Chevalier (2010)	WOMAC Pain	253	Yes	26	NR	NR	6 million Da	Hylan G-F 20	Placebo	-.225(-.473, .022)	No	Inconclusi

Study	Outcome	N	Powered	Week	Severity	# Of Injections	Weight	Group 1	Group 2	SMD (Odds Ratio or Raw Mean Difference When Indicated)	Sig	Clinical Importan
Kahan (2003)	WOMAC Pain	497	Yes	36	K-L 1-4	3	6 million Da	Hylan G-F 20	Usual care	-.60(-.77, -.42)	Favors HA	Clinicall significan
Karlsson (2002)	VAS weight bearing pain	134	Yes	12	Ahlback 1-2	3	7 million Da	Hylan G-F 20	Placebo	-.10(-.45, .24)	No	N/A
Karlsson (2002)	VAS weight bearing pain	134	Yes	20	Ahlback 1-2	3	7 million Da	HA (synvisc)	Placebo	-.07(-.42, .27)	No	N/A
Karlsson (2002)	VAS weight bearing pain	134	Yes	26	Ahlback 1-2	3	7 million Da	HA (synvisc)	Placebo	.016(-.018, .50)	No	N/A
Lundsgaard (2008)	KOOS Pain	162	Unclear	26	K-L 1-4	4	NR	HA	Placebo	.01(-.29, .31)	No	N/A
Petrella (2006)	Change in VAS Walking Pain	106	Unclear	6	NR	6	NR	HA	Placebo	0.00 (-0.38, 0.38)	No	N/A

Study	Outcome	N	Powered	Week	Severity	# Of Injections	Weight	Group 1	Group 2	SMD (Odds Ratio or Raw Mean Difference When Indicated)	Sig	Clinical Importan
Petrella (2006)	Change in VAS Walking Pain	106	Yes	12	NR	6	NR	HA	Placebo	-0.07 (-0.31, 0.45)	No	N/A
Petrella (2006)	Change in VAS stepping Pain	106	Yes	6	NR	6	NR	HA	Placebo	0.04 (-0.42, 0.34)	No	N/A
Petrella (2006)	Change in VAS stepping Pain	106	Yes	12	NR	6	NR	HA	Placebo	-0.06 (-0.32, 0.45)	No	N/A
Lundsgaard (2008)	VAS Pain at movement	162	Yes	26	K-L 1-4	4	NR	HA	Placebo	.06(-.24, .36)	No	N/A
Lundsgaard (2008)	VAS Pain at rest	162	Yes	26	K-L 1-4	4	NR	HA	Placebo	-.02(-.33, .28)	No	N/A
Lundsgaard (2008)	VAS Pain at night	162	Yes	26	K-L 1-4	4	NR	HA	Placebo	-.08(-.39, .22)	No	N/A
Petrella (2006)	WOMAC Pain	106	Yes	6	NR	6	NR	HA	Placebo	.01(-.37, .39)	No	Negative
Altman (2004)	WOMAC Pain	346	Yes	6	NR	NR	NR	HA	Placebo	0.06 (-0.15, 0.27)	No	True negative

Study	Outcome	N	Powered	Week	Severity	# Of Injections	Weight	Group 1	Group 2	SMD (Odds Ratio or Raw Mean Difference When Indicated)	Sig	Clinical Importan
Altman (2004)	WOMAC Pain	346	Yes	13	NR	NR	NR	HA	Placebo	0.14 (-0.08, 0.35)	No	True negative
Altman (2004)	WOMAC Pain	346	Yes	26	NR	NR	NR	HA	Placebo	0.10 (-0.12, 0.31)	No	True negative
Jorgensen (2010)	VAS Pain difference between groups	298	Yes	13	NR	5	NR	Sodium Hyaluronate	Placebo	Raw mean difference= 0.07(-.33, .46)	No	N/A
Jorgensen (2010)	VAS Pain difference between groups	298	Unclear	26	NR	5	NR	Sodium Hyaluronate	Placebo	Raw mean difference= 0.05(-.47, .58)	No	N/A
Jorgensen (2010)	VAS Pain difference between groups	298	Unclear	52	NR	5	NR	Sodium Hyaluronate	Placebo	Raw mean difference= 0.22(-.71, 1.14)	No	N/A

Table 180. High Versus Low Molecular Weight: Pain

Study	Outcome	N	Powered	Week	Severity	# Of Injections	Group 1	Group 2	SMD (Odds Ratio or Raw Mean Difference When Indicated)	Sig	Clinical Importance	Strength of Evidence
Karlsson (2002)	VAS weight bearing pain	153	Yes	12	Ahlback 1-2	3	High Molecular Weight HA ($7x10^6$ Da)	Low Molecular Weight HA (10^6 Da)	.00(-.32, .32)	No	True negative	Moderate
Karlsson (2002)	VAS weight bearing pain	153	Yes	20	Ahlback 1-2	3	High Molecular Weight HA ($7x10^6$ Da)	Low Molecular Weight HA (10^6 Da)	-.22(-.53, .10)	No	True negative	Moderate

Study	Outcome	N	Powered	Week	Severity	# Of Injections	Group 1	Group 2	SMD (Odds Ratio or Raw Mean Difference When Indicated)	Sig	Clinical Importance	Strength of Evidence
Karlsson (2002)	VAS weight bearing pain	153	Yes	26	Ahlback 1-2	3	High Molecular Weight HA ($7x10^6$ Da)	Low Molecular Weight HA (10^6 Da)	-.13(-.45, .19)	No	True negative	Moderate
Juni (2007)	WOMAC Pain	657	Yes	12	K-L 2+	3	High Molecular Weight HA (6 million Da)	Medium or Low Molecular Weight HA	Mean Difference= .1(-.3, .4)	No	N/A	High

Study	Outcome	N	Powered	Week	Severity	# Of Injections	Group 1	Group 2	SMD (Odds Ratio or Raw Mean Difference When Indicated)	Sig	Clinical Importance	Strength of Evidence
Juni (2007)	WOMAC Pain	657	Yes	26	K-L 2+	3	High Molecular Weight HA (6 million Da)	Medium or Low Molecular Weight HA	Mean Difference= .0 (-.3.,2)	No	N/A	High
Berenbaum (2012)	VAS Pain	426	Yes	26	K-L 2-3	3	Medium MW HA (800-1500kDa)	Low MW HA (500-700 kDa)	-.26(-.45, -.07)	Favors MMW	Not clinically important	Moderate
Berenbaum (2012)	ICOAP-total pain	426	Unclear	26	K-L 2-3	3	Medium MW HA (800-1500kDa)	Low MW HA (500-700 kDa)	-0.15 (-0.34, 0.04)	No	Unclear	Moderate

Study	Outcome	N	Powered	Week	Severity	# Of Injections	Group 1	Group 2	SMD (Odds Ratio or Raw Mean Difference When Indicated)	Sig	Clinical Importance	Strength of Evidence
Berenbaum (2012)	ICOAP – constant pain	426	Yes	26	K-L 2-3	3	Medium MW HA (800-1500kDa)	Low MW HA (500-700 kDa)	-0.20 (-0.39, -0.01)	Favors MMW	Unclear	Moderate
Berenbaum (2012)	ICOAP – intermittent pain	426	Unclear	26	K-L 2-3	3	Medium MW HA (800-1500kDa)	Low MW HA (500-700 kDa)	-0.09 (-0.28, 0.10)	No	Unclear	Moderate
Berenbaum (2012)	Pain MCII	426	Yes	26	K-L 2-3	3	Medium MW HA (800-1500kDa)	Low MW HA (500-700 kDa)	OR= 1.70 (1.14, 2.55)	Favors MMW	Unclear	Moderate
Lee (2006)	VAS weight bearing pain	78	Yes	12	K-L 1-3	5	High Molecular weight (3000 kDa)	Low molecular weight (750kD)	-.22(-.70, .26)	No	Not clinically important	Low

Study	Outcome	N	Powered	Week	Severity	# Of Injections	Group 1	Group 2	SMD (Odds Ratio or Raw Mean Difference When Indicated)	Sig	Clinical Importance	Strength of Evidence
Raman (2008)	WOMAC Pain	392	Yes	6	60% with K-L 3	3	Hylan G-F 20 (6 million Daltons)	Sodium Hyaluronate (.5 to .73 million Daltons)	Raw score mean difference = 1.8 (p>.05)	No	N/A	Moderate
Raman (2008)	WOMAC Pain	392	Yes	13	60% with K-L 3	3	Hylan G-F 20 (6 million Daltons)	Sodium Hyaluronate (.5 to .73 million Daltons)	Mean difference =-2.1 (.33, 3.87)	Favors High Molecular Weight (HMW)	Possibly clinically significant	Moderate
Raman (2008)	WOMAC Pain	392	Yes	26	60% with K-L 3	3	Hylan G-F 20 (6 million Daltons)	Sodium Hyaluronate (.5 to .73 million Daltons)	Mean difference =-3.2(.77,5.63)	Favors HMW	Possibly clinically significant	Moderate

Study	Outcome	N	Powered	Week	Severity	# Of Injections	Group 1	Group 2	SMD (Odds Ratio or Raw Mean Difference When Indicated)	Sig	Clinical Importance	Strength of Evidence
Raman (2008)	WOMAC Pain	392	Yes	52	60% with K-L 3	3	Hylan G-F 20 (6 million Daltons)	Sodium Hyaluronate (.5 to .73 million Daltons)	Mean difference =-2.7 (.75,4.65)	Favors HMW	Possibly clinically significant	Moderate
Wobig (1999)	VAS Pain	73	Yes	12	Larsen Grade 1-4	3	Hylan G-F 20 (6 million Daltons)	Low MW Hyaluronic Acid (.75 – million)	Mean difference =16 (p<.05)	Favors HMW	N/A	Moderate
Wobig (1999)	Evaluator VAS overall condition improvement	73	Yes	12	Larsen Grade 1-4	3	Hylan G-F 20 (6 million Daltons)	Low MW Hyaluronic Acid (.75 – million)	Mean difference =14 (p<.05)	Favors HMW	N/A	Moderate

Study	Outcome	N	Powered	Week	Severity	# Of Injections	Group 1	Group 2	SMD (Odds Ratio or Raw Mean Difference When Indicated)	Sig	Clinical Importance	Strength of Evidence
Wobig (1999)	Patient VAS improvement in most painful knee	73	Yes	12	Larsen Grade 1-4	3	Hylan G-F 20 (6 million Daltons)	Low MW Hyaluronic Acid (.75 – million)	Mean difference =16 (p<.05)	Favors HMW	N/A	Moderate
Maheu (2011)	Global pain (change Baseline - W24)	236	yes	24	K-L 2-3	3	Structovial (2.2-2.7 mda)	synsivic (6 million daltons)	SMD=0.07 (-0.19, 0.32)	no	true negative	
Pavelka (2011)	WOMAC pain	380	unclear	26	K-L 2-3	3	synvisc (6 million da)	Sinovial (800kda-1200kda)	mean difference = 0.0 (95% CI -4.7 to 4.8)	no	true negative	

Study	Outcome	N	Powered	Week	Severity	# Of Injections	Group 1	Group 2	SMD (Odds Ratio or Raw Mean Difference When Indicated)	Sig	Clinical Importance	Strength of Evidence
Pavelka (2011)	WOMAC pain	380	unclear	4	K-L 2-3	3	synvisc (6 million da)	Sinovial (800kda-1200kda)	mean difference = 1.3 (95%CI -2.6 to 5.3)	no	true negative	
Pavelka (2011)	WOMAC pain	380	unclear	12	K-L 2-3	3	synvisc (6 million da)	Sinovial (800kda-1200kda)	mean difference = 1.6(-2.8 to 6.0)	no	true negative	

Table 181. Hyaluronic Acid Versus Control: Function

Study	Outcome	N	Powered	Week	Severity	# Of Injections	Weight	Group 1	Group 2	SMD (Odds Ratio or Raw Mean Difference When Indicated)	Sig	Clinical Importance	Strength of evidence
Huang (2011)	WOMAC Function	198	Yes	25	K-L 2-3	5	500-730kda	Hyalgan	Placebo	-0.41 (-0.70, -0.13)	Favors HA	Possibly clinically important	High
Day (2004)	WOMAC Function	240	Yes	18	NR	5	6.2-11.7 x 10^5 Da	Sodium HA	Placebo	-.22(-.48, .03)	No	Inconclusive	Moderate
Heybeli (2008)	WOMAC Function	67	Yes	26	K-L 2-3	3	1-2.9 million Da	HA	Placebo	-0.28 (-0.76, 0.20)	No	Inconclusive	Moderate
Altman (2009)	SF-36 physical Function	586	Yes	26	K-L 2-3	3	2.4-3.6 Million Da	HA	Placebo	.17(.07, .33)	Favors HA	Possibly clinically important	Moderate

Study	Outcome	N	Powered	Week	Severity	# Of Injections	Weight	Group 1	Group 2	SMD (Odds Ratio or Raw Mean Difference When Indicated)	Sig	Clinical Importance	Strength of evidence
Altman (2009)	WOMAC Function	586	Yes	26	K-L 2-3	3	2.4-3.6 Million Da	HA	Placebo	-.19(-.36, -.03)	Favors HA	Possibly Clinically significant	Moderate
Chevalier (2010)	WOMAC Function	253	Yes	26	NR	NR	6 million Da	HylanG-F 20	Placebo	-.044 (-.291, .202)	No	Inconclusive	Moderate
Wobig (1998)	Evaluator Assessment of Loss of Activities (symptom free)	117	Yes	12	Larsen Grade 1-4	3	6 million Da	HA	Placebo	OR=7.39 (3.13, 17.48)	Favors HA	N/A	Moderate

Study	Outcome	N	Powered	Week	Severity	# Of Injections	Weight	Group 1	Group 2	SMD (Odds Ratio or Raw Mean Difference When Indicated)	Sig	Clinical Importance	Strength of evidence
Wobig (1998)	Evaluator Assessment of Loss of Activities (symptom free)	117	Yes	26	Larsen Grade 1-4	3	6 million Da	HA	Placebo	OR=4.07(1.86, 8.86)	Favors HA	N/A	Moderate
Kahan (2003)	WOMAC Function	506	Yes	36	K-L 1-4	3	6 million Da	HA	Conventional Treatment	-.57(-.75, -.39)	Favors HA	Clinically significant	Moderate
Altman (2004)	WOMAC Function	346	Yes	6	NR	NR	NR	HA injection	Placebo	0.08 (-0.13, 0.29)	No	True negative	Moderate
Altman (2004)	WOMAC Function	346	Yes	13	NR	NR	NR	HA injection	Placebo	0.14 (-0.07, 0.35)	No	True negative	Moderate
Altman (2004)	WOMAC Function	346	Yes	26	NR	NR	NR	HA injection	Placebo	0.12 (-0.09, 0.34)	No	True negative	Moderate

Study	Outcome	N	Powered	Week	Severity	# Of Injections	Weight	Group 1	Group 2	SMD (Odds Ratio or Raw Mean Difference When Indicated)	Sig	Clinical Importance	Strength of evidence
Lundsgaard (2008)	KOOS Activities	167	Unclear	26	K-L 1-4	4	NR	HA injection	Placebo	-.01(-.31,.29)	No	N/A	High
Lundsgaard (2008)	KOOS Sports	167	Unclear	26	K-L 1-4	4	NR	HA injection	Placebo	.11(-.20, .41)	No	N/A	High
Petrella (2006)	SF-36 Physical Function	106	Yes	6	NR	6	NR	HA injection	Placebo	0.08 (-0.30, 0.46)	No	Inconclusive	Moderate
Petrella (2006)	SF-36 Physical	106	Yes	12	NR	6	NR	HA injection	Placebo	0.65 (0.26, 1.04)	Favors HA injections	Clinically important	Moderate
Petrella (2006)	WOMAC Function	106	No	12	NR	6	NR	HA injection	Placebo	.02(-.36, .40)	No	Inconclusive	Moderate

Table 182. High Versus Low Molecular Weight: WOMAC Function

Outcome	N	Power	Week	Severity	# Of Injections	Group 1	Group 2	SMD (Odds Ratio or Raw Mean Difference When Indicated)	Sig	Clinical Importance	Strength of Evidence
Juni (2007)	657	Unclear	26	K-L 2+	3	High Molecular Weight HA (6 million Da)	Medium or Low Molecular Weight HA	Mean Difference =.1(-.2, .4)	No	True negative	High
Berenbaum (2012)	426	Yes	26	K-L 2-3	3	Medium MW HA (800-1500kDa)	Low MW HA (500-700 kDa)	-.32 (-.52, -.13)	Favors MMW	Possibly clinically significant	Moderate
Maheu (2011)	236	unclear	24	K-L 2-3	3	Structovial (2.2-2.7 mda)	synsivic (6 million daltons)	SMD=0.17 (-0.09, 0.42)	no	n/a	high
Maheu (2011)	236	unclear	24	K-L 2-3	3	Structovial (2.2-2.7 mda)	synsivic (6 million daltons)	SMD=-0.02 (-0.28, 0.23)	no	n/a	high
Pavelka (2011)	380	unclear	26	K-L 2-3	3	synvisc (6 million da)	Sinovial (800kda-1200kda)	mean difference = 0.2 p>.05	no	n/a	moderate

Table 183. Hyaluronic Acid Versus Control: WOMAC Stiffness

Study	Outcome	N	Power	Week	Severity	# Of Injections	Weight	Group 1	Group 2	SMD (Odds Ratio or Raw Mean Difference When Indicated)	Sig	Clinical Importance	Strength of Evidence
Altman (2004)	WOMAC Stiffness	346	yes	6	NR	NR	NR	HA injections	Placebo	0.09 (-0.12, 0.30)	No	True negative	Moderate
Altman (2004)	WOMAC Stiffness	346	yes	13	NR	NR	NR	HA injections	Placebo	0.18 (-0.03, 0.39)	No	True negative	Moderate
Altman (2004)	WOMAC Stiffness	346	yes	26	NR	NR	NR	HA injections	Placebo	0.19 (-0.02, 0.40)	No	True negative	Moderate
Huang (2011)	WOMAC Stiffness	198	yes	25	K-L 2-3	5	500-730kda	Hyalgan	Placebo	-0.10 (-0.38, 0.18)	No	True negative	High
Altman (2009)	WOMAC Stiffness	586	Yes	26	K-L 2-3	3	2.4-3.6 Million Daltons	HA injections	Placebo	-.14(-.30, .02)	No	negative	Moderate
Day (2004)	WOMAC Stiffness	240	Yes	18	NR	5	6.2-11.7 x 10^5 Da	HA injections	Placebo	-.24(-.5, .01)	No	Inconclusive	Moderate
Kahan	WOMAC	498	Yes	36	K-L	3	6	HA	Usual	-.5(-.68,	Favors	Possibly	Moderate

Study	Outcome	N	Power	Week	Severity	# Of Injections	Weight	Group 1	Group 2	SMD (Odds Ratio or Raw Mean Difference When Indicated)	Sig	Clinical Importance	Strength of Evidence
(2003)	Stiffness				1-4		million Da	Injections	care	-.32)	HA	clinically significant	
Petrella (2006)	WOMAC Stiffness	106	No	6	NR	6	NR	HA injections	Placebo	-.22(-.6, .16)	No	Inconclusive	Moderate

Table 184. High Versus Low Molecular Weight: WOMAC Stiffness

Study	Outcome	N	Power to Detect MCII	Week	Group 1	Group 2	Severity	# Of Injections	SMD (Odds Ratio or Raw Mean Difference When Indicated)	Sig	Clinical Importance	Strength of Evidence
Juni (2009)	WOMAC Stiffness	657	Unclear	26	High Molecular Weight HA (6 million Da)	Medium or Low Molecular Weight HA	K-L 2+	3	Mean Difference= .1(-.3, .4)	No	True negative	High
Berenbaum (2012)	WOMAC Stiffness	426	Yes	26	Medium MW HA (800-1500kDa)	Low MW HA (500-700 kDa)	K-L 2-3	3	-.22 (-.41, -.02)	Favors MMW	Possibly clinically significant	Moderate
Pavelka (2011)	WOMAC stiffness	380	unclear	26	synvisc (6 million da)	Sinovial (800kda-1200kda)	K-L 2-3	3	mean difference = -0.1 p>.05	no	n/a	moderate

Table 185. Hyaluronic Acid Versus Conventional Treatment: WOMAC Total (Kahan et al., 2003)

Outcome	N	Sufficient Power	Week	Severity	# Of Injections	Weight	Group 1	Group 2	SMD (Odds Ratio or Raw Mean Difference When Indicated)	Sig	Clinical Importance	Strength of Evidence
WOMAC Total	495	Yes	36	K-L 1-4	3	6 million Da	Hyaluronic Acid (HA) injection	Conventional Treatment	-.6(-.78, -.42)	Favors HA	Clinically important	Moderate

Table 186. High Versus Low Molecular Weight: WOMAC Total (Juni et al., 2007)

Study	N	Power	Week	Severity	# Of Injections	Group 1	Group 2	SMD (Odds Ratio or Raw Mean Difference When Indicated)	Sig	Clinical Importance	Strength of Evidence
Juni (2007)	657	Unclear	26	K-L 2+	3	High Molecular Weight HA (6 million Da)	Medium or Low Molecular Weight HA	Mean difference= .1(-.2, .4)	No	True negative	High
Berenbaum (2012)	426	Yes	26	K-L 2-3	3	Medium MW HA (800-1500kDa)	Low MW HA (500-700 kDa)	-.31 (-.5, -.11)	Favors MMW	Possibly clinically significant	Moderate
Pavelka (2011)	380	unclear	26	K-L 2-3	3	Synvisc (6 million da)	Sinovial (800kda-1200kda)	mean difference = 0 p>.05	no	n/a	Moderate

Table 187. Hyaluronic Acid Versus Control: Lequesne Index

Study	N	Power	Week	Severity	# Of Injections	Weight	Group 1	Group 2	SMD (Odds Ratio or Raw Mean Difference When Indicated)	Sig	Clinical Importance	Strength of Evidence
Puhl (1993)	195	Yes	10	NR	NR	NR	25mg/2.5 ml Sodium Hyaluronate	.25mg/2.5 ml Sodium Hyaluronate	Mean difference=.9 (p=.0088)	Favors 25mg Sodium HA	N/A	High
Puhl (1993)	195	Yes	14	NR	NR	NR	25mg/2.5 ml Sodium Hyaluronate	.25mg/2.5 ml Sodium Hyaluronate	mean difference=1.6 (p=.0053)	Favors 25mg Sodium HA	N/A	High
Kahan (2003)	506	Yes	36	K-L 1-4	3	6 million Da	HA injection	Conventional treatment	-.49(-.67,-.32)	No	N/A	Moderate
Karlsson (2002)	134	Unclear	20	Ahlback 1-2	3	7 million Da	HA injection	Placebo	.22(-.12, .57)	No	N/A	Moderate
Karlsson (2002)	133	Unclear	20	Ahlback 1-2	3	10^6 Da	HA injection	Placebo	.05(-.29, .39)	No	N/A	Moderate

Study	N	Power	Week	Severity	# Of Injections	Weight	Group 1	Group 2	SMD (Odds Ratio or Raw Mean Difference When Indicated)	Sig	Clinical Importance	Strength of Evidence
Karlsson (2002)	134	Unclear	26	Ahlback 1-2	3	7 million Da	HA injection	Placebo	.18(-.17, .52)	No	N/A	Moderate
Karlsson (2002)	133	Unclear	26	Ahlback 1-2	3	10^6 Da	HA injection	Placebo	.07(-.27, .41)	No	N/A	Moderate
Jorgensen (2010)	298	Unclear	13	NR	5	NR	HA injection	Placebo	Raw mean difference= 0.16(-.45, .78)	No	N/A	Moderate
Jorgensen (2010)	298	Unclear	26	NR	5	NR	HA injection	Placebo	Raw mean difference= 0.44(-.42, 1.3)	No	N/A	Moderate
Jorgensen (2010)	298	Unclear	52	NR	5	NR	HA injection	Placebo	Raw mean difference= 0.81 (-.75, 2.37)	No	N/A	Moderate
Lohmander (1996)	189	Yes	20	Ahlback 1-2	5	1000 kDa	HA injection	Placebo	Mean difference= 1.6 ($p<.05$)	Favors HA	N/A	Moderate

Table 188. High Versus Low Molecular Weight: Other Outcomes

Study	Outcome	N	Sufficient Power	Week	Severity	# Of Injections	Group 1	Group 2	SMD (Odds Ratio or Raw Mean Difference When Indicated)	Sig	Clinical Importance	Strength of Evidence
Karlsson (2002)	Lequesne Index	153	Unclear	20	Ahlback 1-2	3	High Molecular Weight HA	Low Molecular Weight HA (10^6 Da)	.05 (-.29, .39)	No	N/A	Moderate
Karlsson (2002)	Lequesne Index	153	Unclear	26	Ahlback 1-2	3	High Molecular Weight HA	Low Molecular Weight HA (10^6 Da)	.07 (-.27, .41)	No	N/A	Moderate
Berenbaum (2012)	Lequesne Index	426	Yes	26	K-L 2-3	3	Medium MW HA (800-1500kDa)	Low MW HA (500-700 kDa)	-.34 (-.53, -.15)	Favors MMW	Unclear	Moderate
Maheu (2011)	Lequesne index	236	unclear	24	K-L 2-3	3	Structovial (2.2-2.7 mda)	synsivic (6 million daltons)	SMD=0.04 (-0.21 ,0.3)	no	n/a	high

Study	Outcome	N	Sufficient Power	Week	Severity	# Of Injections	Group 1	Group 2	SMD (Odds Ratio or Raw Mean Difference When Indicated)	Sig	Clinical Importance	Strength of Evidence
Maheu (2011)	Investigator's assessment (change Baseline - W24)	236	unclear	24	K-L 2-3	3	Structovial (2.2-2.7 mda)	synsivic (6 million daltons)	SMD=0 (-0.26, 0.25)	no	n/a	high
Maheu (2011)	OARSI OMERACT Responder	236	unclear	12	K-L 2-3	3	Structovial (2.2-2.7 mda)	synsivic (6 million daltons)	OR=1.19 (0.7 ,2.01)	no	n/a	high
Maheu (2011)	OARSI OMERACT Responder	236	unclear	24	K-L 2-3	3	Structovial (2.2-2.7 mda)	synsivic (6 million daltons)	OR=0.88 (0.51 ,1.51)	no	n/a	high
Maheu (2011)	Rescue medication : Patients who did NOT take Paracetamol during the study period	236	unclear	24	K-L 2-3	3	Structovial (2.2-2.7 mda)	synsivic (6 million daltons)	OR=1.24 (0.68 ,2.27)	no	n/a	high

Study	Outcome	N	Sufficient Power	Week	Severity	# Of Injections	Group 1	Group 2	SMD (Odds Ratio or Raw Mean Difference When Indicated)	Sig	Clinical Importance	Strength of Evidence
Maheu (2011)	Rescue medication : Patients who did NOT take Paracetamol during the study period	236	unclear	24	K-L 2-3	3	Structovial (2.2-2.7 mda)	synsivic (6 million daltons)	OR=0.91 (0.52 ,1.58)	no	n/a	high
Pavelka (2011)	Lequesne index	380	unclear	4	K-L 2-3	3	synvisc (6 million da)	Sinovial (800kda-1200kda)	mean difference = -0.2 P>.05	no	n/a	moderate
Pavelka (2011)	Lequesne index	380	unclear	12	K-L 2-3	3	synvisc (6 million da)	Sinovial (800kda-1200kda)	mean difference = -0.5 p=.049	synvisc (6 million da)	n/a	moderate
Pavelka (2011)	Lequesne index	380	unclear	26	K-L 2-3	3	synvisc (6 million da)	Sinovial (800kda-1200kda)	mean difference = -0.3 p>.05	no	n/a	moderate

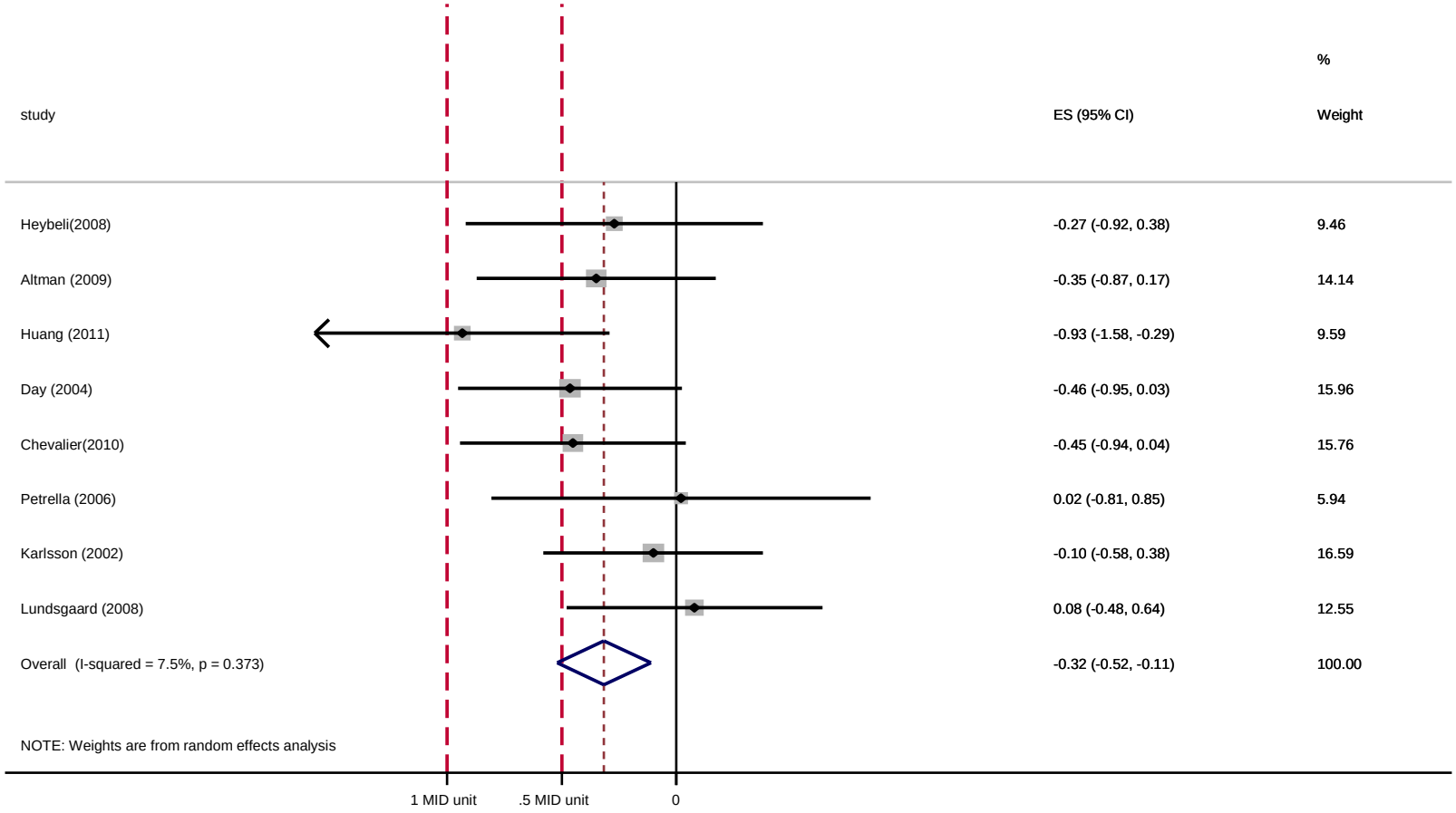
Study	Outcome	N	Sufficient Power	Week	Severity	# Of Injections	Group 1	Group 2	SMD (Odds Ratio or Raw Mean Difference When Indicated)	Sig	Clinical Importance	Strength of Evidence
Pavelka (2011)	percent using rescue medication	380	unclear	4 weeks	K-L 2-3	3	synvisc (6 million da)	Sinovial (800kda-1200kda)	OR=0.74 (0.49 ,1.12)	no	n/a	moderate
Pavelka (2011)	percent using rescue medication	380	unclear	4 to 12 weeks	K-L 2-3	3	synvisc (6 million da)	Sinovial (800kda-1200kda)	OR=0.77 (0.52 ,1.16)	no	n/a	moderate
Pavelka (2011)	percent using rescue medication	380	unclear	12-26 weeks	K-L 2-3	3	synvisc (6 million da)	Sinovial (800kda-1200kda)	OR=0.77 (0.52 ,1.16)	no	n/a	moderate
Pavelka (2011)	percent using rescue medication	380	unclear	baseline to 26 weeks	K-L 2-3	3	synvisc (6 million da)	Sinovial (800kda-1200kda)	OR=0.64 (0.41 ,1.01)	no	n/a	moderate

Table 189. High Versus Low Molecular Weight Hyaluronic Acid: Adverse Events

Study	Outcome	N	Power	Week	Severity	# Of Injections	Group 1	Group 2	Odds Ratio	Sig	Clinical Importance	Strength of Evidence
Juni (2007)	Local adverse event	660	Unclear	26	K-L 2+	3	High Molecular Weight HA (6 million Da)	Medium or Low MW HA	1.33 (0.75, 2.36)	No	N/A	High
Karlsson (2001)	Adverse events	176	Unclear	26	Ahlback 1-2	3	High Molecular Weight HA (7x10^6 Da)	Low Molecular Weight HA(10^6 Da)	1.50 (0.82, 2.73)	No	N/A	Moderate
Lee (2006)	Adverse events	145	Unclear	12	K-L 1-3	5	High Molecular weight (3000 kDa)	Low molecular weight (750kD)	0.83 (0.42, 1.66)	No	N/A	Low
Maheu (2011)	Patients with one or more AE	279	Unclear	24	K-L 2-3	3	Structovial (2.2-2.7 mda)	Synsivic (6 million daltons)	0.88 (0.43, 1.81)	No	N/A	High
Maheu (2011)	Patients with treatment emergent AE	279	Unclear	24	K-L 2-3	3	Structovial (2.2-2.7 mda)	Synsivic (6 million daltons)	1.11 (0.69, 1.79)	No	N/A	High

Study	Outcome	N	Power	Week	Severity	# Of Injections	Group 1	Group 2	Odds Ratio	Sig	Clinical Importance	Strength of Evidence
Maheu (2011)	Patients with serious AE	279	Unclear	24	K-L 2-3	3	Structovial (2.2-2.7 mda)	Synsivic (6 million daltons)	5.11 (0.59, 44.32)	No	N/A	High
Pavelka (2011)	Patients with treatment related adverse events	381	Unclear	26	K-L 2-3	3	Synvisc (6 million da)	Sinovial (800kda-1200kda)	4.13 (0.46, 37.29)	No	N/A	Moderate
Pavelka (2011)	Patients with severe adverse events	381	Unclear	26	K-L 2-3	3	Synvisc (6 million da)	Sinovial (800kda-1200kda)	6.26 (0.75, 52.52)	No	N/A	Moderate
Raman (2008)	Treatment related adverse events	392	Unclear	52	60% with K-L 3	3	Hylan G-F 20 (6 million Daltons)	Sodium Hyalurona te (.5 to .73 Daltons)	1.32 (0.78, 2.24)	No	N/A	Moderate

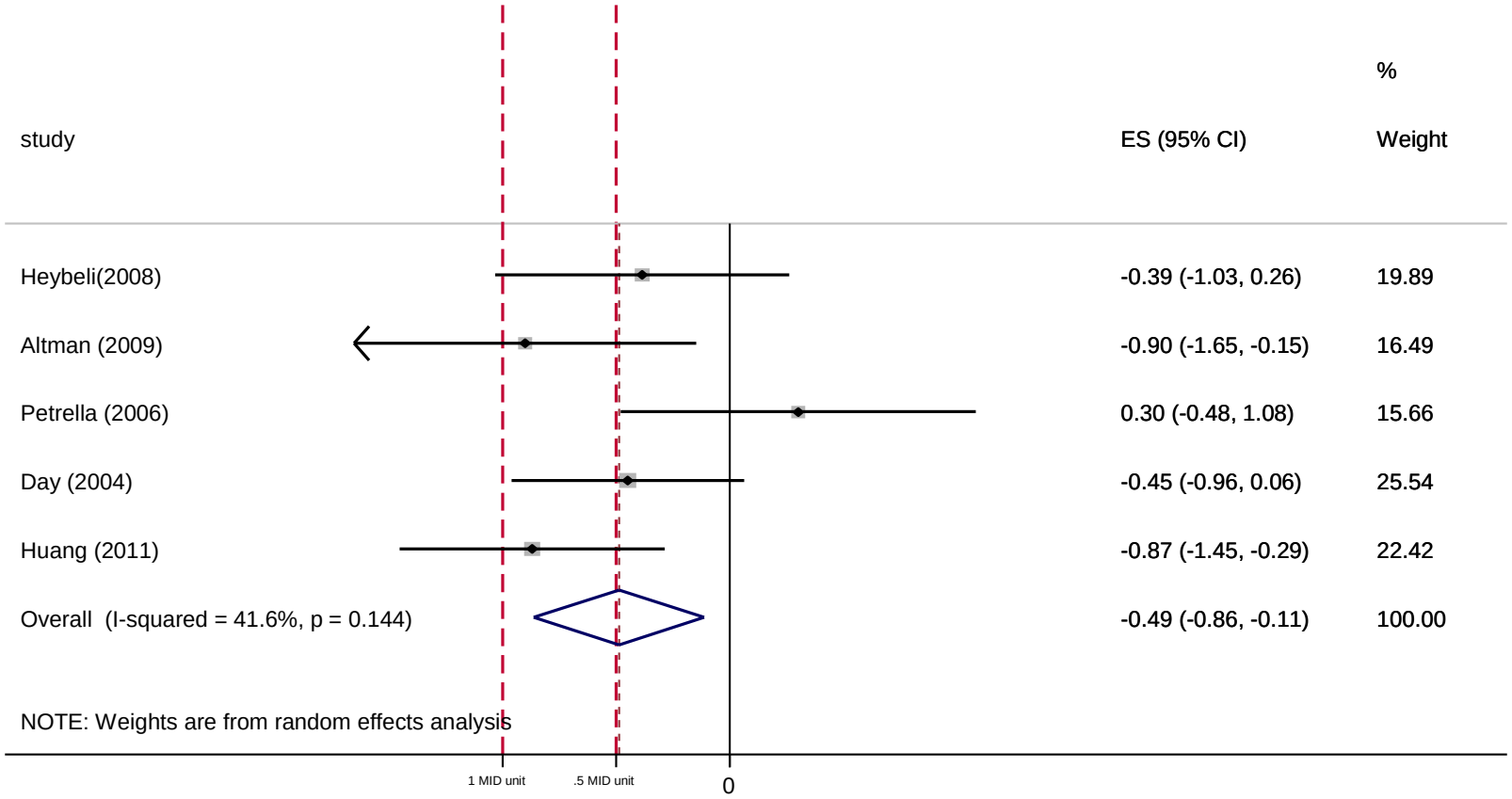
Figure 85. Hyaluronic Acid Versus Placebo: Pain in MID Units*



the red line is the threshold where some patients may benefit from treatment

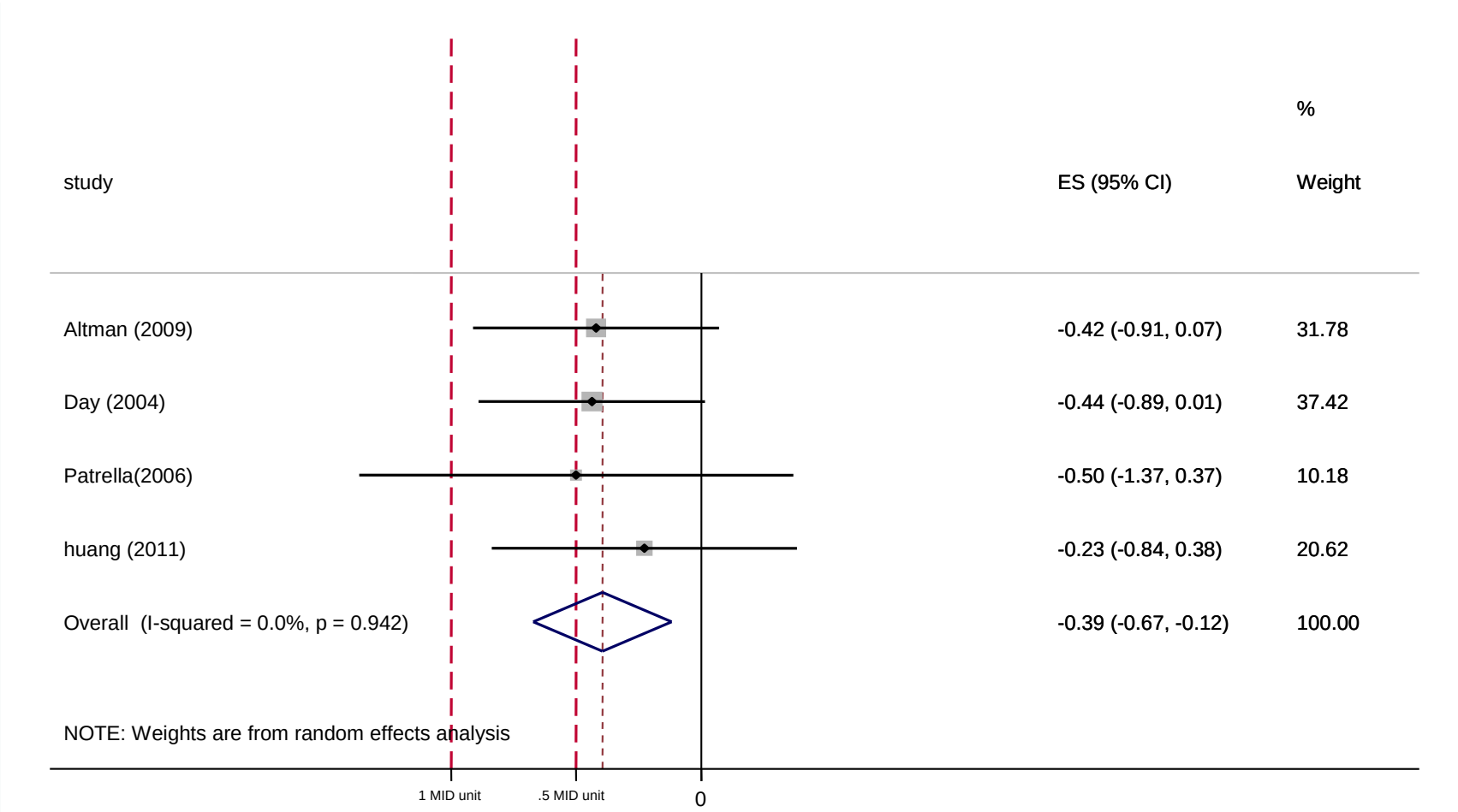
*All WOMAC scores are presented in 100mm VAS units

Figure 86. Hyaluronic Acid Versus Placebo: WOMAC Function in MID Units*



*All WOMAC scores are presented in 100mm VAS units

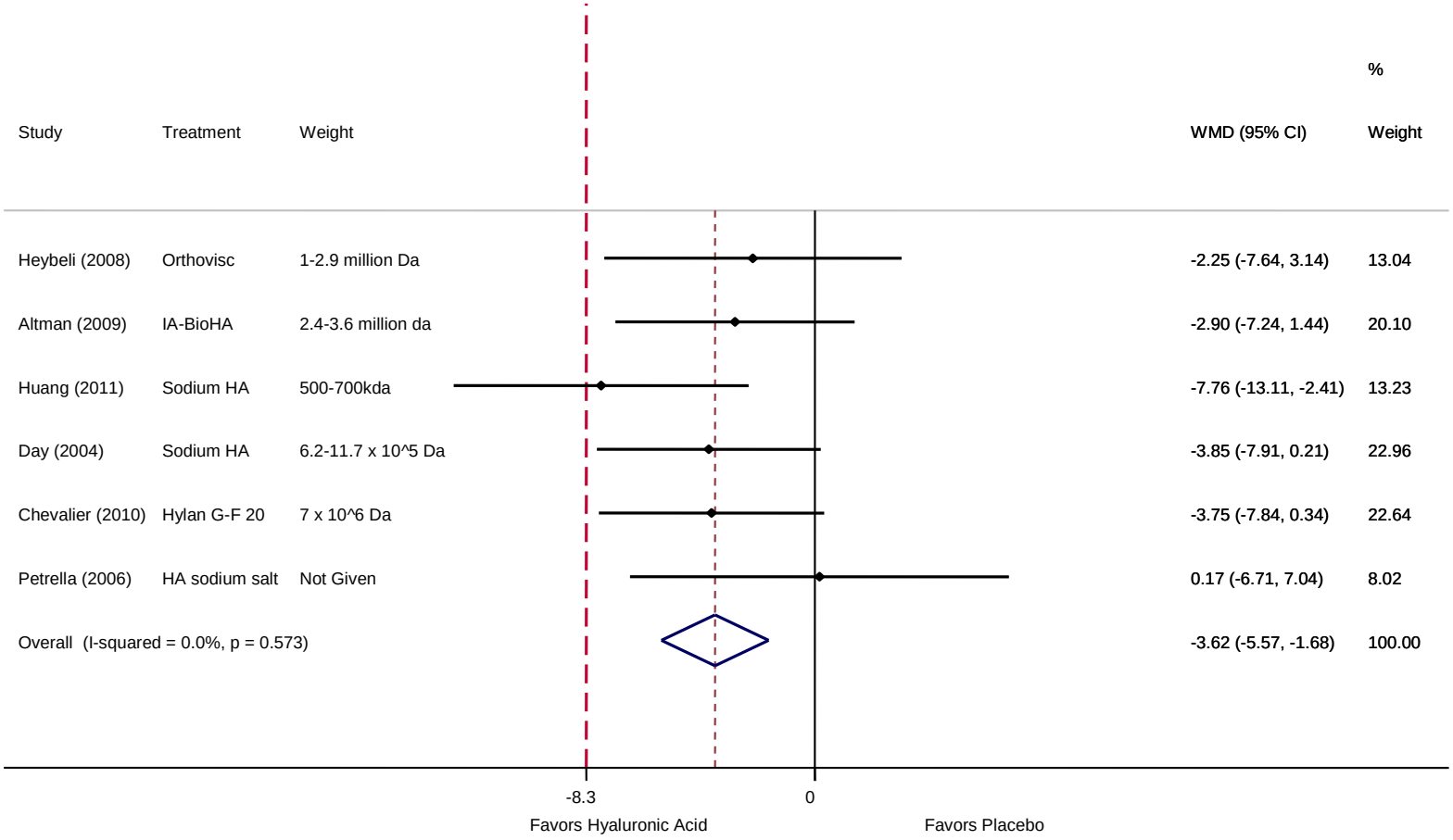
Figure 87. Hyaluronic Acid Versus Placebo: WOMAC Stiffness in MID Units*



The 0.5 MID unit is the threshold indicating when patients may benefit from treatment

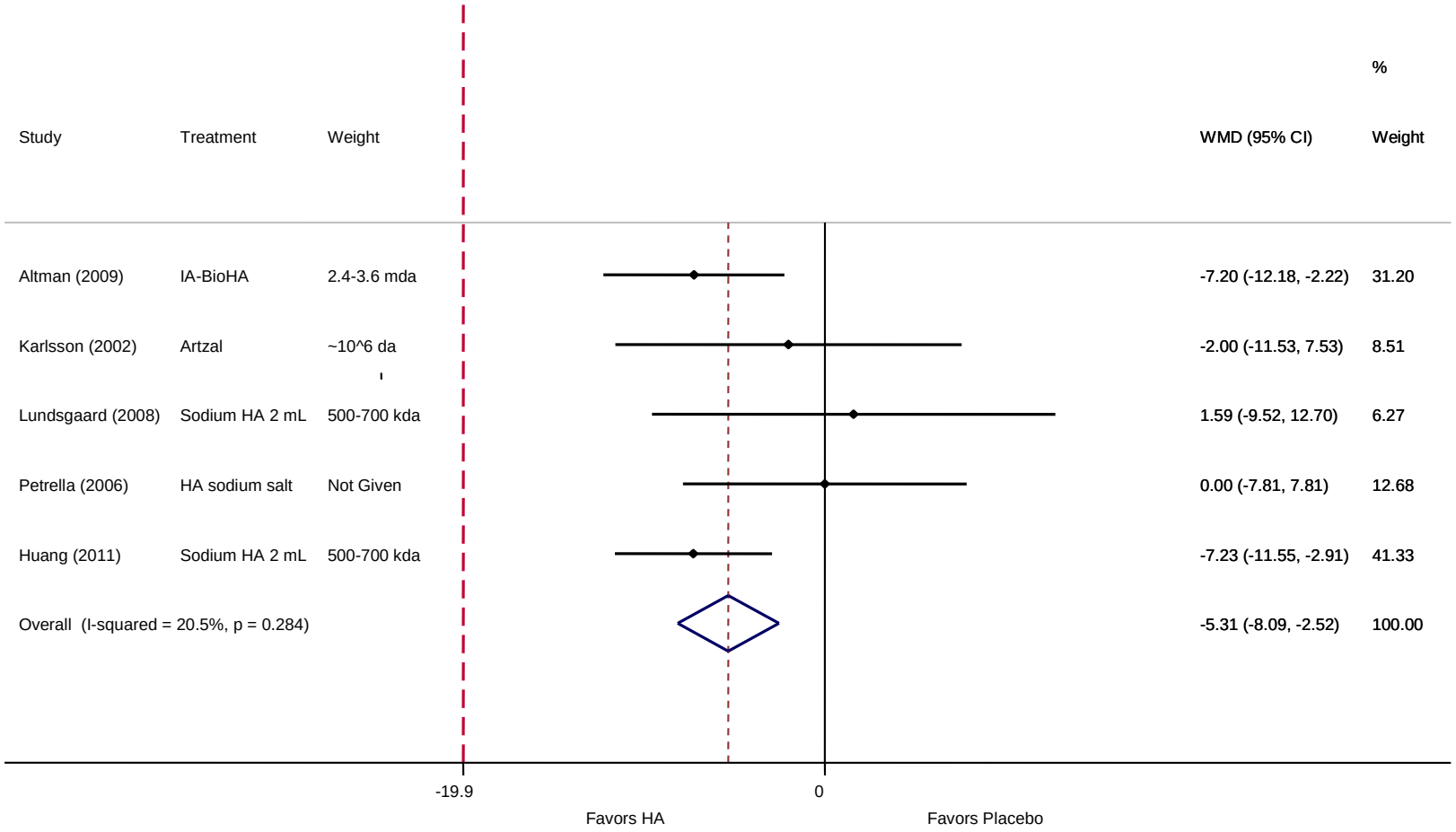
*All WOMAC scores are presented in 100mm VAS units

Figure 88. Hyaluronic Acid Versus Placebo: WOMAC Pain



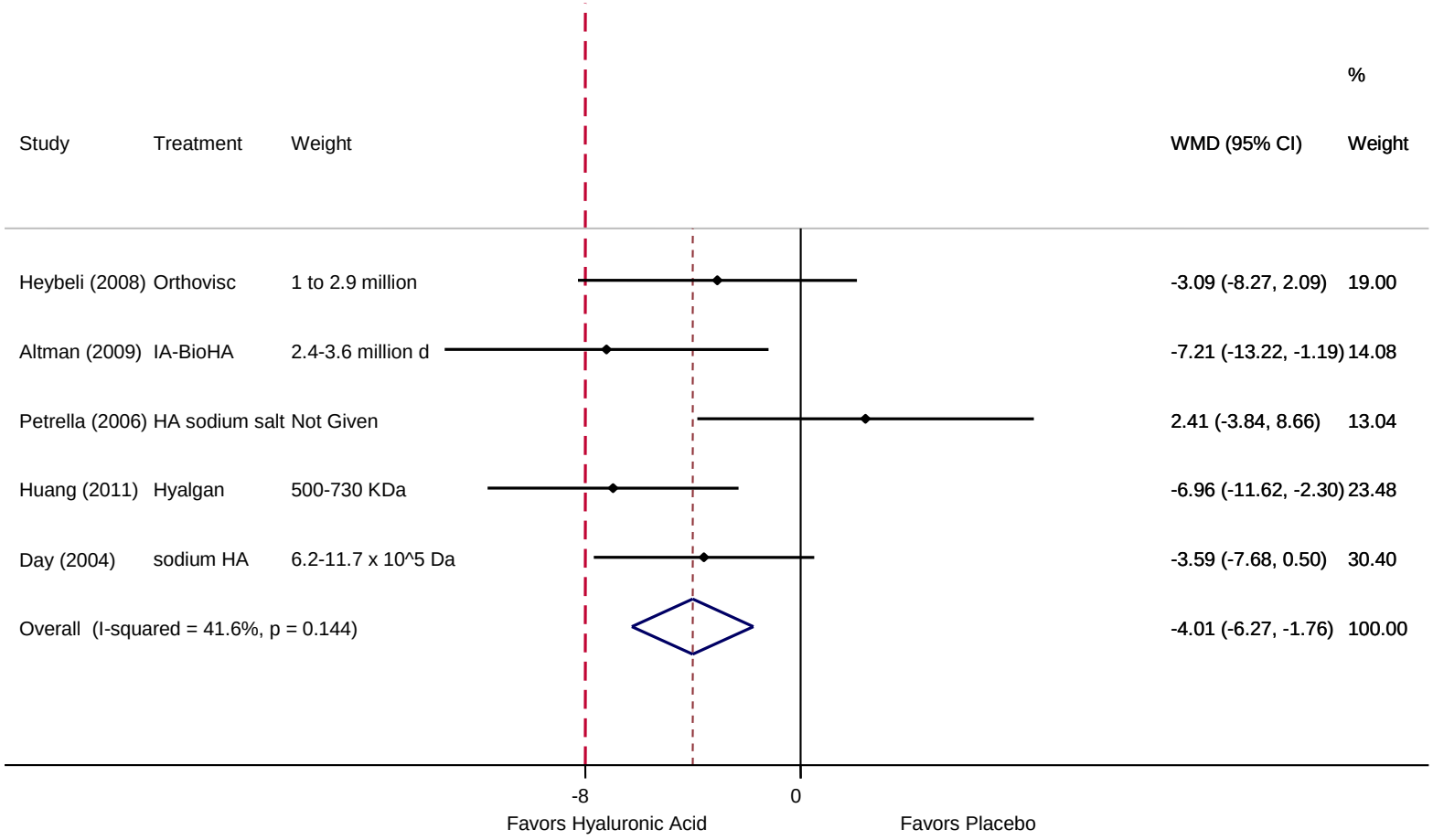
The red line indicates the MCII

Figure 89. Hyaluronic Acid Versus Placebo: VAS Weight Bearing Pain



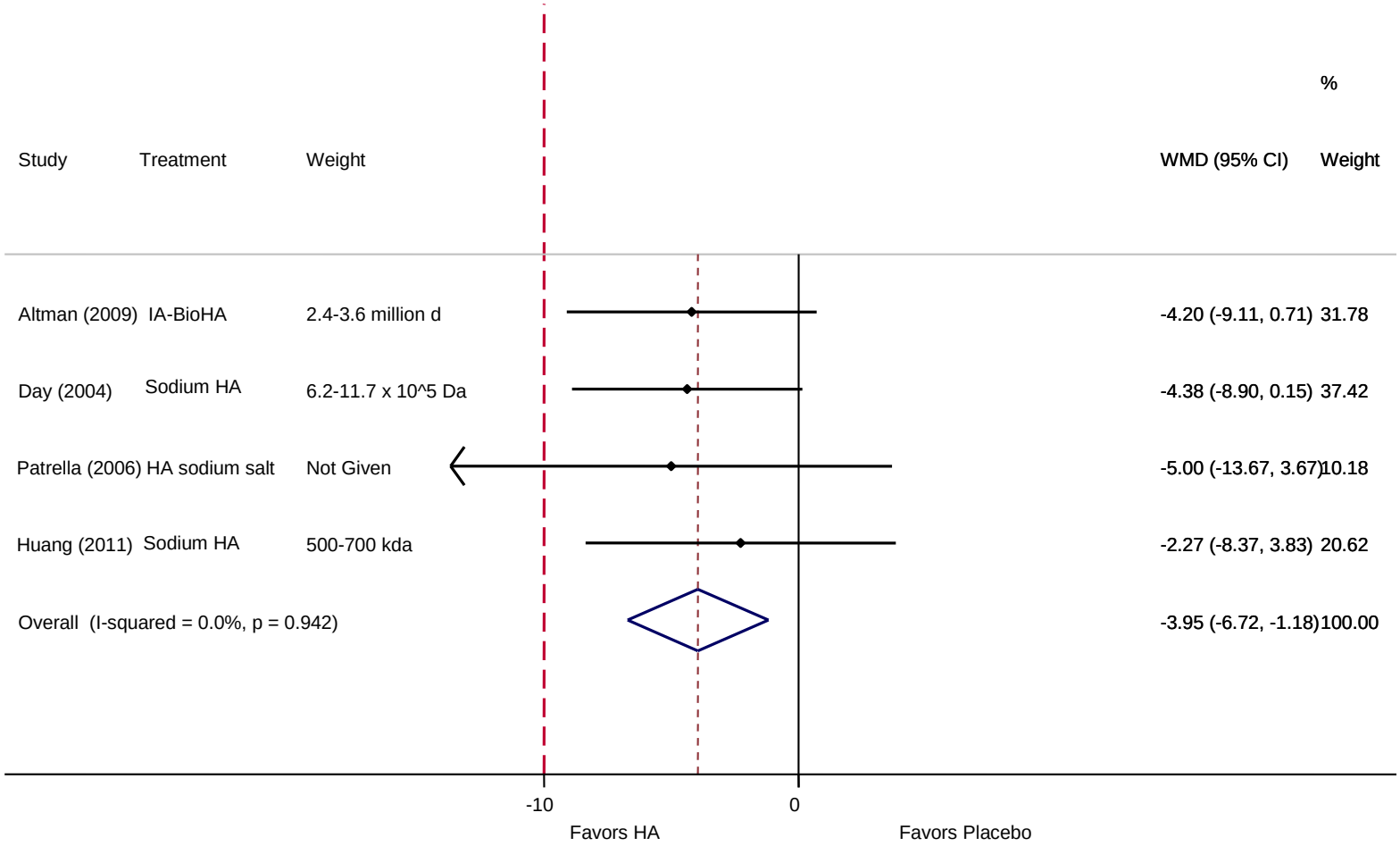
The red line indicates the MCII

Figure 90. Hyaluronic Acid Versus Placebo: Function



The red line indicates the MCII

Figure 91. Hyaluronic Acid Versus Placebo: WOMAC Stiffness



The red line indicates the MCII

RECOMMENDATION 10

We are unable to recommend for or against growth factor injections and/or platelet rich plasma for patients with symptomatic osteoarthritis of the knee.

Strength of Recommendation: Inconclusive

Description: Evidence from a single low quality study or conflicting findings that do not allow a recommendation for or against the intervention. An **Inconclusive** recommendation means that there is a lack of compelling evidence that has resulted in an unclear balance between benefits and potential harm.

Implications: Practitioners should feel little constraint in following a recommendation labeled as **Inconclusive,** exercise clinical judgment, and be alert for emerging evidence that clarifies or helps to determine the balance between benefits and potential harm. Patient preference should have a substantial influencing role.

RATIONALE

There was a paucity of articles on the use of platelet concentrates in the treatment of osteoarthritis. Sanchez et al.[119;120] used activated platelet aggregates in a fibrin matrix and Spakova et al.[121] used a platelet concentrate. None of the studies controlled for platelet volume. All studies used hyaluronic acid as the control group.

The studies showed decreased levels of pain in the post injection period but they were not constructed to allow for a comparative analysis of clinical effectiveness. The lack of controlled prospective blinded randomized clinical trials with a placebo control prevent the work group from making any recommendation on the use of platelets or platelet derived growth factor concentrates in the treatment of osteoarthritis of the knee.

SUPPORTING EVIDENCE

QUALITY

Relevant Tables: Table 190, Table 191

Three studies were evaluated as part of this recommendation. Sanchez et al.[119;120] compared growth factor injections to hyaluronic acid; the other compared platelet rich plasma to hyaluronic acid. [121] Sanchez et al.[119] was retrospective and had flaws in the investigator bias, blinding and group assignment domains. There was also questionable group comparability at baseline. The quality rating was determined to be low. The second study by Sanchez et al.[120] was of high quality; it was not flawed in any domain.

The platelet rich plasma (PRP) study by Spakova et al.[121] was of moderate quality. There was uncertain allocation concealment causing the group assignment domain to be flawed as well as potential for investigator bias.

APPLICABILITY

Relevant Tables: Table 190, Table 191

The participants might not have been representative of the typical patient population in all included studies. In the growth factor studies, the treatment administration might not have been reflective. Patient compliance and adherence were similar to general clinical

settings in all studies and there were a sufficient percentage of originally enrolled patients in the final analyses.

FINAL STRENGTH OF EVIDENCE

Because of their moderate applicability, all studies had the same quality and strength of evidence ratings. Sanchez et al.[119] was of low strength of evidence, and the second Sanchez et al.[120] was of high strength. Spakova et al.[121] was of moderate strength of evidence.

Table 190. Quality and Applicability Summary: Growth Factor and Platelet Rich Plasma

Study	Outcome	Duration (Weeks)	Quality	Applicability	Strength of Evidence
Sanchez (2008)	40% WOMAC Pain subscale	4	Low	Moderate	Low
Sanchez (2008)	WOMAC Function	4	Low	Moderate	Low
Sanchez (2008)	WOMAC Total	4	Low	Moderate	Low
Sanchez (2012)	50% decrease in WOMAC pain	24	High	Moderate	Low
Sanchez (2012)	20% decrease in WOMAC pain	24	High	Moderate	Low
Sanchez (2012)	OARSI responders	24	High	Moderate	Low
Sanchez (2012)	WOMAC stiffness	24	High	Moderate	Low
Sanchez (2012)	WOMAC function	24	High	Moderate	Low
Sanchez (2012)	WOMAC total	24	High	Moderate	Low
Sanchez (2012)	Lequesne index	24	High	Moderate	Low
Sanchez (2012)	Acetaminophen use (g/day)	24	High	Moderate	Low
Spakova (2012)	WOMAC Total	13	Moderate	Moderate	Moderate
Spakova (2012)	WOMAC Total	26	Moderate	Moderate	Moderate
Spakova (2012)	NRS Pain	13	Moderate	Moderate	Moderate
Spakova (2012)	NRS Pain	26	Moderate	Moderate	Moderate

RESULTS

Relevant Tables: Table 192, Table 193

Sanchez et al.[120] compared growth factor injections to hyaluronic acid. The authors found that patients receiving growth factor were significantly more likely to achieve a 40% improvement in WOMAC pain. WOMAC function and total scores were significantly better in the group treated with growth factor than the group treated with hyaluronic acid. However, another study by Sanchez et al.[119] found conflicting results, in which only 1 of 8 outcomes favored growth factor treatments.

Spakova et al.[121] found that patients who received platelet rich plasma reportedly significantly lower pain at 13 and 26 weeks than those who received hyaluronic acid. WOMAC total scores were also significantly lower in the PRP group. The difference was possibly clinically significant at 13 weeks and clinically significant at 26 weeks.

EVIDENCE TABLES AND FIGURES

QUALITY AND APPLICABILITY

Table 191. Quality and Applicability: Platelet Rich Plasma and Growth Factor Injections

●: Domain free of flaws

○: Domain flaws present

◐: Moderate power

Study	*Outcome*	Prospective	Power	Group Assignment	Blinding	Group Comparability	Treatment Integrity	Measurement	Investigator Bias	*Quality*	Participants	Intervention and Expertise	Compliance and Adherence	Analysis	*Applicability Study*
Sanchez (2008)	40% WOMAC Pain subscale	○	●	○	○	○	●	●	○	**Low**	○	○	●	●	**Moderate**
Sanchez (2008)	WOMAC Function	○	●	○	○	○	●	●	○	**Low**	○	○	●	●	**Moderate**
Sanchez (2008)	WOMAC Total	○	●	○	○	○	●	●	○	**Low**	○	○	●	●	**Moderate**
Sanchez (2012)	50% decrease in WOMAC pain	●	●	●	●	●	●	●	●	**High**	○	○	●	●	**Moderate**
Sanchez (2012)	20% decrease in WOMAC pain	●	●	●	●	●	●	●	●	**High**	○	○	●	●	**Moderate**
Sanchez (2012)	OARSI responders	●	●	●	●	●	●	●	●	**High**	○	○	●	●	**Moderate**

●: Domain free of flaws

○: Domain flaws present

◐: Moderate power

Study	*Outcome*	**Prospective**	**Power**	**Group Assignment**	**Blinding**	**Group Comparability**	**Treatment Integrity**	**Measurement**	**Investigator Bias**	*Quality*	**Participants**	**Intervention and Expertise**	**Compliance and Adherence**	**Analysis**	*Applicability Study*
Sanchez (2012)	WOMAC stiffness	●	●	●	●	●	●	●	●	**High**	○	○	●	●	**Moderate**
Sanchez (2012)	WOMAC function	●	●	●	●	●	●	●	●	**High**	○	○	●	●	**Moderate**
Sanchez (2012)	WOMAC total	●	●	●	●	●	●	●	●	**High**	○	○	●	●	**Moderate**
Sanchez (2012)	Lequesne index	●	●	●	●	●	●	●	●	**High**	○	○	●	●	**Moderate**
Sanchez (2012)	Acetaminophen use (g/day)	●	●	●	●	●	●	●	●	**High**	○	○	●	●	**Moderate**
Spakova (2012)	WOMAC Total week 13	●	●	○	●	●	●	●	○	**Moderate**	○	●	●	●	**Moderate**
Spakova (2012)	WOMAC Total week 26	●	●	○	●	●	●	●	○	**Moderate**	○	●	●	●	**Moderate**
Spakova (2012)	NRS Pain week 13	●	●	○	●	●	●	●	○	**Moderate**	○	●	●	●	**Moderate**
Spakova	NRS Pain week 26	●	●	○	●	●	●	●	○	**Moderate**	○	●	●	●	**Moderate**

●: Domain free of flaws

○: Domain flaws present

◐: Moderate power

Study	*Outcome*	**Prospective**	**Power**	**Group Assignment**	**Blinding**	**Group Comparability**	**Treatment Integrity**	**Measurement**	**Investigator Bias**	*Quality*	**Participants**	**Intervention and Expertise**	**Compliance and Adherence**	**Analysis**	*Applicability Study*
(2012)															

FINDINGS

Table 192. Growth Factor Injections Versus Hyaluronic Acid (Sanchez et al., 2008 and Sanchez et al., 2012)

Study	Outcome	N	Powered	Week	Severity	Group 1	Group 2	Standardized Mean Difference(or Odds ratio or P value)	Sig	Clinical Importance	Strength of Evidence
Sanchez (2008)	40% WOMAC Pain subscale	60	Yes	4	Ahlback 1-4	Growth factor	Hyaluronic Acid	4.50 (1.09, 18.50)	Favors growth factor	Unclear	Low
Sanchez (2008)	WOMAC Function	60	Yes	4	Ahlback 1-4	Growth factor	Hyaluronic Acid	p=.043	Favors growth factor	Unclear	Low
Sanchez (2008)	WOMAC Total	60	Yes	4	Ahlback 1-4	Growth factor	Hyaluronic Acid	p=.01	Favors growth factor	Unclear	Low
Sanchez (2012)	50% decrease in WOMAC pain	176	Yes	24	Ahlback 1-3	Growth factor	Hyaluronic Acid	OR=1.94(1.01, 3.73)	Favors growth factor	Unclear	High
Sanchez (2012)	20% decrease in WOMAC pain	176	Yes	24	Ahlback 1-3	Growth factor	Hyaluronic Acid	OR=1.2(.66, 2.2)	No	Unclear	High
Sanchez (2012)	OARSI responders	176	Yes	24	Ahlback 1-3	Growth factor	Hyaluronic Acid	OR=1.15(.63, 2.07)	No	Unclear	High
Sanchez (2012)	WOMAC stiffness	176	Yes	24	Ahlback 1-3	Growth factor	Hyaluronic Acid	-0.02 (-0.31, 0.28)	No	True Negative	High
Sanchez (2012)	WOMAC function	176	Yes	24	Ahlback 1-3	Growth factor	Hyaluronic Acid	-0.07 (-0.36, 0.23)	No	True Negative	High
Sanchez (2012)	WOMAC total	176	Yes	24	Ahlback 1-3	Growth factor	Hyaluronic Acid	-0.09 (-0.39, 0.20)	No	True Negative	High

Study	Outcome	N	Powered	Week	Severity	Group 1	Group 2	Standardized Mean Difference(or Odds ratio or P value)	Sig	Clinical Importance	Strength of Evidence
Sanchez (2012)	Lequesne index	176	Yes	24	Ahlback 1-3	Growth factor	Hyaluronic Acid	-0.06 (-0.35, 0.24)	No	True Negative	High
Sanchez (2012)	Acetaminophen use (g/day)	176	Yes	24	Ahlback 1-3	Growth factor	Hyaluronic Acid	p>.05	No	Unclear	High

Table 193. Platelet Rich Plasma (PRP) Versus Hyaluronic Acid (Spakova et al., 2012)

Outcome	N	Powered	Week	Severity	Group 1	Group 2	Effect size	Sig	Clinical Importance	Strength of Evidence
WOMAC Total	60	Yes	13	K-L 1-3	Platelet rich plasma	Hyaluronic Acid	-0.74 (-1.11, -0.37)	Favors PRP	Possibly clinically important	Moderate
WOMAC Total	60	Yes	26	K-L 1-3	Platelet rich plasma	Hyaluronic Acid	-0.78 (-1.15, -0.41)	Favors PRP	Clinically significant	Moderate
NRS Pain	60	Yes	13	K-L 1-3	Platelet rich plasma	Hyaluronic Acid	-0.89 (-1.26, -0.51)	Favors PRP	Unclear	Moderate
NRS Pain	60	Yes	26	K-L 1-3	Platelet rich plasma	Hyaluronic Acid	-0.81 (-1.19, -0.44)	Favors PRP	Unclear	Moderate

RECOMMENDATION 11

We cannot *suggest* that the practitioner use needle lavage for patients with symptomatic osteoarthritis of the knee.

Strength of Recommendation: Moderate

Description: Evidence from two or more "Moderate" strength studies with consistent findings, or evidence from a single "High" quality study for recommending for or against the intervention. A **Moderate** recommendation means that the benefits exceed the potential harm (or that the potential harm clearly exceeds the benefits in the case of a negative recommendation), but the quality/applicability of the supporting evidence is not as strong.

Implications: Practitioners should generally follow a **Moderate** recommendation but remain alert to new information and be sensitive to patient preferences.

RATIONALE

This recommendation is based on one high strength study by Bradley et al.[122] and one moderate strength study by Vad et al.[123] The evidence showed little or no benefit from needle lavage in the treatment of osteoarthritis of the knee. Fourteen of 15 outcomes were not statistically significant, including three pain and three functional outcomes, indicating no measurable benefit to patients from needle lavage.

SUPPORTING EVIDENCE

QUALITY

Relevant Tables: Table 194, Table 197, Table 198

Two studies compared patients undergoing needle lavage to a control group. The Bradley et al.[122] study did not contain flaws in any of the quality domains and was rated as high quality. The study by Vad et al.[123] was a moderate quality non-randomized control trial. Patients were able to choose their treatment creating a flaw in the group assignment domain. There was also questionable comparability of the groups at baseline; the authors did not use a test of statistical significance when comparing the pre-test outcome scores.

Arden et al.[107] compared needle lavage and intraarticular corticosteroids using a research design that resulted in a moderate quality study. There was questionable comparability of the groups at baseline and potential for investigator bias.

APPLICABILITY

Relevant Tables: Table 194, Table 197, Table 198

All studies were of moderate applicability. Compliance and adherence reflected typical clinical practice. The studies included all originally enrolled patients in the final analyses. However, treatment interventions were applied in a manner that might have been unrepresentative of typical clinical settings in each study. The patients might not have been typical of the osteoarthritis of the knee population in the Bradley et al.[122] and Arden et al.[107] studies.

FINAL STRENGTH OF EVIDENCE

The included studies were of moderate applicability so their strength of evidence ratings were comparable to their study quality ratings. The Bradley et al.[122] study was rated as high strength of evidence, and the Arden et al.[107] study was of moderate strength.

Table 194. Quality and Applicability Summary: Needle Lavage

Study	Outcome	Duration	Quality	Applicability	Strength of Evidence
Bradley (2002)	WOMAC Pain	12 weeks	High	Moderate	High
Bradley (2002)	WOMAC Pain	24 weeks	High	Moderate	High
Bradley (2002)	WOMAC Pain	52 weeks	High	Moderate	High
Bradley (2002)	WOMAC Function	12 weeks	High	Moderate	High
Bradley (2002)	WOMAC Function	24 weeks	High	Moderate	High
Bradley (2002)	WOMAC Function	52 weeks	High	Moderate	High
Bradley (2002)	Acetaminophen/day	12 weeks	High	Moderate	High
Bradley (2002)	Acetaminophen/day	24 weeks	High	Moderate	High
Bradley (2002)	Acetaminophen/day	52 weeks	High	Moderate	High
Bradley (2002)	Quality of Well-Being	24 weeks	High	Moderate	High
Bradley (2002)	Quality of Well-Being	52 weeks	High	Moderate	High
Bradley (2002)	50 ft. Walk time	12 weeks	High	Moderate	High
Bradley (2002)	50 ft. Walk time	24 weeks	High	Moderate	High

Study	Outcome	Duration	Quality	Applicability	Strength of Evidence
Bradley (2002)	50 ft. Walk time	52 weeks	High	Moderate	High
Vad (2003)	VAS Pain	1.1 years	Moderate	Moderate	Moderate

Table 195. Quality and Applicability Summary: Needle Lavage Versus Corticosteroids

Study	Outcome	Weeks	Quality	Applicability	Strength of Evidence
Arden (2008)	WOMAC Pain	4	Moderate	Moderate	Moderate
Arden (2008)	WOMAC Pain	12	Moderate	Moderate	Moderate
Arden (2008)	WOMAC Pain	26	Moderate	Moderate	Moderate
Arden (2008)	WOMAC Total Function	12	Moderate	Moderate	Moderate
Arden (2008)	WOMAC Total Function	26	Moderate	Moderate	Moderate
Arden (2008)	WOMAC Total Stiffness	12	Moderate	Moderate	Moderate
Arden (2008)	WOMAC Total Stiffness	26	Moderate	Moderate	Moderate

RESULTS

Relevant Tables: Table 196, Table 199-Table 203

Fourteen of 15 outcomes were not statistically significant suggesting that there was not any benefit in needle lavage compared to the control group. Pain, function and quality of life provided the critical outcomes. Three of four pain outcomes were not statistically significant. WOMAC function scores were not statistically significant at 12, 24 and 52 weeks. The quality of well-being scores were not statistically significant at 24 weeks and after one year.

There were seven total outcomes comparing needle lavage and IA corticosteroids. Six were possibly clinically significant in favor of lavage. WOMAC pain was the only critical outcome. While not statistically significant at 4 weeks, pain scores at 12 and 26 weeks were significantly lower in patients who received lavage than those treated with corticosteroids.

Table 196. Results Summary: Needle Lavage Versus Sham

		4 weeks	12 weeks	24 weeks	26 weeks	52 weeks	1.1 years
Needle Lavage Versus Control	**WOMAC Pain**			○	○	🔵	
	VAS Pain						🔵
	WOMAC Function			○	○	○	
	Quality of Well-Being				🟡	🟡	
	50-feet walk			○	○	○	
	Acetaminophen use			○	○	○	
Needle Lavage Versus IA Corticosteroids	**WOMAC Pain**		○	🔵	🔵		
	WOMAC Stiffness			🔵	🔵		
	WOMAC Total			🔵	🔵		

○ = **Not statistically significant;** 🔵 **=Possibly Clinically Important;**

🔵 = **Possibly Clinically Significant in Favor of Lavage;**

🟡 = **Statistically Significant in Favor of Lavage**

EVIDENCE TABLES AND FIGURES

QUALITY AND APPLICABILITY

Table 197. Quality and Applicability: Needle Lavage Versus Control

●: Domain free of flaws

○: Domain flaws present

◐: Moderate power

Study	*Outcome*	Prospective	Power	Group Assignment	Blinding	Group Comparability	Treatment Integrity	Measurement	Investigator Bias	*Quality*	Participants	Intervention and Expertise	Compliance and Adherence	Analysis	*Applicability Study*
Bradley (2002)	WOMAC Pain score 12 weeks	●	●	●	●	●	●	●	●	**High**	○	○	●	●	**Moderate**
Bradley (2002)	WOMAC Pain score 24 weeks	●	●	●	●	●	●	●	●	**High**	○	○	●	●	**Moderate**
Bradley (2002)	WOMAC Pain score 52 weeks	●	●	●	●	●	●	●	●	**High**	○	○	●	●	**Moderate**
Bradley (2002)	WOMAC Physical Function 12 weeks	●	●	●	●	●	●	●	●	**High**	○	○	●	●	**Moderate**
Bradley (2002)	WOMAC Physical Function 24 weeks	●	●	●	●	●	●	●	●	**High**	○	○	●	●	**Moderate**

●: Domain free of flaws

○: Domain flaws present

◐: Moderate power

Study	*Outcome*	Prospective	Power	Group Assignment	Blinding	Group Comparability	Treatment Integrity	Measurement	Investigator Bias	*Quality*	Participants	Intervention and Expertise	Compliance and Adherence	Analysis	*Applicability Study*
Bradley (2002)	WOMAC Physical Function 52 weeks	●	●	●	●	●	●	●	●	**High**	○	○	●	●	**Moderate**
Bradley (2002)	Acetaminophen/day 12 weeks	●	◐	●	●	●	●	●	●	**High**	○	○	●	●	**Moderate**
Bradley (2002)	Acetaminophen/day 24 weeks	●	◐	●	●	●	●	●	●	**High**	○	○	●	●	**Moderate**
Bradley (2002)	Acetaminophen/day 52 weeks	●	◐	●	●	●	●	●	●	**High**	○	○	●	●	**Moderate**
Bradley (2002)	Quality of Well-Being 24 Weeks	●	◐	●	●	●	●	●	●	**High**	○	○	●	●	**Moderate**
Bradley (2002)	Quality of Well-Being 52 Weeks	●	◐	●	●	●	●	●	●	**High**	○	○	●	●	**Moderate**

●: Domain free of flaws

○: Domain flaws present

◐: Moderate power

Study	*Outcome*	**Prospective**	**Power**	**Group Assignment**	**Blinding**	**Group Comparability**	**Treatment Integrity**	**Measurement**	**Investigator Bias**	*Quality*	**Participants**	**Intervention and Expertise**	**Compliance and Adherence**	**Analysis**	*Applicability Study*
Bradley (2002)	50 foot walk time 12 weeks	●	◐	●	●	●	●	●	●	**High**	○	○	●	●	**Moderate**
Bradley (2002)	50 foot walk time 24 weeks	●	◐	●	●	●	●	●	●	**High**	○	○	●	●	**Moderate**
Bradley (2002)	50 foot walk time 52 weeks	●	◐	●	●	●	●	●	●	**High**	○	○	●	●	**Moderate**
Vad (2003)	VAS pain 1.1 years	●	●	○	●	○	●	●	●	**Moderate**	●	○	●	●	**Moderate**

Table 198. Quality and Applicability: Needle Lavage Versus IA Corticosteroid

●: Domain free of flaws
○: Domain flaws present
◐: Moderate power

Study	*Outcome*	*Week*	Prospective	Power	Group Assignment	Blinding	Group Comparability	Treatment Integrity	Measurement	Investigator Bias	*Quality*	Participants	Intervention and Expertise	Compliance and Adherence	Analysis	*Applicability Study*
Arden (2008)	WOMAC Pain	**4**	●	●	●	●	○	●	●	○	**Moderate**	○	○	●	●	**Moderate**
Arden (2008)	WOMAC Pain	**12**	●	●	●	●	○	●	●	○	**Moderate**	○	○	●	●	**Moderate**
Arden (2008)	WOMAC Function	**12**	●	●	●	●	○	●	●	○	**Moderate**	○	○	●	●	**Moderate**
Arden (2008)	WOMAC Stiffness	**12**	●	●	●	●	○	●	●	○	**Moderate**	○	○	●	●	**Moderate**
Arden (2008)	WOMAC Pain	**26**	●	●	●	●	○	●	●	○	**Moderate**	○	○	●	●	**Moderate**
Arden (2008)	WOMAC Function	**26**	●	●	●	●	○	●	●	○	**Moderate**	○	○	●	●	**Moderate**
Arden (2008)	WOMAC Stiffness	**26**	●	●	●	●	○	●	●	○	**Moderate**	○	○	●	●	**Moderate**

FINDINGS

Table 199. Needle Lavage Versus Control: WOMAC Pain

Study	Outcome	N	Sufficient Power	Week	K-L Grade	Group 1	Group 2	SMD (Odds Ratio or Raw Mean Difference When Indicated)	Sig	Clinical Importance	Strength of Evidence
Bradley (2002)	WOMAC Pain	178	Yes	12	1 to 4	Needle Lavage	Sham	MD = -.8(p>.05)	No	Inconclusive	High
Bradley (2002)	WOMAC Pain	176	Yes	24	1 to 4	Needle Lavage	Sham	MD = -.7(p>.05)	No	Inconclusive	High
Bradley (2002)	WOMAC Pain	177	Yes	52	1 to 4	Needle Lavage	Sham	MD = -1.5(p>.05)	No	Inconclusive	High
Vad (2003)	VAS Pain	81	Yes	57.2	1 to 4	Needle Lavage plus Hylan GF-20	Hylan GF-20	-0.83 (-1.29, -0.37)	Yes	Possibly Clinically Important	Moderate

Table 200. Needle Lavage Versus Sham: Function

Study	Outcome	N	Sufficient Power	Week	K-L Grade	Group 1	Group 2	SMD (Odds Ratio or Raw Mean Difference When Indicated)	Sig	Clinical Importance	Strength of Evidence
Bradley (2002)	WOMAC Function	178	Yes	12	1 to 4	Needle Lavage	Sham	MD = -4 (p>.05)	No	Inconclusive	High
Bradley (2002)	WOMAC Function	176	Yes	24	1 to 4	Needle Lavage	Sham	MD = -3.9 (p>.05)	No	Inconclusive	High
Bradley (2002)	WOMAC Function	177	Yes	52	1 to 4	Needle Lavage	Sham	MD = -2.8 (p>.05)	No	Inconclusive	High
Bradley (2002)	50 ft. Walk time	178	Unclear	12	1 to 4	Needle Lavage	Sham	MD = -.4 (p>.05)	No	N/A	High
Bradley (2002)	50 ft. Walk time	176	Unclear	24	1 to 4	Needle Lavage	Sham	MD = -.3 (p>.05)	No	N/A	High
Bradley (2002)	50 ft. Walk time	177	Unclear	52	1 to 4	Needle Lavage	Sham	MD = -.7 (p>.05)	No	N/A	High

Table 201. Needle Lavage Versus Sham: Quality of Well-Being Score

Study	Outcome	N	Sufficient Power	Week	K-L grade	Group 1	Group 2	SMD (Odds Ratio or Raw Mean Difference When Indicated)	Sig	Clinical Importance	Strength of Evidence
Bradley (2002)	Quality of Well-Being Score	176	Unclear	24	1 to 4	Needle Lavage	Sham	MD = .02 (p>.05)	No	N/A	High
Bradley (2002)	Quality of Well-Being Score	177	Unclear	52	1 to 4	Needle Lavage	Sham	MD = .02 (p>.05)	No	N/A	High

Table 202. Needle Lavage Versus Sham: Acetaminophen Consumption

Study	Outcome	N	Sufficient Power	Week	K-L grade	Group 1	Group 2	SMD (Odds Ratio or Raw Mean Difference When Indicated)	Sig	Clinical Importance	Strength of Evidence
Bradley (2002)	Acetaminophen Consumption	178	Unclear	12	1 to 4	Needle Lavage	Sham	MD = -.3 (p>.05)	No	N/A	High
Bradley (2002)	Acetaminophen Consumption	176	Unclear	24	1 to 4	Needle Lavage	Sham	MD = -.4 (p>.05)	No	N/A	High
Bradley (2002)	Acetaminophen Consumption	177	Unclear	52	1 to 4	Needle Lavage	Sham	MD = -.1 (p>.05)	No	N/A	High

Table 203. Needle Lavage Versus Corticosteroids

Study	Outcome	N	Sufficient Power	Week	Severity	Group 1	Group 2	SMD (Odds Ratio or Raw Mean Difference When Indicated)	Sig	Clinical Importance	Strength of Evidence
Arden (2008)	WOMAC Pain	146	Yes	4	K-L 1-4	Needle Lavage	IA Corticosteroid	0.24(-0.09, 0.56)	No	Inconclusive	Moderate
Arden (2008)	WOMAC Pain	146	Yes	12	K-L 1-4	Needle Lavage	IA Corticosteroid	0.35(0.02, 0.67)	Favors Needle Lavage	Possibly clinically significant	Moderate
Arden (2008)	WOMAC Total Function	145	Yes	12	K-L 1-4	Needle Lavage	IA Corticosteroid	0.34(0.01, 0.66)	Favors Needle Lavage	Possibly clinically significant	Moderate
Arden (2008)	WOMAC Total Stiffness	138	Yes	12	K-L 1-4	Needle Lavage	IA Corticosteroid	0.4(0.06, 0.74)	Favors Needle Lavage	Possibly clinically significant	Moderate
Arden (2008)	WOMAC Pain	146	Yes	26	K-L 1-4	Needle Lavage	IA Corticosteroid	0.52(0.19, 0.85)	Favors Needle Lavage	Possibly clinically significant	Moderate
Arden (2008)	WOMAC Total Function	145	Yes	26	K-L 1-4	Needle Lavage	IA Corticosteroid	0.44(0.11, 0.77)	Favors Needle Lavage	Possibly clinically significant	Moderate
Arden (2008)	WOMAC Total Stiffness	138	Yes	26	K-L 1-4	Needle Lavage	IA Corticosteroid	0.45(0.11, 0.79)	Favors Needle Lavage	Possibly clinically significant	Moderate

RECOMMENDATION 12

We cannot recommend performing arthroscopy with lavage and/or debridement in patients with a primary diagnosis of symptomatic osteoarthritis of the knee.
Strength of Recommendation: Strong

Description: Evidence is based on two or more "High" strength studies with consistent findings for recommending for or against the intervention. A **Strong** recommendation means that the quality of the supporting evidence is high. A harms analysis on this recommendation was not performed.

Implications: Practitioners should follow a **Strong** recommendation unless a clear and compelling rationale for an alternative approach is present.

RATIONALE

There were three studies that met the inclusion criteria for this recommendation. The Kirkley et. al[124] and Kalunian et. al[125] studies comparing arthroscopic lavage to placebo were rated as moderate strength and the Moseley et al.[126] study comparing arthroscopic lavage to sham arthroscopic surgery was rated as a high strength study.

Kirkley et al.[124] reported that a large number of patients were not eligible for participation in their study (38%) largely due to the exclusion criteria of substantial knee malalignment. In some cases, patients declined participation. Kirkely et al.[124] compared arthroscopic surgery to lavage and debridement combined with usual physical therapy and medical treatment, usual care. The authors used the pain, functional status and other symptoms subscales of the Arthritis Self-Efficacy Scale (ASES) and the McMaster-Toronto Arthritis Patient Preference Disability Questionnaire (MACTAR) at multiple time points (ranging from three months to two years). Out of 20 outcomes, only two were statistically significant in favor of surgery with lavage. Differences in AIMS pain were statistically significant at three months and differences in AIMS-Other Arthritis Symptoms subscale scores remained significant after two years. In summary, this randomized controlled trial demonstrated no benefit of arthroscopic surgery compared to physical therapy and medical treatment for osteoarthritis of the knee.

Kalunian et al.[125] included a large number of enrolled patients from one institution with intraarticular crystals in their knee. They compared arthroscopic lavage with 3,000 ml saline to lavage with 250 ml saline. There were not any statistically significant differences in VAS and WOMAC pain scores between the two treatment groups.

The Moseley et al.[126] study raised questions regarding its limited sampling (mostly male veterans) as well as the number of potential study participants who declined randomization into a treatment group. In this RCT, the effects of arthroscopy with debridement or lavage were not statistically significant in the vast majority of patient oriented outcome measures for pain and function, at multiple time points from one week to two years following surgery.

Collectively all three included studies did not demonstrate clinical benefit of arthroscopic debridement or lavage. The work group also considered the potential risks to patients

(anesthesia intolerance, infection, and venous thrombosis) associated with surgical intervention.

It was agreed that the lacking evidence for treatment benefit and increased risks from surgery were sufficient reasons to recommend against arthroscopic debridement and/or lavage in patients with a primary diagnosis of osteoarthritis of the knee.

None of the evidence we examined specifically included patients who had a primary diagnosis of meniscal tear, loose body, or other mechanical derangement, with concomitant diagnosis of osteoarthritis of the knee. The present recommendation does not apply to such patients.

SUPPORTING EVIDENCE

QUALITY

Relevant Tables: Table 204, Table 205

Three studies met the inclusion criteria for this recommendation. The Moseley et al.[126] study was of high quality. The studies by Kirkely et al.[124] and Kalunian et al.[125] were of moderate quality. The Moseley et al.[126] study was not flawed in any quality domain. Both moderate quality studies[124;125] were flawed in the group assignment and group comparability domains and the Kalunian et al. study was also flawed in treatment integrity.

APPLICABILITY

Relevant Tables: Table 204, Table 205

In all three studies, the participants might not have been representative of the osteoarthritis of the knee patient population. Furthermore, the application of the intervention might not have been the same as what is practiced in regular clinical settings. At the same time, compliance and adherence were typical. Two of the three studies included all originally enrolled patients in the final analyses. [124;125]

FINAL STRENGTH OF EVIDENCE

All moderate and high quality outcomes were paired with comparable ratings for strength of evidence since all study applicability ratings were moderate.

Table 204. Quality and Applicability Summary: Arthroscopy with Lavage and/or Debridement

Study	Outcome	Duration (Weeks)	Comparison	Quality	Applicability	Strength of Evidence
Moseley (2002)	Arthritis Impact Measurement Scale: Pain	6	Debridement versus Placebo	High	Moderate	High
Kalunian (2000)	WOMAC Pain	52	Full irrigation versus minimal irrigation	Moderate	Moderate	Moderate
Kalunian (2000)	VAS Pain	52	Full irrigation versus minimal irrigation	Moderate	Moderate	Moderate
Kirkley (2008)	Arthritis Self-Efficacy Scale: Pain	13	Arthroscopic surgery with debridement and lavage versus usual care	Moderate	Moderate	Moderate
Kirkley (2008)	Arthritis Self-Efficacy Scale: Pain	26	Arthroscopic surgery with debridement and lavage versus usual care	Moderate	Moderate	Moderate
Kirkley (2008)	Arthritis Self-Efficacy Scale: Pain	52	Arthroscopic surgery with debridement and lavage versus usual care	Moderate	Moderate	Moderate
Kirkley (2008)	Arthritis Self-Efficacy	78	Arthroscopic surgery with debridement and	Moderate	Moderate	Moderate

	Scale: Pain		lavage versus usual care			
Kirkley (2008)	Arthritis Self-Efficacy Scale: Pain	104	Arthroscopic surgery with debridement and lavage versus usual care	Moderate	Moderate	Moderate
Kirkley (2008)	Arthritis Self-Efficacy Scale: Functional Status	13	Arthroscopic surgery with debridement and lavage versus usual care	Moderate	Moderate	Moderate
Kirkley (2008)	Arthritis Self-Efficacy Scale: Functional Status	26	Arthroscopic surgery with debridement and lavage versus usual care	Moderate	Moderate	Moderate
Kirkley (2008)	Arthritis Self-Efficacy Scale: Functional Status	52	Arthroscopic surgery with debridement and lavage versus usual care	Moderate	Moderate	Moderate
Kirkley (2008)	Arthritis Self-Efficacy Scale: Functional Status	78	Arthroscopic surgery with debridement and lavage versus usual care	Moderate	Moderate	Moderate
Kirkley (2008)	Arthritis Self-Efficacy Scale: Functional Status	104	Arthroscopic surgery with debridement and lavage versus usual	Moderate	Moderate	Moderate

			care			
Kirkley (2008)	McMaster-Toronto Arthritis Patient Preference Disability Questionnaire (MACTAR)	13	Arthroscopic surgery with debridement and lavage versus usual care	Moderate	Moderate	Moderate
Kirkley (2008)	McMaster-Toronto Arthritis Patient Preference Disability Questionnaire (MACTAR)	26	Arthroscopic surgery with debridement and lavage versus usual care	Moderate	Moderate	Moderate
Kirkley (2008)	McMaster-Toronto Arthritis Patient Preference Disability Questionnaire (MACTAR)	52	Arthroscopic surgery with debridement and lavage versus usual care	Moderate	Moderate	Moderate
Kirkley (2008)	McMaster-Toronto Arthritis Patient Preference Disability Questionnaire (MACTAR)	78	Arthroscopic surgery with debridement and lavage versus usual care	Moderate	Moderate	Moderate
Kirkley (2008)	McMaster-Toronto Arthritis Patient Preference Disability Questionnaire (MACTAR)	104	Arthroscopic surgery with debridement and lavage versus usual care	Moderate	Moderate	Moderate

Kirkley (2008)	Arthritis Self-Efficacy Score: Other Arthritis Related Symptoms	13	Arthroscopic surgery with debridement and lavage versus usual care	Moderate	Moderate	Moderate
Kirkley (2008)	Arthritis Self-Efficacy Score: Other Arthritis Related Symptoms	26	Arthroscopic surgery with debridement and lavage versus usual care	Moderate	Moderate	Moderate
Kirkley (2008)	Arthritis Self-Efficacy Score: Other Arthritis Related Symptoms	52	Arthroscopic surgery with debridement and lavage versus usual care	Moderate	Moderate	Moderate
Kirkley (2008)	Arthritis Self-Efficacy Score: Other Arthritis Related Symptoms	78	Arthroscopic surgery with debridement and lavage versus usual care	Moderate	Moderate	Moderate
Kirkley (2008)	Arthritis Self-Efficacy Score: Other Arthritis Related Symptoms	104	Arthroscopic surgery with debridement and lavage versus usual care	Moderate	Moderate	Moderate
Moseley (2000)	Arthritis Impact Measurement Scale: Pain	13	Debridement versus Placebo	High	Moderate	High
Moseley (2000)	Arthritis Impact Measurement Scale:	26	Debridement versus Placebo	High	Moderate	High

	Pain					
Moseley (2000)	Arthritis Impact Measurement Scale: Pain	52	Debridement versus Placebo	High	Moderate	High
Moseley (2000)	Arthritis Impact Measurement Scale: Pain	78	Debridement versus Placebo	High	Moderate	High
Moseley (2002)	Arthritis Impact Measurement Scale: Pain	104	Debridement versus Placebo	High	Moderate	High
Moseley (2002)	Arthritis Impact Measurement Scale: Walking-Bending	6	Debridement versus Placebo	High	Moderate	High
Moseley (2002)	Arthritis Impact Measurement Scale: Walking-Bending	13	Debridement versus Placebo	High	Moderate	High
Moseley (2002)	Arthritis Impact Measurement Scale: Walking-Bending	26	Debridement versus Placebo	High	Moderate	High
Moseley (2002)	Arthritis Impact Measurement Scale: Walking-Bending	52	Debridement versus Placebo	High	Moderate	High
Moseley (2002)	Arthritis Impact Measurement Scale:	78	Debridement versus	High	Moderate	High

	Walking-Bending		Placebo			
Moseley (2002)	Arthritis Impact Measurement Scale: Walking-Bending	104	Debridement versus Placebo	High	Moderate	High
Moseley (2002)	Arthritis Impact Measurement Scale: Pain	6	Debridement versus lavage	High	Moderate	High
Moseley (2002)	Arthritis Impact Measurement Scale: Pain	13	Debridement versus lavage	High	Moderate	High
Moseley (2002)	Arthritis Impact Measurement Scale: Pain	26	Debridement versus lavage	High	Moderate	High
Moseley (2002)	Arthritis Impact Measurement Scale: Pain	52	Debridement versus lavage	High	Moderate	High
Moseley (2002)	Arthritis Impact Measurement Scale: Pain	78	Debridement versus lavage	High	Moderate	High
Moseley (2002)	Arthritis Impact Measurement Scale: Pain	104	Debridement versus lavage	High	Moderate	High
Moseley (2002)	Arthritis Impact Measurement Scale:	6	Debridement versus	High	Moderate	High

	Walking-Bending		lavage			
Moseley (2002)	Arthritis Impact Measurement Scale: Walking-Bending	13	Debridement versus lavage	High	Moderate	High
Moseley (2002)	Arthritis Impact Measurement Scale: Walking-Bending	26	Debridement versus lavage	High	Moderate	High
Moseley (2002)	Arthritis Impact Measurement Scale: Walking-Bending	52	Debridement versus lavage	High	Moderate	High
Moseley (2002)	Arthritis Impact Measurement Scale: Walking-Bending	78	Debridement versus lavage	High	Moderate	High
Moseley (2002)	Arthritis Impact Measurement Scale: Walking-Bending	104	Debridement versus lavage	High	Moderate	High
Moseley (2002)	Arthritis Impact Measurement Scale: Pain	6	Lavage versus Placebo	High	Moderate	High
Moseley (2002)	Arthritis Impact Measurement Scale: Pain	13	Lavage versus Placebo	High	Moderate	High
Moseley (2002)	Arthritis Impact Measurement Scale:	26	Lavage versus Placebo	High	Moderate	High

	Pain					
Moseley (2002)	Arthritis Impact Measurement Scale: Pain	52	Lavage versus Placebo	High	Moderate	High
Moseley (2002)	Arthritis Impact Measurement Scale: Pain	78	Lavage versus Placebo	High	Moderate	High
Moseley (2002)	Arthritis Impact Measurement Scale: Pain	104	Lavage versus Placebo	High	Moderate	High
Moseley (2002)	Arthritis Impact Measurement Scale: Walking-Bending	6	Lavage versus Placebo	High	Moderate	High
Moseley (2002)	Arthritis Impact Measurement Scale: Walking-Bending	13	Lavage versus Placebo	High	Moderate	High
Moseley (2002)	Arthritis Impact Measurement Scale: Walking-Bending	26	Lavage versus Placebo	High	Moderate	High
Moseley (2002)	Arthritis Impact Measurement Scale: Walking-Bending	52	Lavage versus Placebo	High	Moderate	High
Moseley (2002)	Arthritis Impact Measurement Scale:	78	Lavage versus Placebo	High	Moderate	High

	Walking-Bending					
Moseley (2002)	Arthritis Impact Measurement Scale: Walking-Bending	104	Lavage versus Placebo	High	Moderate	High
Moseley (2002)	Arthritis Impact Measurement Scale: Pain	6	Debridement versus Placebo	High	Moderate	High
Kalunian (2000)	WOMAC Pain	52	Full irrigation versus minimal irrigation	Moderate	Moderate	Moderate
Kalunian (2000)	VAS Pain	52	Full irrigation versus minimal irrigation	Moderate	Moderate	Moderate
Kirkley (2008)	Arthritis Self-Efficacy Scale: Pain	13	Arthroscopic surgery with debridement and lavage versus usual care	Moderate	Moderate	Moderate
Kirkley (2008)	Arthritis Self-Efficacy Scale: Pain	26	Arthroscopic surgery with debridement and lavage versus usual care	Moderate	Moderate	Moderate
Kirkley (2008)	Arthritis Self-Efficacy Scale: Pain	52	Arthroscopic surgery with debridement and lavage versus usual care	Moderate	Moderate	Moderate

Kirkley (2008)	Arthritis Self-Efficacy Scale: Pain	78	Arthroscopic surgery with debridement and lavage versus usual care	Moderate	Moderate	Moderate
Kirkley (2008)	Arthritis Self-Efficacy Scale: Pain	104	Arthroscopic surgery with debridement and lavage versus usual care	Moderate	Moderate	Moderate

RESULTS

Relevant Tables: Figure 92, Table-206- Table 215

Moseley et al.[126] compared arthroscopic debridement and arthroscopic lavage to placebo using the AIMS-pain and AIMS-walking and bending instruments. Each outcome was measured at six weeks, 13 weeks, 26 weeks, 1 year, 78 weeks, and 2 years. Neither debridement nor lavage was associated with statistically significant treatment effects over placebo at any follow-up time. Also, debridement was not statistically better than lavage.

As indicated above, Kirkley et al.[124] compared arthroscopic surgery with lavage and debridement combined with usual physical and medical therapy to a control group who only received usual care. The authors used the pain, functional status and other symptoms subscales of the Arthritis Self-Efficacy Scale (ASES) and the McMaster-Toronto Arthritis Patient Preference Disability Questionnaire (MACTAR). The follow up periods were three months, six months, one year, 18 months and two years. Out of 20 outcomes, only two were statistically significant in favor of surgery with lavage. Differences in AIMS pain were statistically significant at three months and differences in AIMS-Other Arthritis Symptoms scores remained significant after two years.

Kalunian et al.[125] compared arthroscopic lavage with 3,000 ml saline to lavage with 250 ml saline. There were not any statistically significant differences in VAS and WOMAC pain scores between the two groups.

Figure 92. Results Summary: Arthroscopic Surgery, Lavage, and Debridement Versus Control

	Outcome	6	13	26	52	78	104
Debridement	Arthritis Impact Measurement Scale: Pain	●	●	●	●	●	●
	Arthritis Impact Measurement Scale: Walking-Bending	●	●	●	●	●	●
Lavage	Arthritis Impact Measurement Scale: Pain	●	●	●	●	●	●
	Arthritis Impact Measurement Scale: Walking-Bending	●	●	●	●	●	●
Arthroscopic Surgery with Debridement and Lavage	Arthritis Self-Efficacy Scale: Functional Status		●	●	●	●	●
	Arthritis Self-Efficacy Scale: Other Symptoms		●	●	●	●	●
	Arthritis Self-Efficacy Scale: Pain		●	●	●	●	●
	McMaster-Toronto Arthritis Patient Preference		●	●	●	●	●
Full Versus Minimal Irrigation	VAS Pain				●		
	WOMAC Pain				●		

Key: ●=Not Significant; ●=Statistically Significant

EVIDENCE TABLES AND FIGURES

QUALITY AND APPLICABILITY

Table 205. Quality and Applicability: Arthroscopy with Lavage and/or Debridement

●: Domain free of flaws

○: Domain flaws present

◐: Moderate power

Study	*Outcome*	*Week*	*Comparison*	Prospective	Power	Group Assignment	Blinding	Group Comparability	Treatment Integrity	Measurement	Investigator Bias	*Quality*	Participants	Intervention and Expertise	Compliance and Adherence	Analysis	*Applicability Study*
Moseley (2002)	Arthritis Impact Measurement Scale: Pain	6	Debridement versus Placebo	●	◐	●	●	●	●	●	●	**High**	○	○	●	○	**Moderate**
Kalunian (2000)	WOMAC Pain	52	Full irrigation versus minimal irrigation	●	●	○	●	○	○	●	●	**Moderate**	○	○	●	●	**Moderate**
Kalunian (2000)	VAS Pain	52	Full irrigation versus minimal irrigation	●	●	○	●	○	○	●	●	**Moderate**	○	○	●	●	**Moderate**

●: Domain free of flaws

○: Domain flaws present

◐: Moderate power

Study	*Outcome*	*Week*	*Comparison*	**Prospective**	**Power**	**Group Assignment**	**Blinding**	**Group Comparability**	**Treatment Integrity**	**Measurement**	**Investigator Bias**	*Quality*	**Participants**	**Intervention and Expertise**	**Compliance and Adherence**	**Analysis**	*Applicability Study*
Kirkley (2008)	Arthritis Self-Efficacy Scale: Pain	13	Arthroscopic surgery with debridement and lavage versus usual care	●	●	○	●	○	●	●	●	**Moderate**	○	○	●	●	**Moderate**
Kirkley (2008)	Arthritis Self-Efficacy Scale: Pain	26	Arthroscopic surgery with debridement and lavage versus usual care	●	◐	○	●	○	●	●	●	**Moderate**	○	○	●	●	**Moderate**

●: Domain free of flaws

○: Domain flaws present

◐: Moderate power

Study	*Outcome*	*Week*	*Comparison*	**Prospective**	**Power**	**Group Assignment**	**Blinding**	**Group Comparability**	**Treatment Integrity**	**Measurement**	**Investigator Bias**	*Quality*	**Participants**	**Intervention and Expertise**	**Compliance and Adherence**	**Analysis**	*Applicability Study*
Kirkley (2008)	Arthritis Self-Efficacy Scale: Pain	52	Arthroscopic surgery with debridement and lavage versus usual care	●	◐	○	●	○	●	●	●	**Moderate**	○	○	●	●	**Moderate**
Kirkley (2008)	Arthritis Self-Efficacy Scale: Pain	78	Arthroscopic surgery with debridement and lavage versus usual care	●	◐	○	●	○	●	●	●	**Moderate**	○	○	●	●	**Moderate**

●: Domain free of flaws

○: Domain flaws present

◐: Moderate power

Study	*Outcome*	*Week*	*Comparison*	**Prospective**	**Power**	**Group Assignment**	**Blinding**	**Group Comparability**	**Treatment Integrity**	**Measurement**	**Investigator Bias**	*Quality*	**Participants**	**Intervention and Expertise**	**Compliance and Adherence**	**Analysis**	*Applicability Study*
Kirkley (2008)	Arthritis Self-Efficacy Scale: Pain	104	Arthroscopic surgery with debridement and lavage versus usual care	●	◐	○	●	○	●	●	●	**Moderate**	○	○	●	●	**Moderate**
Kirkley (2008)	Arthritis Self-Efficacy Scale: Functional Status	13	Arthroscopic surgery with debridement and lavage versus usual care	●	◐	○	●	○	●	●	●	**Moderate**	○	○	●	●	**Moderate**

●: Domain free of flaws

○: Domain flaws present

◐: Moderate power

Study	*Outcome*	*Week*	*Comparison*	**Prospective**	**Power**	**Group Assignment**	**Blinding**	**Group Comparability**	**Treatment Integrity**	**Measurement**	**Investigator Bias**	*Quality*	**Participants**	**Intervention and Expertise**	**Compliance and Adherence**	**Analysis**	*Applicability Study*
Kirkley (2008)	Arthritis Self-Efficacy Scale: Functional Status	26	Arthroscopic surgery with debridement and lavage versus usual care	●	◐	○	●	○	●	●	●	**Moderate**	○	○	●	●	**Moderate**
Kirkley (2008)	Arthritis Self-Efficacy Scale: Functional Status	52	Arthroscopic surgery with debridement and lavage versus usual care	●	◐	○	●	○	●	●	●	**Moderate**	○	○	●	●	**Moderate**

●: Domain free of flaws

○: Domain flaws present

◐: Moderate power

Study	*Outcome*	*Week*	*Comparison*	**Prospective**	**Power**	**Group Assignment**	**Blinding**	**Group Comparability**	**Treatment Integrity**	**Measurement**	**Investigator Bias**	*Quality*	**Participants**	**Intervention and Expertise**	**Compliance and Adherence**	**Analysis**	*Applicability Study*
Kirkley (2008)	Arthritis Self-Efficacy Scale: Functional Status	78	Arthroscopic surgery with debridement and lavage versus usual care	●	◐	○	●	○	●	●	●	**Moderate**	○	○	●	●	**Moderate**
Kirkley (2008)	Arthritis Self-Efficacy Scale: Functional Status	104	Arthroscopic surgery with debridement and lavage versus usual care	●	◐	○	●	○	●	●	●	**Moderate**	○	○	●	●	**Moderate**

●: Domain free of flaws

○: Domain flaws present

◐: Moderate power

Study	*Outcome*	*Week*	*Comparison*	**Prospective**	**Power**	**Group Assignment**	**Blinding**	**Group Comparability**	**Treatment Integrity**	**Measurement**	**Investigator Bias**	*Quality*	**Participants**	**Intervention and Expertise**	**Compliance and Adherence**	**Analysis**	*Applicability Study*
Kirkley (2008)	McMaster-Toronto Arthritis Patient Preference Disability Questionnaire (MACTAR)	13	Arthroscopic surgery with debridement and lavage versus usual care	●	◐	○	●	○	●	●	●	**Moderate**	○	○	●	●	**Moderate**
Kirkley (2008)	McMaster-Toronto Arthritis Patient Preference Disability Questionnaire (MACTAR)	26	Arthroscopic surgery with debridement and lavage versus usual care	●	◐	○	●	○	●	●	●	**Moderate**	○	○	●	●	**Moderate**

●: Domain free of flaws

○: Domain flaws present

◐: Moderate power

Study	*Outcome*	*Week*	*Comparison*	**Prospective**	**Power**	**Group Assignment**	**Blinding**	**Group Comparability**	**Treatment Integrity**	**Measurement**	**Investigator Bias**	*Quality*	**Participants**	**Intervention and Expertise**	**Compliance and Adherence**	**Analysis**	*Applicability Study*
Kirkley (2008)	McMaster-Toronto Arthritis Patient Preference Disability Questionnaire (MACTAR)	52	Arthroscopic surgery with debridement and lavage versus usual care	●	◐	○	●	○	●	●	●	**Moderate**	○	○	●	●	**Moderate**
Kirkley (2008)	McMaster-Toronto Arthritis Patient Preference Disability Questionnaire (MACTAR)	78	Arthroscopic surgery with debridement and lavage versus usual care	●	◐	○	●	○	●	●	●	**Moderate**	○	○	●	●	**Moderate**

●: Domain free of flaws

○: Domain flaws present

◐: Moderate power

Study	*Outcome*	*Week*	*Comparison*	**Prospective**	**Power**	**Group Assignment**	**Blinding**	**Group Comparability**	**Treatment Integrity**	**Measurement**	**Investigator Bias**	*Quality*	**Participants**	**Intervention and Expertise**	**Compliance and Adherence**	**Analysis**	*Applicability Study*
Kirkley (2008)	McMaster-Toronto Arthritis Patient Preference Disability Questionnaire (MACTAR)	104	Arthroscopic surgery with debridement and lavage versus usual care	●	◐	○	●	○	●	●	●	**Moderate**	○	○	●	●	**Moderate**
Kirkley (2008)	Arthritis Self-Efficacy Score: Other Arthritis Related Symptoms	13	Arthroscopic surgery with debridement and lavage versus usual care	●	◐	○	●	○	●	●	●	**Moderate**	○	○	●	●	**Moderate**

●: Domain free of flaws

○: Domain flaws present

◐: Moderate power

Study	*Outcome*	*Week*	*Comparison*	**Prospective**	**Power**	**Group Assignment**	**Blinding**	**Group Comparability**	**Treatment Integrity**	**Measurement**	**Investigator Bias**	*Quality*	**Participants**	**Intervention and Expertise**	**Compliance and Adherence**	**Analysis**	*Applicability Study*
Kirkley (2008)	Arthritis Self-Efficacy Score: Other Arthritis Related Symptoms	26	Arthroscopic surgery with debridement and lavage versus usual care	●	◐	○	●	○	●	●	●	**Moderate**	○	○	●	●	**Moderate**
Kirkley (2008)	Arthritis Self-Efficacy Score: Other Arthritis Related Symptoms	52	Arthroscopic surgery with debridement and lavage versus usual care	●	◐	○	●	○	●	●	●	**Moderate**	○	○	●	●	**Moderate**

●: Domain free of flaws

○: Domain flaws present

◐: Moderate power

Study	*Outcome*	*Week*	*Comparison*	**Prospective**	**Power**	**Group Assignment**	**Blinding**	**Group Comparability**	**Treatment Integrity**	**Measurement**	**Investigator Bias**	*Quality*	**Participants**	**Intervention and Expertise**	**Compliance and Adherence**	**Analysis**	*Applicability Study*
Kirkley (2008)	Arthritis Self-Efficacy Score: Other Arthritis Related Symptoms	78	Arthroscopic surgery with debridement and lavage versus usual care	●	◐	○	●	○	●	●	●	**Moderate**	○	○	●	●	**Moderate**
Kirkley (2008)	Arthritis Self-Efficacy Score: Other Arthritis Related Symptoms	104	Arthroscopic surgery with debridement and lavage versus usual care	●	◐	○	●	○	●	●	●	**Moderate**	○	○	●	●	**Moderate**
Moseley (2000)	Arthritis Impact Measurement Scale: Pain	13	Debridement versus Placebo	●	◐	●	●	●	●	●	●	**High**	○	○	●	○	**Moderate**

●: Domain free of flaws

○: Domain flaws present

◐: Moderate power

Study	*Outcome*	*Week*	*Comparison*	**Prospective**	**Power**	**Group Assignment**	**Blinding**	**Group Comparability**	**Treatment Integrity**	**Measurement**	**Investigator Bias**	*Quality*	**Participants**	**Intervention and Expertise**	**Compliance and Adherence**	**Analysis**	*Applicability Study*
Moseley (2000)	Arthritis Impact Measurement Scale: Pain	26	Debridement versus Placebo	●	◐	●	●	●	●	●	●	**High**	○	○	●	○	**Moderate**
Moseley (2000)	Arthritis Impact Measurement Scale: Pain	52	Debridement versus Placebo	●	◐	●	●	●	●	●	●	**High**	○	○	●	○	**Moderate**
Moseley (2000)	Arthritis Impact Measurement Scale: Pain	78	Debridement versus Placebo	●	◐	●	●	●	●	●	●	**High**	○	○	●	○	**Moderate**

●: Domain free of flaws

○: Domain flaws present

◐: Moderate power

Study	*Outcome*	*Week*	*Comparison*	**Prospective**	**Power**	**Group Assignment**	**Blinding**	**Group Comparability**	**Treatment Integrity**	**Measurement**	**Investigator Bias**	*Quality*	**Participants**	**Intervention and Expertise**	**Compliance and Adherence**	**Analysis**	*Applicability Study*
Moseley (2002)	Arthritis Impact Measurement Scale: Pain	104	Debridement versus Placebo	●	◐	●	●	●	●	●	●	**High**	○	○	●	○	**Moderate**
Moseley (2002)	Arthritis Impact Measurement Scale: Walking-Bending	6	Debridement versus Placebo	●	◐	●	●	●	●	●	●	**High**	○	○	●	○	**Moderate**
Moseley (2002)	Arthritis Impact Measurement Scale: Walking-Bending	13	Debridement versus Placebo	●	◐	●	●	●	●	●	●	**High**	○	○	●	○	**Moderate**

●: Domain free of flaws

○: Domain flaws present

◐: Moderate power

Study	*Outcome*	*Week*	*Comparison*	**Prospective**	**Power**	**Group Assignment**	**Blinding**	**Group Comparability**	**Treatment Integrity**	**Measurement**	**Investigator Bias**	*Quality*	**Participants**	**Intervention and Expertise**	**Compliance and Adherence**	**Analysis**	*Applicability Study*
Moseley (2002)	Arthritis Impact Measurement Scale: Walking-Bending	26	Debridement versus Placebo	●	◐	●	●	●	●	●	●	**High**	○	○	●	○	**Moderate**
Moseley (2002)	Arthritis Impact Measurement Scale: Walking-Bending	52	Debridement versus Placebo	●	◐	●	●	●	●	●	●	**High**	○	○	●	○	**Moderate**

●: Domain free of flaws

○: Domain flaws present

◐: Moderate power

Study	*Outcome*	*Week*	*Comparison*	**Prospective**	**Power**	**Group Assignment**	**Blinding**	**Group Comparability**	**Treatment Integrity**	**Measurement**	**Investigator Bias**	*Quality*	**Participants**	**Intervention and Expertise**	**Compliance and Adherence**	**Analysis**	*Applicability Study*
Moseley (2002)	Arthritis Impact Measurement Scale: Walking-Bending	78	Debridement versus Placebo	●	◐	●	●	●	●	●	●	**High**	○	○	●	○	**Moderate**
Moseley (2002)	Arthritis Impact Measurement Scale: Walking-Bending	104	Debridement versus Placebo	●	◐	●	●	●	●	●	●	**High**	○	○	●	○	**Moderate**
Moseley (2002)	Arthritis Impact Measurement Scale: Pain	6	Debridement versus lavage	●	◐	●	●	●	●	●	●	**High**	○	○	●	○	**Moderate**

●: Domain free of flaws

○: Domain flaws present

◐: Moderate power

Study	*Outcome*	*Week*	*Comparison*	Prospective	Power	Group Assignment	Blinding	Group Comparability	Treatment Integrity	Measurement	Investigator Bias	*Quality*	Participants	Intervention and Expertise	Compliance and Adherence	Analysis	*Applicability Study*
Moseley (2002)	Arthritis Impact Measurement Scale: Pain	13	Debridement versus lavage	●	◐	●	●	●	●	●	●	**High**	○	○	●	○	**Moderate**
Moseley (2002)	Arthritis Impact Measurement Scale: Pain	26	Debridement versus lavage	●	◐	●	●	●	●	●	●	**High**	○	○	●	○	**Moderate**
Moseley (2002)	Arthritis Impact Measurement Scale: Pain	52	Debridement versus lavage	●	◐	●	●	●	●	●	●	**High**	○	○	●	○	**Moderate**

●: Domain free of flaws

○: Domain flaws present

◐: Moderate power

Study	*Outcome*	*Week*	*Comparison*	**Prospective**	**Power**	**Group Assignment**	**Blinding**	**Group Comparability**	**Treatment Integrity**	**Measurement**	**Investigator Bias**	*Quality*	**Participants**	**Intervention and Expertise**	**Compliance and Adherence**	**Analysis**	*Applicability Study*
Moseley (2002)	Arthritis Impact Measurement Scale: Pain	78	Debridement versus lavage	●	◐	●	●	●	●	●	●	**High**	○	○	●	○	**Moderate**
Moseley (2002)	Arthritis Impact Measurement Scale: Pain	104	Debridement versus lavage	●	◐	●	●	●	●	●	●	**High**	○	○	●	○	**Moderate**
Moseley (2002)	Arthritis Impact Measurement Scale: Walking-Bending	6	Debridement versus lavage	●	◐	●	●	●	●	●	●	**High**	○	○	●	○	**Moderate**

●: Domain free of flaws

○: Domain flaws present

◐: Moderate power

Study	*Outcome*	*Week*	*Comparison*	**Prospective**	**Power**	**Group Assignment**	**Blinding**	**Group Comparability**	**Treatment Integrity**	**Measurement**	**Investigator Bias**	*Quality*	**Participants**	**Intervention and Expertise**	**Compliance and Adherence**	**Analysis**	*Applicability Study*
Moseley (2002)	Arthritis Impact Measurement Scale: Walking-Bending	13	Debridement versus lavage	●	◐	●	●	●	●	●	●	**High**	○	○	●	○	**Moderate**
Moseley (2002)	Arthritis Impact Measurement Scale: Walking-Bending	26	Debridement versus lavage	●	◐	●	●	●	●	●	●	**High**	○	○	●	○	**Moderate**

●: Domain free of flaws

○: Domain flaws present

◐: Moderate power

Study	*Outcome*	*Week*	*Comparison*	**Prospective**	**Power**	**Group Assignment**	**Blinding**	**Group Comparability**	**Treatment Integrity**	**Measurement**	**Investigator Bias**	*Quality*	**Participants**	**Intervention and Expertise**	**Compliance and Adherence**	**Analysis**	*Applicability Study*
Moseley (2002)	Arthritis Impact Measurement Scale: Walking-Bending	52	Debridement versus lavage	●	◐	●	●	●	●	●	●	**High**	○	○	●	○	**Moderate**
Moseley (2002)	Arthritis Impact Measurement Scale: Walking-Bending	78	Debridement versus lavage	●	◐	●	●	●	●	●	●	**High**	○	○	●	○	**Moderate**

●: Domain free of flaws

○: Domain flaws present

◐: Moderate power

Study	*Outcome*	*Week*	*Comparison*	**Prospective**	**Power**	**Group Assignment**	**Blinding**	**Group Comparability**	**Treatment Integrity**	**Measurement**	**Investigator Bias**	*Quality*	**Participants**	**Intervention and Expertise**	**Compliance and Adherence**	**Analysis**	*Applicability Study*
Moseley (2002)	Arthritis Impact Measurement Scale: Walking-Bending	104	Debridement versus lavage	●	◐	●	●	●	●	●	●	**High**	○	○	●	○	**Moderate**
Moseley (2002)	Arthritis Impact Measurement Scale: Pain	6	Lavage versus Placebo	●	◐	●	●	●	●	●	●	**High**	○	○	●	○	**Moderate**
Moseley (2002)	Arthritis Impact Measurement Scale: Pain	13	Lavage versus Placebo	●	◐	●	●	●	●	●	●	**High**	○	○	●	○	**Moderate**

●: Domain free of flaws

○: Domain flaws present

◐: Moderate power

Study	*Outcome*	*Week*	*Comparison*	**Prospective**	**Power**	**Group Assignment**	**Blinding**	**Group Comparability**	**Treatment Integrity**	**Measurement**	**Investigator Bias**	*Quality*	**Participants**	**Intervention and Expertise**	**Compliance and Adherence**	**Analysis**	*Applicability Study*
Moseley (2002)	Arthritis Impact Measurement Scale: Pain	26	Lavage versus Placebo	●	◐	●	●	●	●	●	●	**High**	○	○	●	○	**Moderate**
Moseley (2002)	Arthritis Impact Measurement Scale: Pain	52	Lavage versus Placebo	●	◐	●	●	●	●	●	●	**High**	○	○	●	○	**Moderate**
Moseley (2002)	Arthritis Impact Measurement Scale: Pain	78	Lavage versus Placebo	●	◐	●	●	●	●	●	●	**High**	○	○	●	○	**Moderate**

●: Domain free of flaws

○: Domain flaws present

◐: Moderate power

Study	*Outcome*	*Week*	*Comparison*	**Prospective**	**Power**	**Group Assignment**	**Blinding**	**Group Comparability**	**Treatment Integrity**	**Measurement**	**Investigator Bias**	*Quality*	**Participants**	**Intervention and Expertise**	**Compliance and Adherence**	**Analysis**	*Applicability Study*
Moseley (2002)	Arthritis Impact Measurement Scale: Pain	104	Lavage versus Placebo	●	◐	●	●	●	●	●	●	**High**	○	○	●	○	**Moderate**
Moseley (2002)	Arthritis Impact Measurement Scale: Walking-Bending	6	Lavage versus Placebo	●	◐	●	●	●	●	●	●	**High**	○	○	●	○	**Moderate**
Moseley (2002)	Arthritis Impact Measurement Scale: Walking-Bending	13	Lavage versus Placebo	●	◐	●	●	●	●	●	●	**High**	○	○	●	○	**Moderate**

●: Domain free of flaws

○: Domain flaws present

◐: Moderate power

Study	*Outcome*	*Week*	*Comparison*	**Prospective**	**Power**	**Group Assignment**	**Blinding**	**Group Comparability**	**Treatment Integrity**	**Measurement**	**Investigator Bias**	*Quality*	**Participants**	**Intervention and Expertise**	**Compliance and Adherence**	**Analysis**	*Applicability Study*
Moseley (2002)	Arthritis Impact Measurement Scale: Walking-Bending	26	Lavage versus Placebo	●	◐	●	●	●	●	●	●	**High**	○	○	●	○	**Moderate**
Moseley (2002)	Arthritis Impact Measurement Scale: Walking-Bending	52	Lavage versus Placebo	●	◐	●	●	●	●	●	●	**High**	○	○	●	○	**Moderate**

●: Domain free of flaws

○: Domain flaws present

◐: Moderate power

Study	*Outcome*	*Week*	*Comparison*	**Prospective**	**Power**	**Group Assignment**	**Blinding**	**Group Comparability**	**Treatment Integrity**	**Measurement**	**Investigator Bias**	*Quality*	**Participants**	**Intervention and Expertise**	**Compliance and Adherence**	**Analysis**	*Applicability Study*
Moseley (2002)	Arthritis Impact Measurement Scale: Walking-Bending	78	Lavage versus Placebo	●	◐	●	●	●	●	●	●	**High**	○	○	●	○	**Moderate**
Moseley (2002)	Arthritis Impact Measurement Scale: Walking-Bending	104	Lavage versus Placebo	●	◐	●	●	●	●	●	●	**High**	○	○	●	○	**Moderate**

FINDINGS

Table 206. Debridement Versus Placebo: Pain

Study	Outcome	N	Sufficient Power to Detect MCII	Week	Severity	Group 1	Group 2	SMD (Odds Ratio or Raw Mean Difference When Indicated)	Sig	Clinical Importance	Strength of Evidence
Moseley (2002)	Arthritis Impact Measurement Scale: Pain	116	Unclear	6	K-L 0-4	Debridement	Placebo	-0.04 (-0.40, 0.33)	No	N/A	High
Moseley (2002)	Arthritis Impact Measurement Scale: Pain	114	Unclear	13	K-L 0-4	Debridement	Placebo	-0.01 (-0.38, 0.36)	No	N/A	High
Moseley (2002)	Arthritis Impact Measurement Scale: Pain	112	Unclear	26	K-L 0-4	Debridement	Placebo	0.10 (-0.27, 0.47)	No	N/A	High
Moseley (2002)	Arthritis Impact Measurement Scale: Pain	105	Unclear	52	K-L 0-4	Debridement	Placebo	-0.01 (-0.40, 0.37)	No	N/A	High
Moseley (2002)	Arthritis Impact Measurement Scale: Pain	103	Unclear	78	K-L 0-4	Debridement	Placebo	-0.20 (-0.59, 0.18)	No	N/A	High

Study	Outcome	N	Sufficient Power to Detect MCII	Week	Severity	Group 1	Group 2	SMD (Odds Ratio or Raw Mean Difference When Indicated)	Sig	Clinical Importance	Strength of Evidence
Moseley (2002)	Arthritis Impact Measurement Scale: Pain	108	Unclear	104	K-L 0-4	Debridement	Placebo	0.06 (-0.32, 0.44)	No	N/A	High

Table 207. Debridement Versus Placebo: Function

Study	Outcome	N	Sufficient Power to Detect MCII	Week	Severity	Group 1	Group 2	SMD (Odds Ratio or Raw Mean Difference When Indicated)	Sig	Clinical Importance	Strength of Evidence
Moseley (2002)	Arthritis Impact Measurement Scale: Walking-Bending	116	Unclear	6	K-L 0-4	Debridement	Placebo	0.10 (-0.27, 0.46)	No	N/A	High

Study	Outcome	N	Sufficient Power to Detect MCII	Week	Severity	Group 1	Group 2	SMD (Odds Ratio or Raw Mean Difference When Indicated)	Sig	Clinical Importance	Strength of Evidence
Moseley (2002)	Arthritis Impact Measurement Scale: Walking-Bending	114	Unclear	13	K-L 0-4	Debridement	Placebo	0.14 (-0.23, 0.51)	No	N/A	High
Moseley (2002)	Arthritis Impact Measurement Scale: Walking-Bending	112	Unclear	26	K-L 0-4	Debridement	Placebo	0.12 (-0.25, 0.49)	No	N/A	High
Moseley (2002)	Arthritis Impact Measurement Scale: Walking-Bending	105	Unclear	52	K-L 0-4	Debridement	Placebo	0.26 (-0.13, 0.64)	No	N/A	High

Study	Outcome	N	Sufficient Power to Detect MCII	Week	Severity	Group 1	Group 2	SMD (Odds Ratio or Raw Mean Difference When Indicated)	Sig	Clinical Importance	Strength of Evidence
Moseley (2002)	Arthritis Impact Measurement Scale: Walking-Bending	103	Unclear	78	K-L 0-4	Debridement	Placebo	-0.09 (-0.48, 0.30)	No	N/A	High
Moseley (2002)	Arthritis Impact Measurement Scale: Walking-Bending	108	Unclear	104	K-L 0-4	Debridement	Placebo	0.09 (-0.29, 0.47)	No	N/A	High

Table 208. Debridement Versus Lavage: Pain

Study	Outcome	N	Sufficient Power to Detect MCII	Week	Severity	Group 1	Group 2	SMD (Odds Ratio or Raw Mean Difference When Indicated)	Sig	Clinical Importance	Strength of Evidence

Study	Outcome	N	Sufficient Power to Detect MCII	Week	Severity	Group 1	Group 2	SMD (Odds Ratio or Raw Mean Difference When Indicated)	Sig	Clinical Importance	Strength of Evidence
Moseley (2002)	Arthritis Impact Measurement Scale: Pain	116	Unclear	6	K-L 0-4	Debridement	Lavage	-0.11 (-0.47, 0.25)	No	N/A	High
Moseley (2002)	Arthritis Impact Measurement Scale: Pain	114	Unclear	13	K-L 0-4	Debridement	Lavage	-0.17 (-0.53, 0.19)	No	N/A	High
Moseley (2002)	Arthritis Impact Measurement Scale: Pain	112	Unclear	26	K-L 0-4	Debridement	Lavage	-0.13 (-0.50, 0.24)	No	N/A	High
Moseley (2002)	Arthritis Impact Measurement Scale: Pain	105	Unclear	52	K-L 0-4	Debridement	Lavage	-0.18 (-0.56, 0.20)	No	N/A	High
Moseley (2002)	Arthritis Impact Measurement Scale: Pain	103	Unclear	78	K-L 0-4	Debridement	Lavage	-0.19 (-0.57, 0.19)	No	N/A	High

Study	Outcome	N	Sufficient Power to Detect MCII	Week	Severity	Group 1	Group 2	SMD (Odds Ratio or Raw Mean Difference When Indicated)	Sig	Clinical Importance	Strength of Evidence
Moseley (2002)	Arthritis Impact Measurement Scale: Pain	108	Unclear	104	K-L 0-4	Debridement	Lavage	-0.11 (-0.49, 0.26)	No	N/A	High

Table 209. Debridement Versus Lavage: Function

Study	Outcome	N	Sufficient Power to Detect MCII	Week	Severity	Group 1	Group 2	SMD (Odds Ratio or Raw Mean Difference When Indicated)	Sig	Clinical Importance	Strength of Evidence
Moseley (2002)	Arthritis Impact Measurement Scale: Walking-Bending	116	Unclear	6	K-L 0-4	Debridement	Lavage	0.09 (-0.27, 0.45)	No	N/A	High

Study	Outcome	N	Sufficient Power to Detect MCII	Week	Severity	Group 1	Group 2	SMD (Odds Ratio or Raw Mean Difference When Indicated)	Sig	Clinical Importance	Strength of Evidence
Moseley (2002)	Arthritis Impact Measurement Scale: Walking-Bending	114	Unclear	13	K-L 0-4	Debridement	Lavage	0.19 (-0.17, 0.55)	No	N/A	High
Moseley (2002)	Arthritis Impact Measurement Scale: Walking-Bending	112	Unclear	26	K-L 0-4	Debridement	Lavage	0.12 (-0.24, 0.49)	No	N/A	High
Moseley (2002)	Arthritis Impact Measurement Scale: Walking-Bending	105	Unclear	52	K-L 0-4	Debridement	Lavage	0.23 (-0.14, 0.61)	No	N/A	High

Study	Outcome	N	Sufficient Power to Detect MCII	Week	Severity	Group 1	Group 2	SMD (Odds Ratio or Raw Mean Difference When Indicated)	Sig	Clinical Importance	Strength of Evidence
Moseley (2002)	Arthritis Impact Measurement Scale: Walking-Bending	103	Unclear	78	K-L 0-4	Debridement	Lavage	0.09 (-0.29, 0.47)	No	N/A	High
Moseley (2002)	Arthritis Impact Measurement Scale: Walking-Bending	108	Unclear	104	K-L 0-4	Debridement	Lavage	0.18 (-0.19, 0.56)	No	N/A	High

Table 210. Arthroscopic Lavage Versus Placebo: Pain

Study	Outcome	N	Sufficient Power to Detect MCII	Week	Severity	Group 1	Group 2	SMD (Odds Ratio or Raw Mean Difference When Indicated)	Sig	Clinical Importance	Strength of Evidence
Moseley (2002)	Arthritis Impact Measurement Scale: Pain	114	Unclear	6	K-L 0-4	Lavage	Placebo	0.07 (-0.30, 0.44)	No	N/A	High
Moseley (2002)	Arthritis Impact Measurement Scale: Pain	115	Unclear	13	K-L 0-4	Lavage	Placebo	0.16 (-0.21, 0.53)	No	N/A	High
Moseley (2002)	Arthritis Impact Measurement Scale: Pain	116	Unclear	26	K-L 0-4	Lavage	Placebo	0.23 (-0.14, 0.59)	No	N/A	High
Moseley (2002)	Arthritis Impact Measurement Scale: Pain	111	Unclear	52	K-L 0-4	Lavage	Placebo	0.18 (-0.19, 0.56)	No	N/A	High
Moseley (2002)	Arthritis Impact Measurement Scale: Pain	109	Unclear	78	K-L 0-4	Lavage	Placebo	-0.01 (-0.38, 0.37)	No	N/A	High
Moseley (2002)	Arthritis Impact Measurement Scale: Pain	111	Unclear	104	K-L 0-4	Lavage	Placebo	0.17 (-0.20, 0.54)	No	N/A	High

Table 211. Arthroscopic Lavage Versus Placebo: Function

Study	Outcome	N	Sufficient Power to Detect MCII	Week	Severity	Group 1	Group 2	SMD (Odds Ratio or Raw Mean Difference When Indicated)	Sig	Clinical Importance	Strength of Evidence
Moseley (2002)	Arthritis Impact Measurement Scale: Walking-Bending	114	Unclear	6	K-L 0-4	Lavage	Placebo	-0.00 (-0.37, 0.36)	No	N/A	High
Moseley (2002)	Arthritis Impact Measurement Scale: Walking-Bending	115	Unclear	13	K-L 0-4	Lavage	Placebo	-0.08 (-0.44, 0.29)	No	N/A	High
Moseley (2002)	Arthritis Impact Measurement Scale: Walking-Bending	116	Unclear	26	K-L 0-4	Lavage	Placebo	-0.01 (-0.38, 0.35)	No	N/A	High

Study	Outcome	N	Sufficient Power to Detect MCII	Week	Severity	Group 1	Group 2	SMD (Odds Ratio or Raw Mean Difference When Indicated)	Sig	Clinical Importance	Strength of Evidence
Moseley (2002)	Arthritis Impact Measurement Scale: Walking-Bending	111	Unclear	52	K-L 0-4	Lavage	Placebo	0.01 (-0.36, 0.38)	No	N/A	High
Moseley (2002)	Arthritis Impact Measurement Scale: Walking-Bending	109	Unclear	78	K-L 0-4	Lavage	Placebo	-0.18 (-0.56, 0.19)	No	N/A	High
Moseley (2002)	Arthritis Impact Measurement Scale: Walking-Bending	111	Unclear	104	K-L 0-4	Lavage	Placebo	-0.10 (-0.47, 0.28)	No	N/A	High

Table 212. Arthroscopic Surgery with Lavage and Debridement Versus Usual Care: Pain

Study	Outcome	N	Sufficient Power	Week	Severity	Group 1	Group 2	SMD (Odds Ratio or Raw Mean Difference When Indicated)	Sig	Clinical Importance	Strength of Evidence
Kirkley (2008)	Arthritis Self-Efficacy Scale: Pain	170	Yes	13	K-L 2 to 4	Arthroscopic surgery with debridement and lavage	Usual care	0.32 (0.02, 0.63)	Favors surgery with lavage and debridement	N/A	Moderate
Kirkley (2008)	Arthritis Self-Efficacy Scale: Pain	163	Unclear	26	2 to 4	Arthroscopic surgery with debridement and lavage	Usual care	0.21 (-0.10, 0.52)	No	N/A	Moderate
Kirkley (2008)	Arthritis Self-Efficacy Scale: Pain	157	Unclear	52	2 to 4	Arthroscopic surgery with debridement and lavage	Usual care	0.05 (-0.26, 0.37)	No	N/A	Moderate

Study	Outcome	N	Sufficient Power	Week	Severity	Group 1	Group 2	SMD (Odds Ratio or Raw Mean Difference When Indicated)	Sig	Clinical Importance	Strength of Evidence
Kirkley (2008)	Arthritis Self-Efficacy Scale: Pain	148	Unclear	78	2 to 4	Arthroscopic surgery with debridement and lavage	Usual care	0.17 (-0.16, 0.49)	No	N/A	Moderate
Kirkley (2008)	Arthritis Self-Efficacy Scale: Pain	168	Unclear	104	2 to 4	Arthroscopic surgery with debridement and lavage	Usual care	0.26 (-0.04, 0.56)	No	N/A	Moderate

Table 213. Arthroscopic Surgery with Lavage and Debridement Versus Usual Care: Function

Study	Outcome	N	Powered	Week	Severity	Group 1	Group 2	SMD (Odds Ratio or Raw Mean Difference When Indicated)	Sig	Clinical Importance	Strength of Evidence
Kirkley (2008)	Arthritis Self-Efficacy Scale: Functional Status	170	Unclear	13	2 to 4	Arthroscopic surgery with debridement and lavage	Usual care	-0.06 (-0.37, 0.25)	No	N/A	Moderate
Kirkley (2008)	Arthritis Self-Efficacy Scale: Functional Status	163	Unclear	26	2 to 4	Arthroscopic Surgery with debridement and lavage	Usual care	0.04 (-0.27, 0.35)	No	N/A	Moderate
Kirkley (2008)	Arthritis Self-Efficacy Scale: Functional Status	157	Unclear	52	2 to 4	Arthroscopic Surgery with debridement and lavage	Usual care	-0.17 (-0.48, 0.14)	No	N/A	Moderate
Kirkley (2008)	Arthritis Self-Efficacy Scale: Functional Status	148	Unclear	78	2 to 4	Arthroscopic Surgery with debridement and lavage	Usual care	-0.06 (-0.39, 0.26)	No	N/A	Moderate

Study	Outcome	N	Powered	Week	Severity	Group 1	Group 2	SMD (Odds Ratio or Raw Mean Difference When Indicated)	Sig	Clinical Importance	Strength of Evidence
Kirkley (2008)	Arthritis Self-Efficacy Scale: Functional Status	168	Unclear	104	2 to 4	Arthroscopic Surgery with debridement and lavage	Usual care	0.09 (-0.21, 0.39)	No	N/A	Moderate
Kirkley (2008)	McMaster-Toronto Arthritis Patient Preference Disability Questionnaire (MACTAR)	170	Unclear	13	2 to 4	Arthroscopic Surgery with debridement and lavage	Usual care	0.07 (-0.23, 0.37)	No	N/A	Moderate
Kirkley (2008)	McMaster-Toronto Arthritis Patient Preference Disability Questionnaire (MACTAR)	163	Unclear	26	2 to 4	Arthroscopic surgery with debridement and lavage	Usual care	-0.10 (-0.41, 0.21)	No	N/A	Moderate

Study	Outcome	N	Powered	Week	Severity	Group 1	Group 2	SMD (Odds Ratio or Raw Mean Difference When Indicated)	Sig	Clinical Importance	Strength of Evidence
Kirkley (2008)	McMaster-Toronto Arthritis Patient Preference Disability Questionnaire (MACTAR)	157	Unclear	52	2 to 4	Arthroscopic surgery with debridement and lavage	Usual care	0.06 (-0.26, 0.37)	No	N/A	Moderate
Kirkley (2008)	McMaster-Toronto Arthritis Patient Preference Disability Questionnaire (MACTAR)	148	Unclear	78	2 to 4	Arthroscopic surgery with debridement and lavage	Usual care	0.23 (-0.09, 0.55)	No	N/A	Moderate

Study	Outcome	N	Powered	Week	Severity	Group 1	Group 2	SMD (Odds Ratio or Raw Mean Difference When Indicated)	Sig	Clinical Importance	Strength of Evidence
Kirkley (2008)	McMaster-Toronto Arthritis Patient Preference Disability Questionnaire (MACTAR)	168	Unclear	104	2 to 4	Arthroscopic surgery with debridement and lavage	Usual care	-0.04 (-0.35, 0.26)	No	N/A	Moderate

Table 214. Arthroscopic Surgery with Lavage and Debridement Versus Usual Care: Arthritis Self-Efficacy Score (Other Arthritis Related Symptoms)

Study	N	Sufficient Power to Detect MCII	Week	Severity	Group 1	Group 2	SMD (Odds Ratio or Raw Mean Difference When Indicated)	Sig	Clinical Importance	Strength of Evidence
Kirkley (2008)	148	Unclear	13	K-L 2 to 4	Arthroscopic Surgery with debridement and lavage	Usual care	0.16 (-0.14, 0.47)	No	N/A	Moderate
Kirkley (2008)	148	Unclear	26	K-L 2 to 4	Arthroscopic Surgery with debridement and lavage	Usual care	0.26 (-0.05, 0.57)	No	N/A	Moderate
Kirkley (2008)	148	Unclear	52	K-L 2 to 4	Arthroscopic Surgery with debridement and lavage	Usual care	0.13 (-0.18, 0.44)	No	N/A	Moderate
Kirkley (2008)	148	Unclear	78	K-L 2 to 4	Arthroscopic Surgery with debridement and lavage	Usual care	0.18 (-0.14, 0.51)	No	N/A	Moderate
Kirkley (2008)	148	Unclear	104	K-L 2 to 4	Arthroscopic Surgery with debridement and lavage	Usual care	0.31 (0.01, 0.62)	Favors surgery	N/A	Moderate

Table 215. Full Versus Minimal Irrigation at One Year

Study	Outcome	N	Powered	Severity	Group 1	Group 2	SMD (Odds Ratio or Raw Mean Difference When Indicated)	Sig	Clinical Importance	Strength of Evidence
Kaluni an (2000)	WOMAC Pain	90	Yes	K-L 0-2	Full irrigation	Minimal irrigation	-0.15 (-0.56, 0.27)	No	Inconclusive	Low
Kaluni an (2000)	VAS Pain	90	Yes	K-L 0-2	Full irrigation	Minimal irrigation	-0.23 (-0.65, 0.19)	No	True negative	Low

RECOMMENDATION 13

We are unable to recommend for or against arthroscopic partial meniscectomy in patients with osteoarthritis of the knee with a torn meniscus.

Strength of Recommendation: Inconclusive

Description: Evidence from a single low quality study or conflicting findings that do not allow a recommendation for or against the intervention. An **Inconclusive** recommendation means that there is a lack of compelling evidence that has resulted in an unclear balance between benefits and potential harm.

Implications: Practitioners should feel little constraint in following a recommendation labeled as **Inconclusive,** exercise clinical judgment, and be alert for emerging evidence that clarifies or helps to determine the balance between benefits and potential harm. Patient preference should have a substantial influencing role.

RATIONALE

Currently, arthroscopic partial meniscectomy is routinely performed in patients with symptomatic osteoarthritis of the knee who also have primary signs and symptoms of a torn meniscus.

Herrlin et al.[127] compared arthroscopic partial meniscectomy followed by supervised exercise to supervised exercise alone and measured KOOS pain, symptoms, activities of daily life, sports/recreation, and quality of life subscales scores as outcomes. The study was downgraded from moderate- to low- strength because 40% of patients declined participation and the arthroscopic group had non-homogeneous preoperative KOOS scores. The authors reported no significant treatment benefits of meniscectomy using any of the outcomes at eight weeks and six months. Since there was only one low-strength study, the recommendation was graded inconclusive.

SUPPORTING EVIDENCE

QUALITY

Relevant Tables: Table 216-Table 217

One moderate quality study by Herrlin et al.[127] met the inclusion criteria for this recommendation. The study was flawed in the group assignment, group comparability and investigator bias domains.

APPLICABILITY

Relevant Tables: Table 216-Table 217

The patients and the treatment administration might not have been representative of typical clinical practice settings.

FINAL STRENGTH OF EVIDENCE

Ratings of moderate quality and applicability resulted in a moderate strength of evidence rating for all included outcomes in the study.

Table 216. Quality and Applicability Summary: Arthroscopic Partial Meniscectomy

Study	Outcome	Quality	Applicability	Strength of Evidence
Herrlin (2007)	KOOS Pain Week 8	Moderate	Moderate	Moderate
Herrlin (2007)	KOOS Symptoms Week 8	Moderate	Moderate	Moderate
Herrlin (2007)	KOOS Activities of Daily Life Week 8	Moderate	Moderate	Moderate
Herrlin (2007)	KOOS Sports/Rec Week 8	Moderate	Moderate	Moderate
Herrlin (2007)	KOOS Quality of Life Week 8	Moderate	Moderate	Moderate
Herrlin (2007)	KOOS Pain 6 months	Moderate	Moderate	Moderate
Herrlin (2007)	KOOS Symptoms 6 months	Moderate	Moderate	Moderate
Herrlin (2007)	KOOS Activities of Daily Life 6 months	Moderate	Moderate	Moderate
Herrlin (2007)	KOOS Sports/Rec 6 months	Moderate	Moderate	Moderate
Herrlin (2007)	KOOS Quality of Life 6 months	Moderate	Moderate	Moderate

RESULTS

Relevant Tables: Table 218

KOOS pain, symptoms, activities of daily life, sports/recreation, and quality of life subscales were the outcomes studied by Herrlin et al.[127]The authors reported no significant treatment benefits of meniscectomy using any of the outcomes at eight weeks and six months.

EVIDENCE TABLES AND FIGURES

QUALITY AND APPLICABILITY

Table 217. Quality and Applicability: Partial Meniscectomy with Exercise Versus Exercise Only

●: Domain free of flaws

○: Domain flaws present

◐: Moderate power

Study	*Outcome*	Prospective	Power	Group Assignment	Blinding	Group Comparability	Treatment Integrity	Measurement	Investigator Bias	*Quality*	Participants	Intervention and Expertise	Compliance and Adherence	Analysis	*Applicability Study*
Herrlin (2007)	KOOS Pain Week 8	●	◐	○	●	○	●	●	○	**Moderate**	○	○	●	●	**Moderate**
Herrlin (2007)	KOOS Symptoms Week 8	●	◐	○	●	○	●	●	○	**Moderate**	○	○	●	●	**Moderate**
Herrlin (2007)	KOOS Activities of Daily Life Week 8	●	◐	○	●	○	●	●	○	**Moderate**	○	○	●	●	**Moderate**
Herrlin (2007)	KOOS Sports/Rec Week 8	●	◐	○	●	○	●	●	○	**Moderate**	○	○	●	●	**Moderate**
Herrlin (2007)	KOOS Quality of Life Week 8	●	◐	○	●	○	●	●	○	**Moderate**	○	○	●	●	**Moderate**

●: Domain free of flaws

○: Domain flaws present

◐: Moderate power

Study	*Outcome*	**Prospective**	**Power**	**Group Assignment**	**Blinding**	**Group Comparability**	**Treatment Integrity**	**Measurement**	**Investigator Bias**	*Quality*	**Participants**	**Intervention and Expertise**	**Compliance and Adherence**	**Analysis**	*Applicability Study*
Herrlin (2007)	KOOS Pain 6 months	●	◐	○	●	○	●	●	○	**Moderate**	○	○	●	●	**Moderate**
Herrlin (2007)	KOOS Symptoms 6 months	●	◐	○	●	○	●	●	○	**Moderate**	○	○	●	●	**Moderate**
Herrlin (2007)	KOOS Activities of Daily Life 6 months	●	◐	○	●	○	●	●	○	**Moderate**	○	○	●	●	**Moderate**
Herrlin (2007)	KOOS Sports/Rec 6 months	●	◐	○	●	○	●	●	○	**Moderate**	○	○	●	●	**Moderate**
Herrlin (2007)	KOOS Quality of Life 6 months	●	◐	○	●	○	●	●	○	**Moderate**	○	○	●	●	**Moderate**

FINDINGS

Table 218. Exercise and Meniscectomy Versus Exercise Only (Herrlin et al., 2007)

Outcome	N	Sufficient Power	Week	Age	Ahlback Grade	Meniscal Tear	Loose Bodies	Group 1	Group 2	Author Reported Results
KOOS Pain	90	Unclear	8	45-64	0-1	Yes	No	Exercise plus meniscectomy	Exercise only	Not Statistically Significant
KOOS Symptoms	90	Unclear	8	45-64	0-1	Yes	No	Exercise plus meniscectomy	Exercise only	Not Statistically Significant
KOOS Activities of Daily Life	90	Unclear	8	45-64	0-1	Yes	No	Exercise plus meniscectomy	Exercise only	Not Statistically Significant
KOOS Sports/Rec	90	Unclear	8	45-64	0-1	Yes	No	Exercise plus meniscectomy	Exercise only	Not Statistically Significant
KOOS Quality of Life	90	Unclear	8	45-64	0-1	Yes	No	Exercise plus meniscectomy	Exercise only	Not Statistically Significant
KOOS Pain	90	Unclear	26	45-64	0-1	Yes	No	Exercise plus meniscectomy	Exercise only	Not Statistically Significant

Outcome	N	Sufficient Power	Week	Age	Ahlback Grade	Meniscal Tear	Loose Bodies	Group 1	Group 2	Author Reported Results
KOOS Symptoms	90	Unclear	26	45-64	0-1	Yes	No	Exercise plus meniscectomy	Exercise only	Not Statistically Significant
KOOS Activities of Daily Life	90	Unclear	26	45-64	0-1	Yes	No	Exercise plus meniscectomy	Exercise only	Not Statistically Significant
KOOS Sports/Rec	90	Unclear	26	45-64	0-1	Yes	No	Exercise plus meniscectomy	Exercise only	Not Statistically Significant
KOOS Quality of Life	90	Unclear	26	45-64	0-1	Yes	No	Exercise plus meniscectomy	Exercise only	Not Statistically Significant

RECOMMENDATION 14

The practitioner might perform a valgus producing proximal tibial osteotomy in patients with symptomatic medial compartment osteoarthritis of the knee.

Strength of Recommendation: Limited

Description: Evidence from two or more "Low" strength studies with consistent findings, or evidence from a single Moderate quality study recommending for or against the intervention or diagnostic. A **Limited** recommendation means that the quality of the supporting evidence is unconvincing, or that well-conducted studies show little clear advantage to one approach over another.

Implications: Practitioners should exercise clinical judgment when following a recommendation classified as **Limited**, and should be alert to emerging evidence that might counter the current findings. Patient preference should have a substantial influencing role.

RATIONALE

Nine low-strength case series studies found nine out of 10 outcomes significantly improved from baseline. A cross-sectional time series regression analysis was used to predict the placebo effect on VAS pain for comparison to that of the treatment group. Compared to the predicted placebo effect on VAS pain, the proximal tibial osteotomy group reported decreased pain on the VAS.

Based on a lack of appropriate studies, distal femoral (varus producing) osteotomy was not evaluated.

SUPPORTING EVIDENCE

QUALITY

Relevant Tables: Table 219-Table 220, Table 221-Table 222

Data on 48 outcomes in nine studies were analyzed for this recommendation. Eight studies were prospective case series, and were flawed in the group assignment, blinding, group comparability, and treatment integrity domains. Six included studies had some form of investigator bias. All studies used valid measurements for the outcomes. All eight case series studies were given low quality ratings.

Two additional studies were included that compared closed to open wedge osteotomy. Brouwer et al.[128] was not flawed in six of the seven quality domains, giving it a high rating. Its only quality flaw was that the evaluators were not blinded to the treatment patients received. The Song et al.[129] study was of low quality, and was flawed in every domain except treatment integrity and measurement validity.

APPLICABILITY

Relevant Tables: Table 219-Table 220, Table 221-Table 222

All case series studies were rated as having moderate applicability. Each study raised uncertainty about whether or not the treatment and practitioners who administered them were typical of those encountered in clinical practice. Patients in four out of eight case series studies might not have been representative of the treatment seeking population.

Two case series studies did not include all enrolled patients in the final data analyses of its outcomes. The applicability of the studies comparing open to closed wedge osteotomy was rated as moderate. There was uncertainty regarding whether the treatment and practitioners who administered them were similar to those seen in typical clinical practice.

FINAL STRENGTH OF EVIDENCE

Since all the case series osteotomy outcomes were of low quality and were paired with moderate applicability ratings, they were evaluated as comprising low strength of evidence. Of the studies that compared open to closed wedge osteotomy, one was of high and the other was of low strength of evidence.

Table 219. Quality and Applicability Summary: Osteotomy

Study	Outcome	Duration	Quality	Applicability	Strength of Evidence
Bachhal (2005)	Pin tract infection	Final follow-up	Low	Moderate	Low
Bachhal (2005)	Lateral cortex fracture	Final follow-up	Low	Moderate	Low
Bachhal (2005)	Delayed union	Final follow-up	Low	Moderate	Low
Bachhal (2005)	Knee stiffness	Final follow-up	Low	Moderate	Low
Bachhal (2005)	Ring sequestrum	Final follow-up	Low	Moderate	Low
Bachhal (2005)	Deep infection/chronic osteomyelitis	Final follow-up	Low	Moderate	Low
Bachhal (2005)	Intraarticular fractures	Final follow-up	Low	Moderate	Low
Bachhal (2005)	Neurovascular injury	Final follow-up	Low	Moderate	Low
Bachhal (2005)	Symptomatic deep-vein thrombosis	Final follow-up	Low	Moderate	Low

Study	Outcome	Duration	Quality	Applicability	Strength of Evidence
El-Azab (2011)	Lysholm-Gillquist	Baseline-post-op	Low	Moderate	Low
El-Azab (2011)	Lysholm-Gillquist 3 months	3 months	Low	Moderate	Low
El-Azab (2011)	Lysholm-Gillquist 6 months	6 months	Low	Moderate	Low
El-Azab (2011)	Lysholm-Gillquist 3 years	3 years	Low	Moderate	Low
Flamme (2003)	N cases of distal deep vein thrombosis (DVT)	10 years	Low	Moderate	Low
Flamme (2003)	N cases of proximal deep vein thrombosis (DVT)	10 years	Low	Moderate	Low
Flamme (2003)	N cases of bony non-union	10 years	Low	Moderate	Low
Flamme (2003)	N cases of lesions of the fibular nerve	10 years	Low	Moderate	Low
Flamme (2003)	N cases of superficial wound infections	10 years	Low	Moderate	Low
Flamme (2003)	Percentage with adverse events	10 years	Low	Moderate	Low
Flamme (2003)	N cases of bony non-union	10 years	Low	Moderate	Low
Flamme (2003)	International Knee Score	Final follow-up	Low	Moderate	Low

Study	Outcome	Duration	Quality	Applicability	Strength of Evidence
Niemeyer (2010)	International Knee Documentation Committee Score	Final follow-up	Low	Moderate	Low
Niemeyer (2010)	Lysholm-Tenger Score	Final follow-up	Low	Moderate	Low
Niemeyer (2010)	Intraarticular fractures	3 years	Low	Moderate	Low
Niemeyer (2010)	Over correction	3 years	Low	Moderate	Low
Niemeyer (2010)	Delayed union	3 years	Low	Moderate	Low
Niemeyer (2010)	Overall adverse events	3 years	Low	Moderate	Low
Pongsoipetch (2009)	Superficial incision wound infection	2 years	Low	Moderate	Low
Pongsoipetch (2009)	Knee Society Score	1 year	Low	Moderate	Low
Pongsoipetch (2009)	Knee Society Score	2 years	Low	Moderate	Low
Pongsoipetch (2009)	VAS Pain	3 months	Low	Moderate	Low
Pongsoipetch (2009)	VAS Pain	6 months	Low	Moderate	Low
Pongsoipetch (2009)	VAS Pain	1 year	Low	Moderate	Low
Pongsoipetch (2009)	VAS Pain	2 years	Low	Moderate	Low

Study	Outcome	Duration	Quality	Applicability	Strength of Evidence
Rudan (1990)	Hospital for Special Surgery-Pain	Final follow-up	Low	Moderate	Low
Rudan (1990)	Hospital for Special Surgery-Function	Final follow-up	Low	Moderate	Low
Saragaglia (2010)	Lysholm-Tenger Score	Final follow-up	Low	Moderate	Low
Saragaglia (2010)	Knee Outcome Osteoarthritis score	Final follow-up	Low	Moderate	Low
Saragaglia (2010)	Lateral tibial plateau fractures	Final follow-up	Low	Moderate	Low
Saragaglia (2010)	Deep vein thrombosis (DVT)	Final follow-up	Low	Moderate	Low
Saragaglia (2010)	Pulmonary embolism	Final follow-up	Low	Moderate	Low
Saragaglia (2010)	Failure of fixation (screw breakage)	Final follow-up	Low	Moderate	Low
Saragaglia (2010)	Loss of angulation	Final follow-up	Low	Moderate	Low
Saragaglia (2010)	TKA Revision	Final follow-up	Low	Moderate	Low
Schroter (2011)	Improvement in Lysholm-Gillquist	1 year	Low	Moderate	Low
Schroter (2011)	Improvement in Tenger activity level	1 year	Low	Moderate	Low

Study	Outcome	Duration	Quality	Applicability	Strength of Evidence
Schroter (2011)	Improvement in International Knee Documentation Committee Subjective score	1 year	Low	Moderate	Low

Table 220. Quality and Applicability Summary: Lateral Closing Wedge Versus Medial Open Wedge with Puddu Plate

Study	Outcome	Duration	Quality	Applicability	Strength of Evidence
Song (2012)	40+ VAS Pain Score	Final follow-up	Low	Moderate	Low
Brouwer (2006)	VAS Pain	Final follow-up	High	Moderate	High
Brouwer (2006)	Walking distance	Final follow-up	High	Moderate	High
Brouwer (2006)	Wound infection	Final follow-up	High	Moderate	High
Brouwer (2006)	Nonunion	Final follow-up	High	Moderate	High
Brouwer (2006)	Palsy of the common peroneal nerve	Final follow-up	High	Moderate	High
Brouwer (2006)	Pain in proximal tibiofibular joint	Final follow-up	High	Moderate	High
Brouwer (2006)	Iliac-crest morbidity	Final follow-up	High	Moderate	High
Brouwer (2006)	Fracture of the tibial plateau	Final follow-up	High	Moderate	High

Study	Outcome	Duration	Quality	Applicability	Strength of Evidence
Brouwer (2006)	Re-operation (further valgus correction)	Final follow-up	High	Moderate	High
Brouwer (2006)	Re-operation (reduction of valgus correction)	Final follow-up	High	Moderate	High
Brouwer (2006)	Revision to joint replacement	Final follow-up	High	Moderate	High
Brouwer (2006)	Removal of osteosynthesis material	Final follow-up	High	Moderate	High

RESULTS

Relevant Tables: Figure 93-Figure 103, Table 223-Table 226

Pongsoipetch et al.[130] measured VAS pain at 3, 6, 12, and 24 months. El-Azab et al.[131] also measured VAS pain in patients three years after receiving osteotomy. A cross sectional time series regression equation computed from the placebo data allowed the prediction of expected reduction in pain based on these two studies, given the average age of the sample, average baseline score, and follow-up duration if osteotomy were no more effective than a placebo. At each follow-up period, pain scores were significantly lower than predicted placebo scores in the Pongsoipetch et al. study. [130] The predicted placebo VAS pain score after three years for the patient population was 40.35(34.33, 46.35). The actual VAS pain score after three years in the osteotomy group was 23(13.3, 32.7), which was significantly lower than the predicted placebo score.

Another study measured the Hospital for Special Surgery pain and function scores.[132] While pain was found to have significantly improved from baseline, function did not. Other outcomes included the International Knee Documentation Subjective Score, Knee Society Score, and the International Knee Society Score. All outcomes were associated with statistically significant improvements from baseline. The remaining outcomes were used to indicate prevalence of the different types of adverse events among patients who underwent osteotomy (see Table 224).

VAS pain and walking distance (in km) were not significantly different in patients who received open wedge osteotomy compared to those who underwent the closed procedure. However, patients who underwent closed wedge osteotomy were at significantly lower odds of iliac crest morbidity and of requiring removal of osteosynthesis material

EVIDENCE TABLES AND FIGURES

QUALITY AND APPLICABILITY

Table 221. Quality and Applicability: Osteotomy

●: Domain free of flaws

○: Domain flaws present

◐: Moderate power

Study	*Outcome*	Prospective	Power	Group Assignment	Blinding	Group Comparability	Treatment Integrity	Measurement	Investigator Bias	*Quality*	Participants	Intervention and Expertise	Compliance and Adherence	Analysis	*Applicability Study*
Rudan (1990)	HSS pain	●	◐	○	○	○	○	●	○	**Low**	●	○	●	●	**Moderate**
Rudan (1990)	HSS function	●	◐	○	○	○	○	●	○	**Low**	●	○	●	●	**Moderate**
Saragaglia (2010)	Lysholm-Tenger Score	●	◐	○	○	○	○	●	○	**Low**	●	○	●	○	**Moderate**
Saragaglia (2010)	KOOS	●	◐	○	○	○	○	●	○	**Low**	●	○	●	○	**Moderate**
Saragaglia (2010)	Lateral tibial plateau fractures	●	◐	○	○	○	○	●	○	**Low**	●	○	●	○	**Moderate**
Saragaglia (2010)	Deep vein thrombosis (DVT)	●	◐	○	○	○	○	●	○	**Low**	●	○	●	○	**Moderate**

●: Domain free of flaws

○: Domain flaws present

◐: Moderate power

Study	*Outcome*	**Prospective**	**Power**	**Group Assignment**	**Blinding**	**Group Comparability**	**Treatment Integrity**	**Measurement**	**Investigator Bias**	*Quality*	**Participants**	**Intervention and Expertise**	**Compliance and Adherence**	**Analysis**	*Applicability Study*
Saragaglia (2010)	Pulmonary embolism	●	◐	○	○	○	○	●	○	**Low**	●	○	●	○	**Moderate**
Saragaglia (2010)	Failure of fixation (screw breakage)	●	◐	○	○	○	○	●	○	**Low**	●	○	●	○	**Moderate**
Saragaglia (2010)	Loss of angulation	●	◐	○	○	○	○	●	○	**Low**	●	○	●	○	**Moderate**
Saragaglia (2010)	Revised to TKA	●	◐	○	○	○	○	●	○	**Low**	●	○	●	○	**Moderate**
Niemeyer (2010)	IKDC Score	●	◐	○	○	○	○	●	○	**Low**	○	○	●	○	**Moderate**
Niemeyer (2010)	Lysholm-Tenger Score	●	◐	○	○	○	○	●	○	**Low**	○	○	●	○	**Moderate**
Niemeyer (2010)	Intraarticular fractures	●	◐	○	○	○	○	●	○	**Low**	○	○	●	○	**Moderate**
Niemeyer (2010)	Over correction	●	◐	○	○	○	○	●	○	**Low**	○	○	●	○	**Moderate**

●: Domain free of flaws

○: Domain flaws present

◐: Moderate power

Study	*Outcome*	**Prospective**	**Power**	**Group Assignment**	**Blinding**	**Group Comparability**	**Treatment Integrity**	**Measurement**	**Investigator Bias**	*Quality*	**Participants**	**Intervention and Expertise**	**Compliance and Adherence**	**Analysis**	*Applicability Study*
Niemeyer (2010)	Delayed union	●	◐	○	○	○	○	●	○	**Low**	○	○	●	○	**Moderate**
Niemeyer (2010)	Adverse events	●	◐	○	○	○	○	●	○	**Low**	○	○	●	○	**Moderate**
Pongsoipetch (2009)	KSS 2 years	●	◐	○	○	○	○	●	○	**Low**	○	○	●	●	**Moderate**
Pongsoipetch (2009)	KSS 1 year	●	◐	○	○	○	○	●	○	**Low**	○	○	●	●	**Moderate**
Pongsoipetch (2009)	VAS 24 months	●	◐	○	○	○	○	●	○	**Low**	○	○	●	●	**Moderate**
Pongsoipetch (2009)	VAS 1 year	●	◐	○	○	○	○	●	○	**Low**	○	○	●	●	**Moderate**
Pongsoipetch (2009)	VAS 6 months	●	◐	○	○	○	○	●	○	**Low**	○	○	●	●	**Moderate**
Pongsoipetch (2009)	VAS 3 months	●	◐	○	○	○	○	●	○	**Low**	○	○	●	●	**Moderate**

●: Domain free of flaws

○: Domain flaws present

◐: Moderate power

Study	*Outcome*	**Prospective**	**Power**	**Group Assignment**	**Blinding**	**Group Comparability**	**Treatment Integrity**	**Measurement**	**Investigator Bias**	*Quality*	**Participants**	**Intervention and Expertise**	**Compliance and Adherence**	**Analysis**	*Applicability Study*
Pongsoipetch (2009)	Superficial incision wound infection	●	◐	○	○	○	○	●	○	**Low**	○	○	●	●	**Moderate**
El-Azab (2011)	Lysholm-Gillquist 3 months	●	◐	○	○	○	○	●	○	**Low**	●	○	●	●	**Moderate**
El-Azab (2011)	Lysholm-Gillquist 6 months	●	◐	○	○	○	○	●	○	**Low**	●	○	●	●	**Moderate**
El-Azab (2011)	Lysholm-Gillquist 3 years	●	◐	○	○	○	○	●	○	**Low**	●	○	●	●	**Moderate**
Schroter (2011)	Improvement in Lysholm-Gillquist	●	◐	○	○	○	○	●	●	**Low**	○	○	●	●	**Moderate**
Schroter (2011)	Improvement in Tenger activity level	●	◐	○	○	○	○	●	●	**Low**	○	○	●	●	**Moderate**
Schroter	Improvement in International Knee	●	◐	○	○	○	○	●	●	**Low**	○	○	●	●	**Moderate**

●: Domain free of flaws

○: Domain flaws present

◐: Moderate power

Study	*Outcome*	**Prospective**	**Power**	**Group Assignment**	**Blinding**	**Group Comparability**	**Treatment Integrity**	**Measurement**	**Investigator Bias**	*Quality*	**Participants**	**Intervention and Expertise**	**Compliance and Adherence**	**Analysis**	*Applicability Study*
(2011)	Documentation Committee Subjective score														
Flamme (2003)	International Knee Society Score	●	◐	○	○	○	○	●	○	**Low**	○	○	●	●	**Moderate**
Flamme (2003)	N cases of distal deep vein thrombosis (DVT)	●	◐	○	○	○	○	●	○	**Low**	○	○	●	●	**Moderate**
Flamme (2003)	N cases of Proximal deep vein thrombosis (DVT)	●	◐	○	○	○	○	●	○	**Low**	○	○	●	●	**Moderate**
Flamme (2003)	N cases of bony non-union	●	◐	○	○	○	○	●	○	**Low**	○	○	●	●	**Moderate**

●: Domain free of flaws

○: Domain flaws present

◐: Moderate power

Study	*Outcome*	**Prospective**	**Power**	**Group Assignment**	**Blinding**	**Group Comparability**	**Treatment Integrity**	**Measurement**	**Investigator Bias**	*Quality*	**Participants**	**Intervention and Expertise**	**Compliance and Adherence**	**Analysis**	*Applicability Study*
Flamme (2003)	N cases of lesions of the fibular nerve	●	◐	○	○	○	○	●	○	**Low**	○	○	●	●	**Moderate**
Flamme (2003)	N cases of superficial wound infections	●	◐	○	○	○	○	●	○	**Low**	○	○	●	●	**Moderate**
Flamme (2003)	Percentage with adverse events	●	◐	○	○	○	○	●	○	**Low**	○	○	●	●	**Moderate**
Bachhal (2005)	Pin tract infection	●	◐	○	○	○	○	●	●	**Low**	●	○	●	●	**Moderate**
Bachhal (2005)	Lateral cortex fracture	●	◐	○	○	○	○	●	●	**Low**	●	○	●	●	**Moderate**
Bachhal (2005)	Delayed union	●	◐	○	○	○	○	●	●	**Low**	●	○	●	●	**Moderate**

●: Domain free of flaws

○: Domain flaws present

◐: Moderate power

Study	*Outcome*	**Prospective**	**Power**	**Group Assignment**	**Blinding**	**Group Comparability**	**Treatment Integrity**	**Measurement**	**Investigator Bias**	*Quality*	**Participants**	**Intervention and Expertise**	**Compliance and Adherence**	**Analysis**	*Applicability Study*
Bachhal (2005)	Knee stiffness	●	◐	○	○	○	○	●	●	**Low**	●	○	●	●	**Moderate**
Bachhal (2005)	Ring sequestrum	●	◐	○	○	○	○	●	●	**Low**	●	○	●	●	**Moderate**
Bachhal (2005)	Deep infection/chronic osteomyelitis	●	◐	○	○	○	○	●	●	**Low**	●	○	●	●	**Moderate**
Bachhal (2005)	Intraarticular fractures	●	◐	○	○	○	○	●	●	**Low**	●	○	●	●	**Moderate**
Bachhal (2005)	Neurovascular injury	●	◐	○	○	○	○	●	●	**Low**	●	○	●	●	**Moderate**
Bachhal (2005)	Symptomatic deep-vein Thrombosis	●	◐	○	○	○	○	●	●	**Low**	●	○	●	●	**Moderate**

Table 222. Quality and Applicability: Closing Wedge Versus Open Wedge Osteotomy

●: Domain free of flaws
○: Domain flaws present
◐: Moderate power

Study	*Outcome*	Prospective	Power	Group Assignment	Blinding	Group Comparability	Treatment Integrity	Measurement	Investigator Bias	*Quality*	Participants	Intervention and Expertise	Compliance and Adherence	Analysis	*Applicability Study*
Song(2012)	VAS Pain	○	●	○	○	○	●	●	○	**Low**	○	○	●	●	**Moderate**
Brouwer (2006)	VAS Pain	●	◐	●	○	●	●	●	●	**High**	●	○	●	●	**Moderate**
Brouwer (2006)	Walking distance	●	◐	●	○	●	●	●	●	**High**	●	○	●	●	**Moderate**
Brouwer (2006)	Walking distance	●	◐	●	○	●	●	●	●	**High**	●	○	●	●	**Moderate**
Brouwer (2006)	Wound infection	●	◐	●	○	●	●	●	●	**High**	●	○	●	●	**Moderate**
Brouwer (2006)	Nonunion	●	◐	●	○	●	●	●	●	**High**	●	○	●	●	**Moderate**
Brouwer (2006)	Palsy of the common peroneal nerve	●	◐	●	○	●	●	●	●	**High**	●	○	●	●	**Moderate**

●: Domain free of flaws

○: Domain flaws present

◐: Moderate power

Study	*Outcome*	**Prospective**	**Power**	**Group Assignment**	**Blinding**	**Group Comparability**	**Treatment Integrity**	**Measurement**	**Investigator Bias**	*Quality*	**Participants**	**Intervention and Expertise**	**Compliance and Adherence**	**Analysis**	*Applicability Study*
Brouwer (2006)	Pain in proximal tibiofibular joint	●	◐	●	○	●	●	●	●	**High**	●	○	●	●	**Moderate**
Brouwer (2006)	Iliac-crest morbidity	●	◐	●	○	●	●	●	●	**High**	●	○	●	●	**Moderate**
Brouwer (2006)	Fracture of the tibial plateau	●	◐	●	○	●	●	●	●	**High**	●	○	●	●	**Moderate**
Brouwer (2006)	Re-operation (further valgus correction)	●	◐	●	○	●	●	●	●	**High**	●	○	●	●	**Moderate**
Brouwer (2006)	Re-operation (reduction of valgus correction)	●	◐	●	○	●	●	●	●	**High**	●	○	●	●	**Moderate**
Brouwer (2006)	Revision to joint replacement	●	◐	●	○	●	●	●	●	**High**	●	○	●	●	**Moderate**

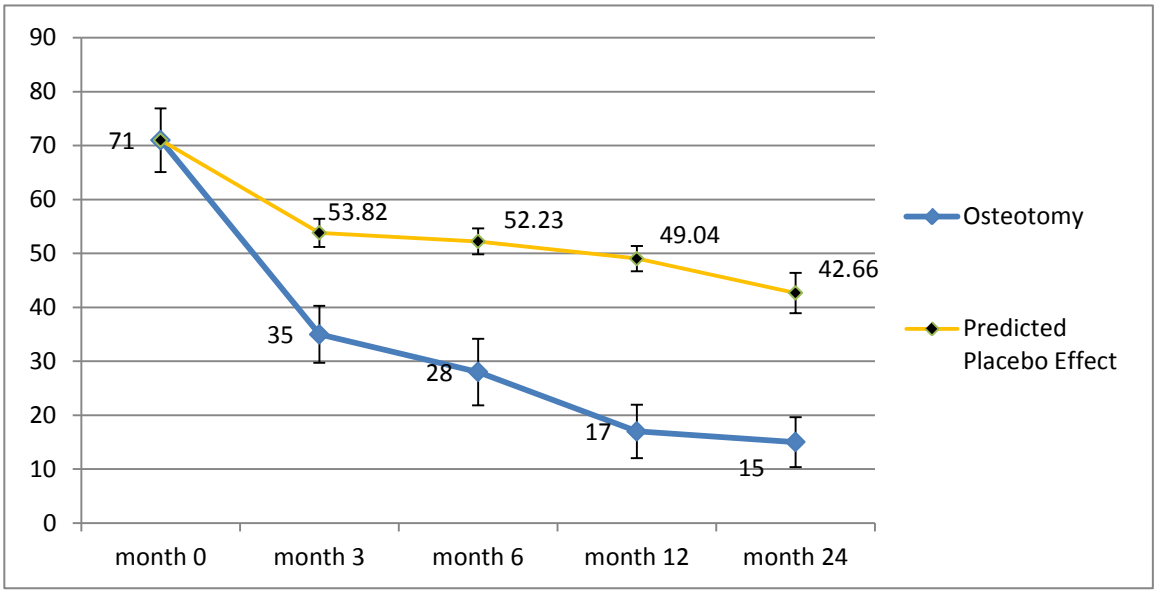
●: Domain free of flaws

○: Domain flaws present

◐: Moderate power

Study	*Outcome*	**Prospective**	**Power**	**Group Assignment**	**Blinding**	**Group Comparability**	**Treatment Integrity**	**Measurement**	**Investigator Bias**	*Quality*	**Participants**	**Intervention and Expertise**	**Compliance and Adherence**	**Analysis**	*Applicability Study*
Brouwer (2006)	Removal of osteosynthesis material	●	◐	●	○	●	●	●	●	**High**	●	○	●	●	**Moderate**

Figure 93. Open-Wedge High Tibial Osteotomy: VAS Pain Change from Baseline (Pongsoipetch et al., 2009)



*The predicted placebo effect is based on a cross-sectional time series regression analysis of all extracted placebo data.

Figure 94. Open Wedge High Tibial Osteotomy with TomoFix Plate: VAS Pain at 3 Year Follow-Up (El-Azab et al., 2011)

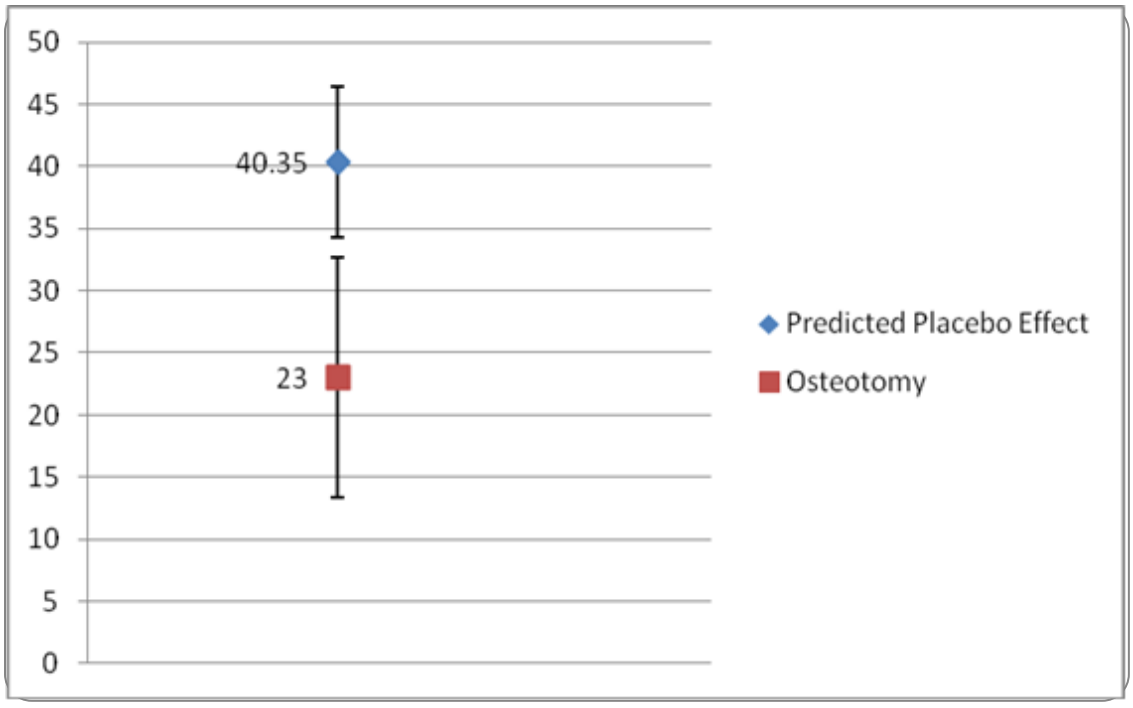
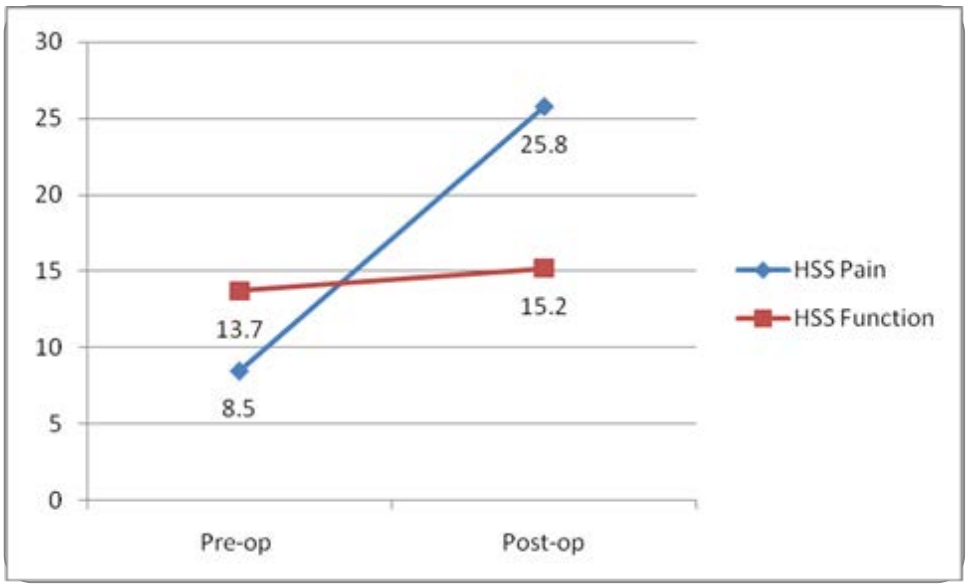
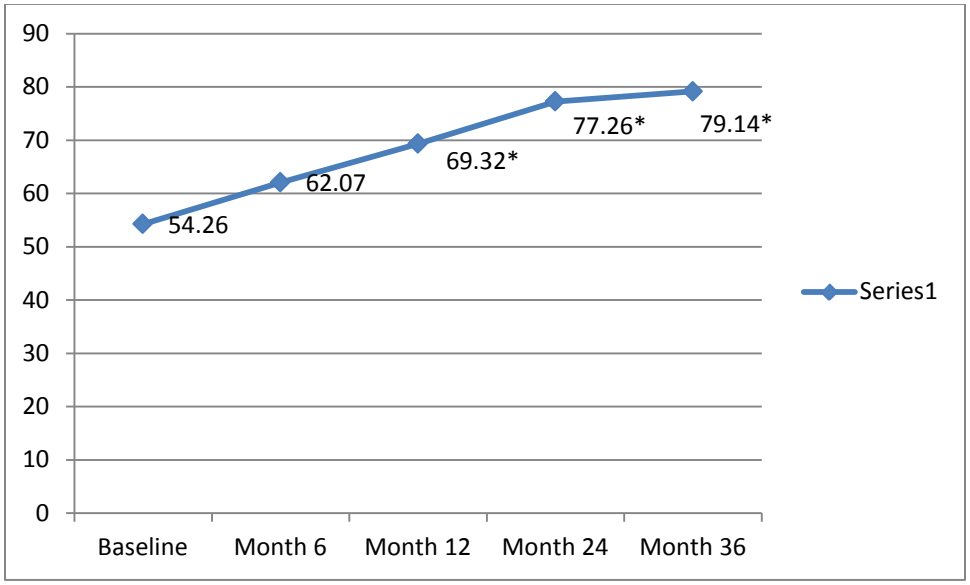


Figure 95. Hospital for Special Surgery: Pain and Function (Rudan and Simurda, 1990)



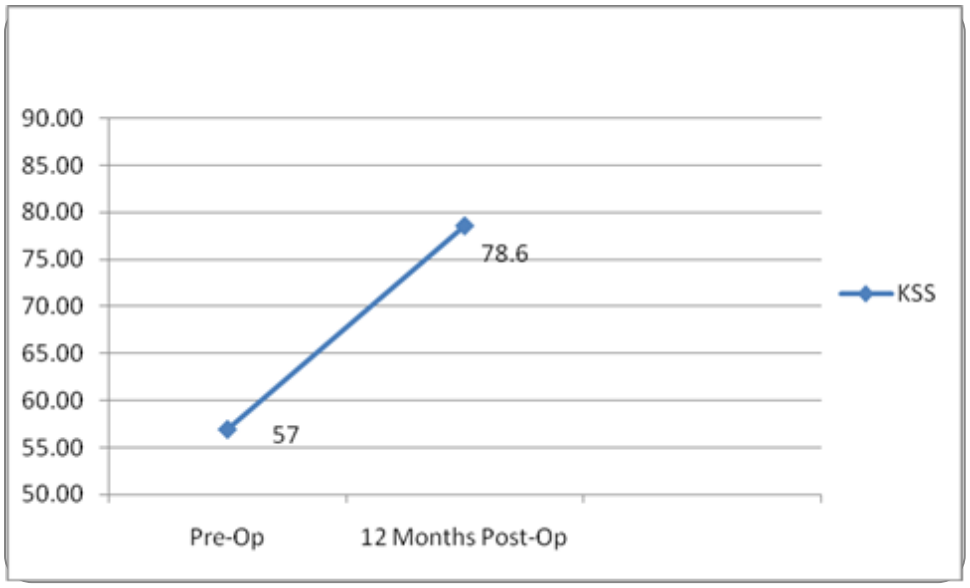
Author reported HSS Pain is statistically significant p<.001.

Figure 96. International Knee Documentation Committee Score: Open-Wedge HTO with Internal Fixator Plate (Niemeyer et al., 2010)



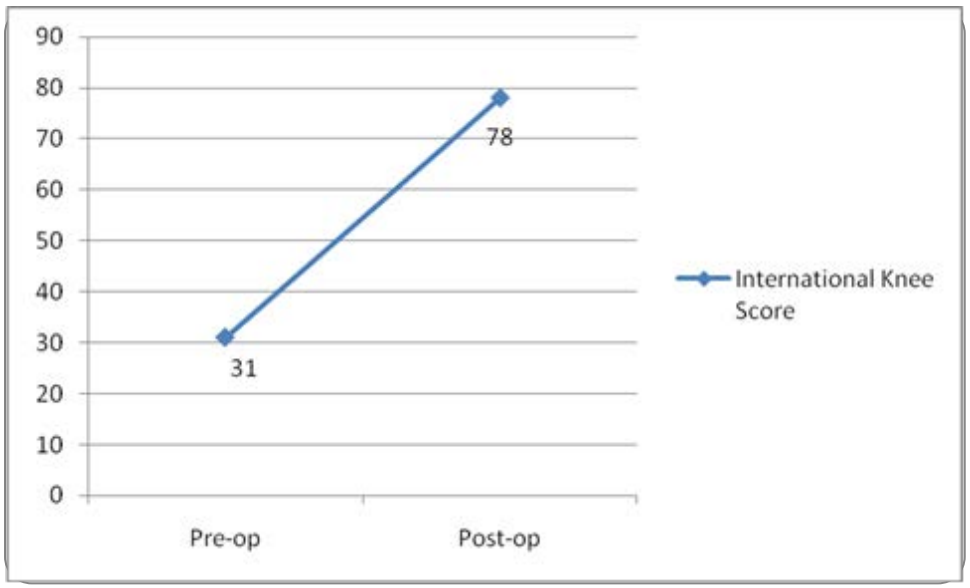
*Author reported Mann Whitney Test was significant (P<.05) for both outcomes at month 12, 24 and 36.

Figure 97. Open-Wedge High Tibial Osteotomy: Knee Society Score (Pongsoipetch et al., 2009)



Author results from a paired t-test. P<.001

Figure 98. High Tibial Osteotomy: International Knee Society Score (Flamme et al., 2003)



The authors reported results of a t-test, where P<.05

Table 223. High Tibial Osteotomy: Other Outcomes

Study	Treatment	Follow-Up	Outcome	Mean (95% CI)	P-Value
Schroter (2011)	Biplanar Open Wedge HTO with spacer plate	1 year	Improvement in Tenger activity level	1.1 (1.7 , 0.5)	p< .02
Schroter (2011)	Biplanar Open Wedge HTO with spacer plate	1 year	Improvement in International Knee Documentation Committee Subjective Score	23.7 (28.6 , 18.8)	p< .0001

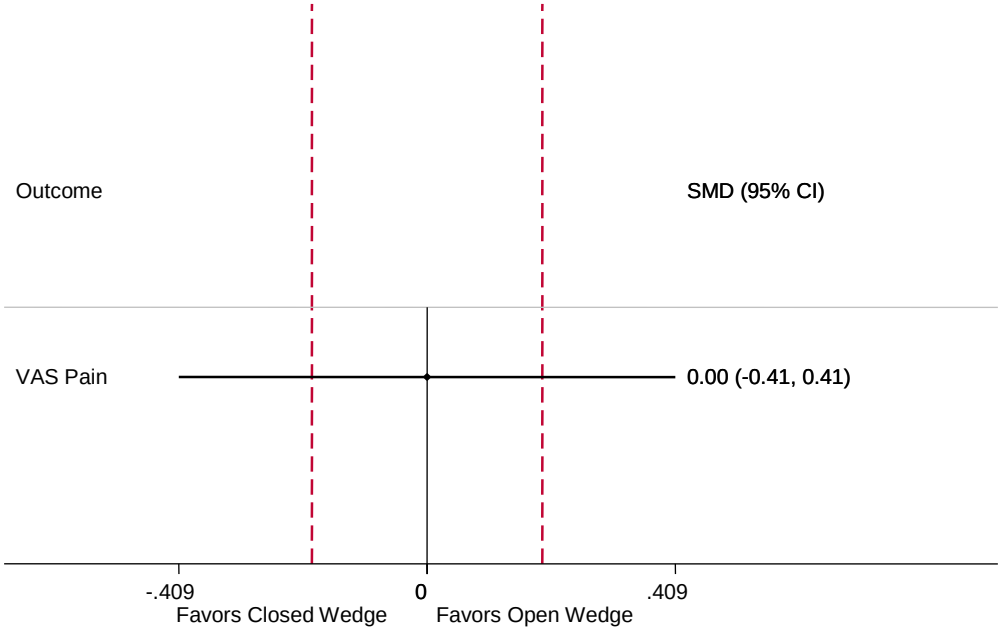
Table 224. Osteotomy: Adverse Events

Study	Treatment	Duration/Follow-Up	Adverse Event	Incidence of Adverse Events
Bachhal (2005)	HTO with dynamic axial fixator	Final follow-up	Pin tract infection	62.20%
Bachhal (2005)	HTO with dynamic axial fixator	Final follow-up	Lateral cortex fracture	2.70%
Bachhal (2005)	HTO with dynamic axial fixator	Final follow-up	Delayed union	5.40%
Bachhal (2005)	HTO with dynamic axial fixator	Final follow-up	Knee stiffness	10.8
Bachhal (2005)	HTO with dynamic axial fixator	Final follow-up	Ring sequestrum	2.70%
Bachhal (2005)	HTO with dynamic axial fixator	Final follow-up	Deep infection/chronic osteomyelitis	0%
Bachhal (2005)	HTO with dynamic axial fixator	Final follow-up	Intraarticular fractures	0%

Study	Treatment	Duration/Follow-Up	Adverse Event	Incidence of Adverse Events
Bachhal (2005)	HTO with dynamic axial fixator	Final follow-up	Neurovascular injury	0%
Bachhal (2005)	HTO with dynamic axial fixator	Final follow-up	Symptomatic deep-vein thrombosis	0%
Niemeyer (2010)	HTO with Internal Fixator Plate	3 years	Intraarticular fractures	1.45
Niemeyer (2010)	HTO with Internal Fixator Plate	3 years	Over correction	4.35
Niemeyer (2010)	HTO with Internal Fixator Plate	3 years	Delayed union	2.9
Niemeyer (2010)	HTO with Internal Fixator Plate	3 years	Overall adverse events	8.60%
Saragaglia (2010)	HTO with T-shaped Plate	Final follow-up	Lateral tibial plateau fractures	5.20%
Saragaglia (2010)	HTO with T-shaped Plate	Final follow-up	Deep vein thrombosis (DVT)	1.10%
Saragaglia (2010)	HTO with T-shaped Plate	Final follow-up	Pulmonary embolism	1.70%
Saragaglia (2010)	HTO with T-shaped Plate	Final follow-up	Failure of fixation (screw breakage)	1.70%
Saragaglia (2010)	HTO with T-shaped Plate	Final follow-up	Loss of angulation	0.60%
Saragaglia (2010)	HTO with T-shaped Plate	Final follow-up	Revised to TKA	12.90%
Flame (2003)	High Tibial Osteotomy	10 years	N cases of distal deep vein thrombosis (DVT)	2

Study	Treatment	Duration/Follow-Up	Adverse Event	Incidence of Adverse Events
Flame (2003)	High Tibial Osteotomy	10 years	N cases of proximal deep vein thrombosis (DVT)	2
Flame (2003)	High Tibial Osteotomy	10 years	N cases of bony non-union	3
Flame (2003)	High Tibial Osteotomy	10 years	N cases of lesions of the fibular nerve	2
Flame (2003)	High Tibial Osteotomy	10 years	N cases of superficial wound infections	3
Flame (2003)	High Tibial Osteotomy	10 years	Percentage with adverse events	11.20%
Pongsiopetch (2009)	Medial Open-Wedge High Tibial Osteotomy	2 years	Superficial incision wound infection	7.50%

Figure 99. Closed Versus Open Osteotomy: VAS Pain (Brouwer et al., 2006)



The red line indicates the MCII

Figure 100. Open Versus Closed Wedge Osteotomy: Mild to Severe Knee Pain on Stair Climb (Song et al., 2012)

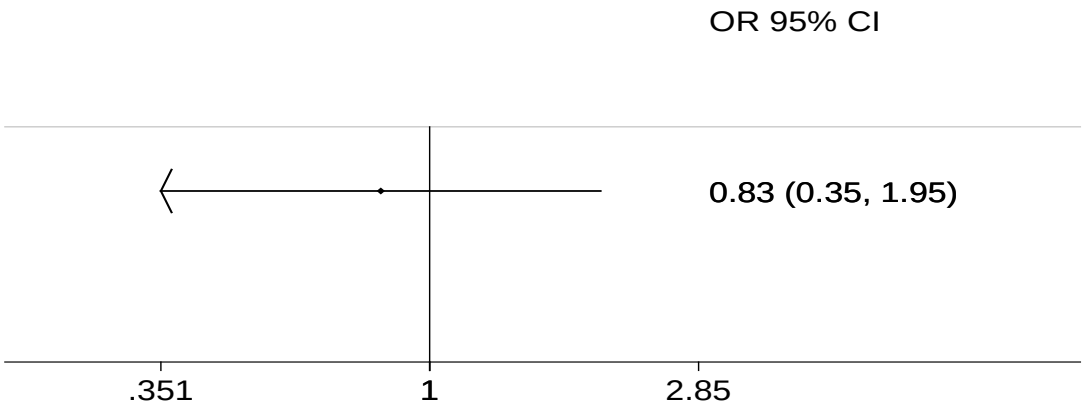


Figure 101. Open Versus Closed Wedge Osteotomy (Brouwer et al., 2006)

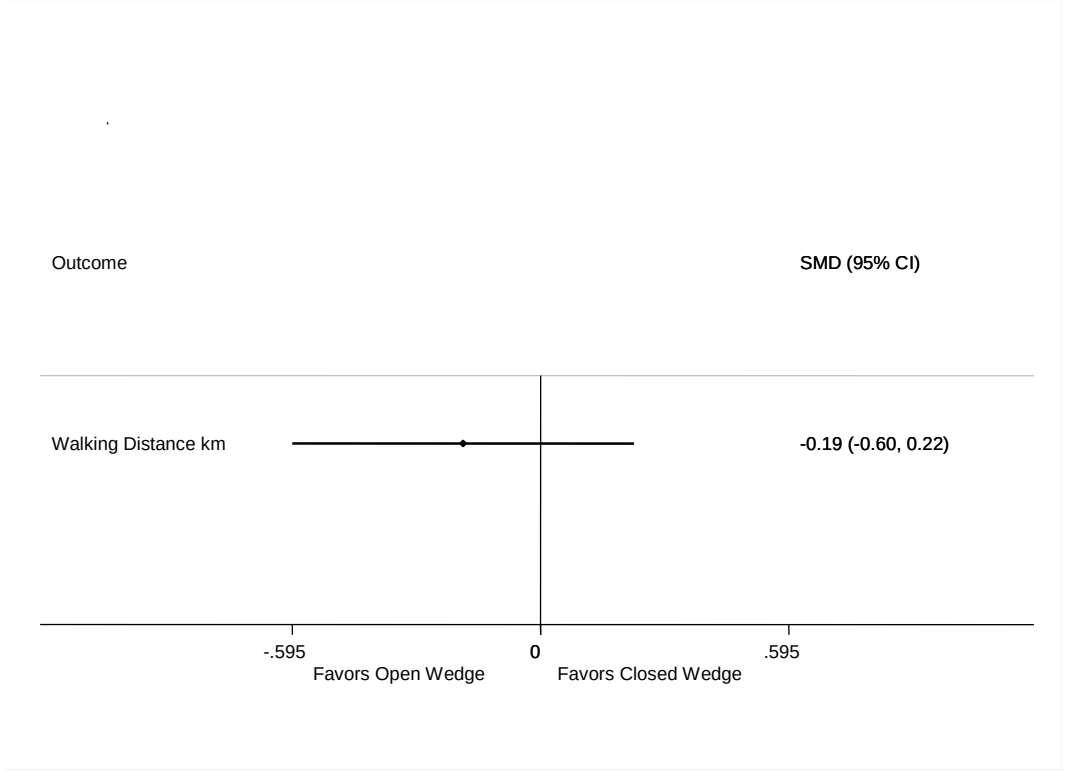


Table 225. Open Versus Closed Wedge Osteotomy

Study	Outcome	N	Group 1	Group 2	Effect size	Sig.	Clinical Significance	Strength of Evidence
Brouwer (2006)	VAS Pain	92	Open wedge	Closed wedge	0 (-.41, .41)	No	True negative	High
Brouwer (2006)	Walk distance (km)	92	Open wedge	Closed wedge	-.19 (-.6, .22)	No	Unclear	High
Song (2012)	40+ VAS Pain rating	100	Open wedge	Closed wedge	Or= 0.85 (0.28, 2.57)	No	Unclear	Low

Figure 102. Adverse Events: Open Versus Closed Wedge Osteotomy (Brouwer et al., 2006)

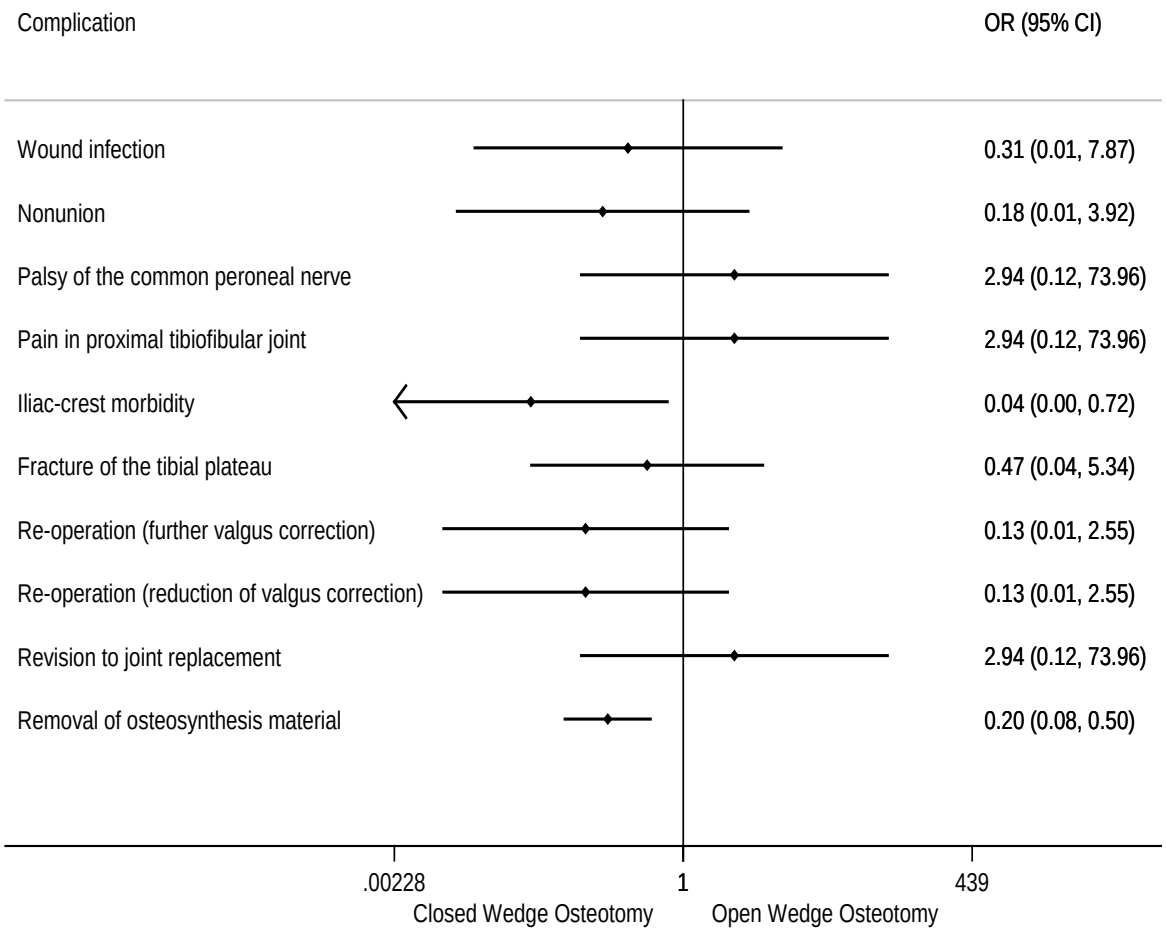
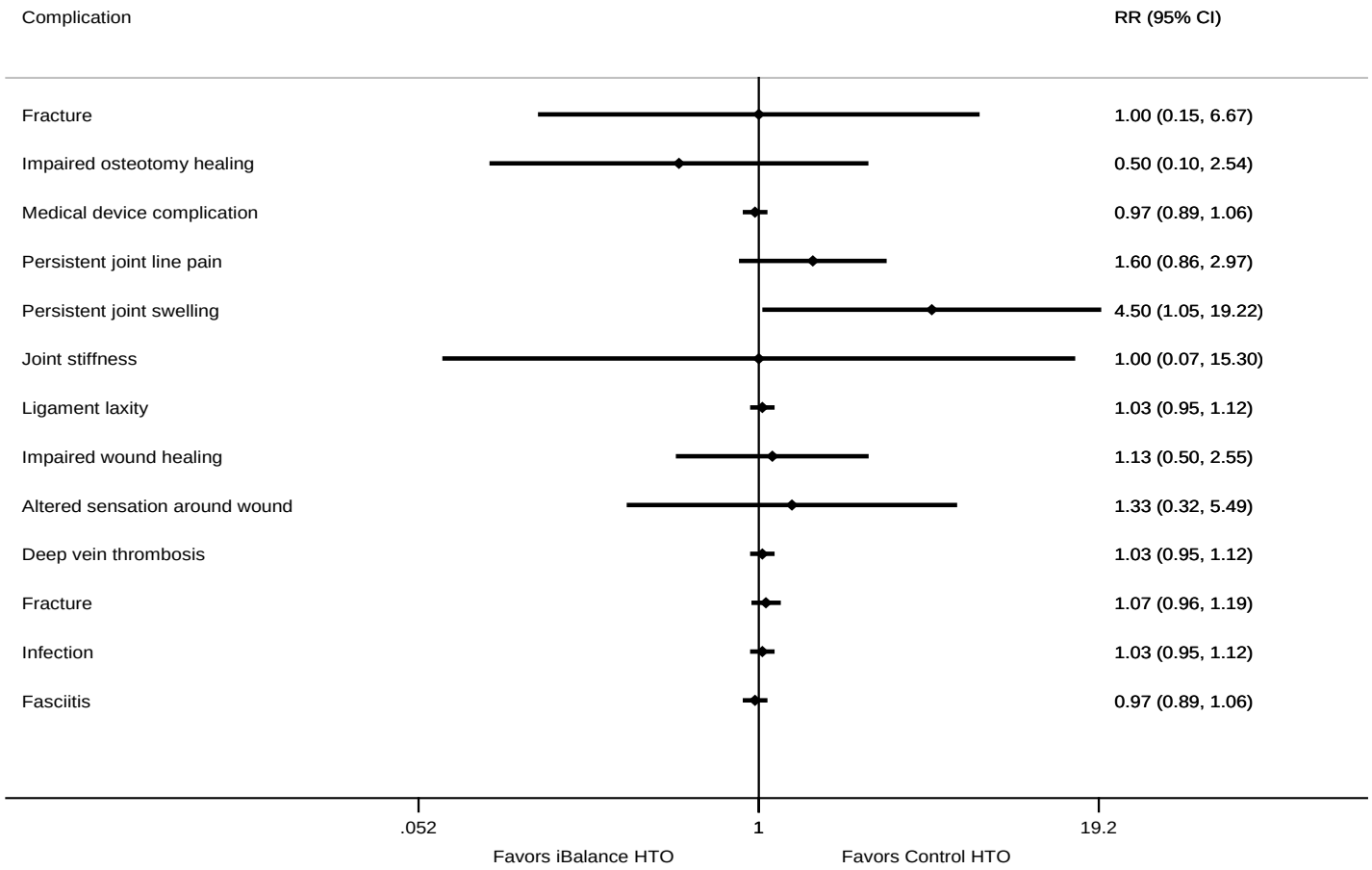


Table 226. iBalance HTO Versus Control HTO (Getgood et al., 2011)

Outcome	Duration	Results
KOOS Pain	6	Not statistically significant
KOOS Pain	12	Not statistically significant
KOOS Other Symptoms	6	Not statistically significant
KOOS Other Symptoms	12	Not statistically significant
KOOS Functions of Daily Life	6	Not statistically significant
KOOS Functions of Daily Life	12	Not statistically significant
KOOS Sports and Recreation	6	Not statistically significant
KOOS Sports and Recreation	12	Not statistically significant
KOOS Quality of Life	6	Not statistically significant
KOOS Quality of Life	12	Not statistically significant
SF-36 Physical Health	6	Not statistically significant
SF-36 Physical Health	12	Not statistically significant
SF-36 Mental Health	6	Not statistically significant
SF-36 Mental Health	12	Not statistically significant

Figure 103. iBalance HTO Versus Control HTO: Adverse Events (Getgood et al., 2011)



RECOMMENDATION 15

In the absence of reliable evidence, it is the opinion of the work group not to use the free-floating (un-fixed) interpositional device in patients with symptomatic medial compartment osteoarthritis of the knee.

Strength of Recommendation: Consensus

Description: The supporting evidence is lacking and requires the work group to make a recommendation based on expert opinion by considering the known potential harm and benefits associated with the treatment. A **Consensus** recommendation means that expert opinion supports the guideline recommendation even though there is no available empirical evidence that meets the inclusion criteria of the guideline's systematic review.

Implications: Practitioners should be flexible in deciding whether to follow a recommendation classified as **Consensus,** although they may give it preference over alternatives. Patient preference should have a substantial influencing role.

RATIONALE

One published case series reported the results of free-floating (un-fixed) interpositional device surgery for treatment of medial unicompartmental OA of the knee.[129] We determined that the evidence was low-strength.

The evidence indicated high reoperation rates in the patients who were followed. Thirty-two percent of patients were revised to total knee arthroplasty. The evidence showed differences from baseline that were not clinically or statistically significant for increased pain measured with the VAS two years postoperatively. Knee Society Score function subscale scores were "poor" postoperatively.

The AAOS workgroup modified the grade of this recommendation to consensus, because of the high revision rates in this study, increased pain, and the potential harm associated with this intervention (anesthesia risks, VTE, infection, and reoperation).

SUPPORTING EVIDENCE

QUALITY

Relevant Tables: Table 227, Table 228

All four of the included outcomes were from a study by Sisto and Mitchell[133] that followed a prospective case series design. Every outcome was flawed in the group assignment, blinding, group comparability and treatment integrity domains. Consequently, they were all rated as low quality.

APPLICABILITY

Relevant Tables: Table 227, Table 228

The Sisto and Mitchell[133] study was of moderate applicability because of uncertainty regarding whether the treatment was delivered in the same manner as in regular clinical practice, and the enrolled patients might not have been representative of patients typically seen in clinical practice.

FINAL STRENGTH OF EVIDENCE

The moderate applicability of the Sisto and Mitchell[133] study in combination with low quality of its outcomes resulted in a low strength of evidence rating.

Table 227. Quality and Applicability Summary: Free-floating Interpositional Device

Study	Outcome	Duration	Quality	Applicability	Strength of Evidence
Sisto (2005)	Knee Society Objective Score	Average follow-up of 26 months	Low	Moderate	Low
Sisto (2005)	Knee Society Function Score	Average follow-up of 26 months	Low	Moderate	Low
Sisto (2005)	Percent needing TKA revision	Average follow-up of 26 months	Low	Moderate	Low
Sisto (2005)	VAS Pain	Average follow-up of 26 months	Low	Moderate	Low

RESULTS

Relevant Tables: Figure 104-Figure 106

The included study did not support the use of free-floating interpositional devices for medial compartment OA knee.[133] The authors reported results of a Wilcoxon Signed-Rank test assessing the effect of the Unispacer interpositional device on Knee Society Objective and functional scores. Neither outcome showed significant improvement. Two year post-operative VAS Pain scores were actually higher than pre-operative scores and 32.4 % of knees had to be revised with total knee arthroplasty.

EVIDENCE TABLES AND FIGURES

QUALITY AND APPLICABILITY

Table 228. Quality and Applicability: Free-Floating Interpositional Device

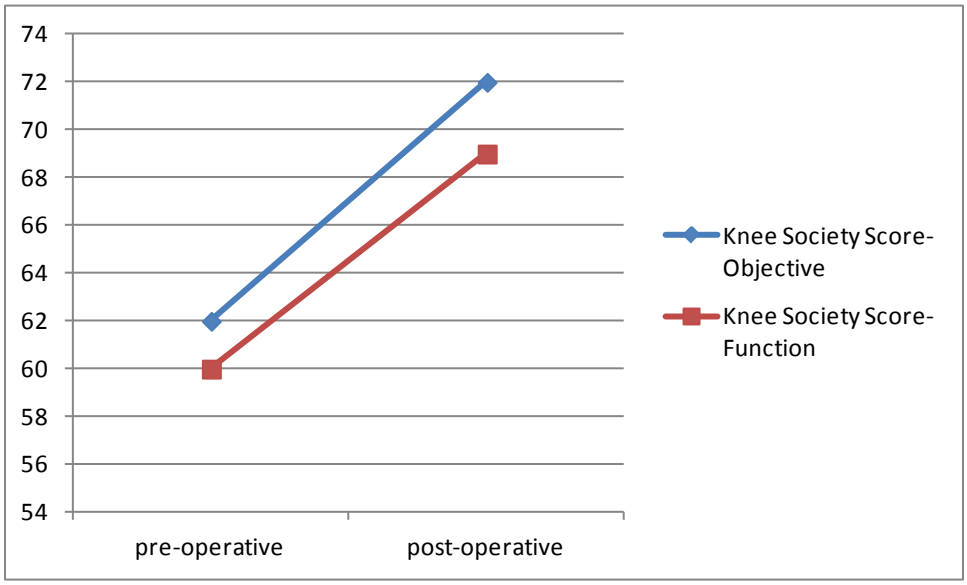
●: Domain free of flaws

○: Domain flaws present

◐: Moderate power

Study	Outcome	Prospective	Power	Group Assignment	Blinding	Group Comparability	Treatment Integrity	Measurement	Investigator Bias	*Quality*	Participants	Intervention and Expertise	Compliance and Adherence	Analysis	*Applicability* Study
Sisto 2005	Knee Society Objective Score	●	◐	○	○	○	○	●	●	**Low**	○	○	●	●	**Moderate**
Sisto 2005	Knee Society Function Score	●	◐	○	○	○	○	●	●	**Low**	○	○	●	●	**Moderate**
Sisto 2005	Percent revised to Total Knee Arthroplasty	●	◐	○	○	○	○	●	●	**Low**	○	○	●	●	**Moderate**

Figure 104. Knee Society Scores (Sisto and Mitchell 2005)



*These are author reported results of a Wilcoxon Signed-Rank test. The results are not significantly improved from baseline

Figure 105. VAS Pain (Sisto and Mitchell, 2005)

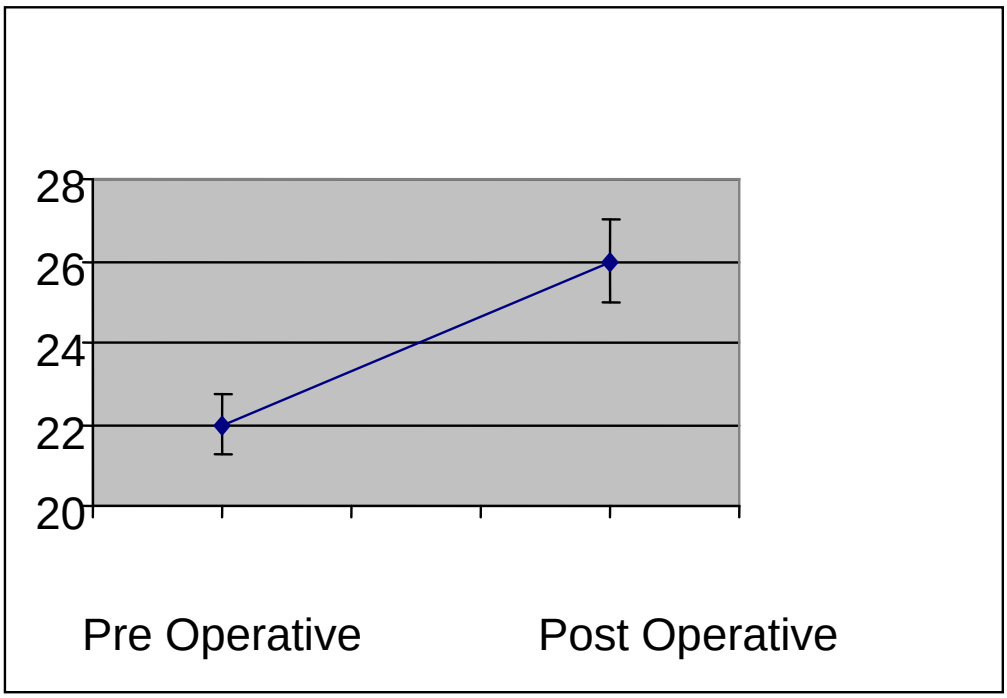
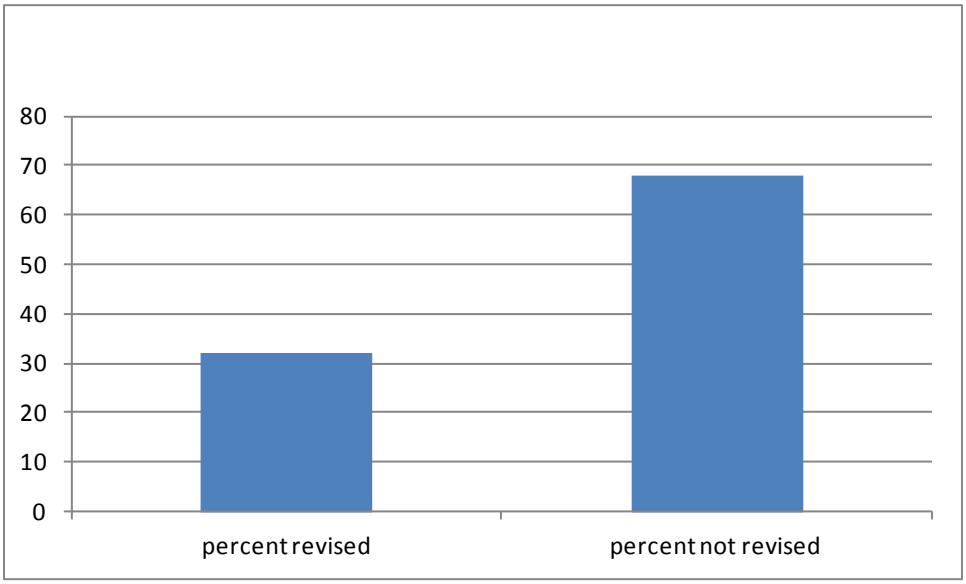


Figure 106. Percent Revised to Total Knee Arthroplasty (Sisto and Mitchell, 2005)



FUTURE RESEARCH

Many treatments for osteoarthritis of the knee are addressed by randomized controlled trials. The quality of these trials is, in some cases, questionable. To achieve a high quality literature base, clinicians and scientists should invest their time and effort in studies designed to avoid bias. Some techniques to limit bias include stochastic randomization and blinding of investigators or evaluators and patients. Future studies should include a priori power analyses to adequately power the studies to be able to detect minimum clinically important improvements (MCII; improvements that matters to the patient). Studies should likewise utilize patient reported outcomes (i.e. Oxford Knee Score, EQ-5D, and Visual Analog Scales) whose measurement properties have been validated. The use of standardized pain and function measures will ensure that efficacy evaluated in future studies can be analyzed on the basis of clinical significance to offset the limitations of interpreting only the p-value. Commensurate with these steps, investigators should better define the hypotheses of the treatment studies. For example, does a two year follow-up analysis accurately reflect the expected outcomes of one intraarticular corticosteroid injection?

While some of the non-operative treatments of knee osteoarthritis have higher level clinical evidence, the availability of strong evidence is not consistent across interventions. Several of the relatively commonly prescribed treatments, such as the use of acetaminophen and intraarticular corticosteroid injections, are in need of higher strength studies to support and define their use and indications. Better and higher strength evidence for surgical treatment (up to but not including knee arthroplasty) of knee osteoarthritis has been published since the original CPG, but is still insufficient to answer the questions that patients and orthopaedic surgeons have regarding their use. The resource difficulties and ethical concerns about conducting placebo controlled studies of operative interventions compromise the quality of these studies. To improve the quality of future studies of operative treatments, the use of nonsurgical, non-placebo control groups should be considered. Surgical treatments for knee osteoarthritis are often indicated in patients exhibiting unique symptoms from other pathologies (i.e. loose body, meniscal tear) in addition to the symptoms from osteoarthritis of the knee, or in patients with a specific characteristics (i.e. young age, high activity level, or end-stage severity of the osteoarthritis). Investigators should develop rigorous patient inclusion criteria to ensure that patients who typically receive the surgical intervention in clinical practice are adequately represented in the study population (including adequate statistical power of key patient subgroups to allow subgroup analyses).

The evidence analysis of this second edition raised specific questions for the clinicians who were either directly involved in its development or indirectly involved through peer review. The lack of clinically significant outcomes in viscosupplementation treatment groups could be due to the inability to distinguish responders from non-responders. Additionally, it might be that current widely used outcome measures are not broad enough in scope to detect such improvements as, for example, family reported gains in functional autonomy in patients who themselves report no effect. Higher statistically powered studies are needed to allow for these types of subgroup analyses. Without an

evidence-based method of identifying prognostic characteristics of patients who might benefit from the treatment, non-operative treatment options for patients with serious medical co-morbidities and who are not candidates for knee arthroplasty are limited.

There are valid concerns about the side effect profile of nonsteroidal anti-inflammatory drugs and tramadol (addiction and withdrawal). As future measures are developed it might be possible to evaluate gastrointestinal bleeds and infection not detected in Oxford Knee Score, EQ-5D, and VAS outcomes. Currently, the adverse effects of tramadol have not been adequately reported in the knee osteoarthritis literature, perhaps because efficacy studies have focused on short-term outcomes (up to 13 weeks). The data reported in this guideline focuses on treatment efficacy.

Reviewing the potential risks of every medication was beyond the scope of this clinical practice guideline from the beginning. Physicians must be knowledgeable about the potential side effects of the treatments they prescribe especially when using them long term. Complicating this task is that tramadol is studied less frequently than other medications. Additionally, randomized clinical trials cannot reliably identify uncommon and serious adverse reactions or the effects of long term use. Observational studies and registries are needed to provide robust estimates of adverse event rates based on patient demographics and co-morbidities. Empirical evidence will always be limited by the "rules" of evidence-based medicine.

It is the hope of this Work Group that the detailed review of knee osteoarthritis treatment evidence will provide a background for future high-quality clinical trials to improve our evidence base and improve the clinical treatment of patients with osteoarthritis of the knee.

APPENDIX I
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APPENDIX II
DECISION-MAKERS WHO APPROVE THIS CLINICAL PRACTICE GUIDELINE

Committee on Evidence Based Quality and Value

The committee on Evidence Based Quality and Value (EBQV) consists of twenty AAOS members who implement evidence-based quality initiatives such as clinical practice guidelines (CPGs) and appropriate use criteria (AUCs). They also oversee the dissemination of related educational materials and promote the utilization of orthopaedic value products by the Academy's leadership and its members.

Council on Research and Quality

The Council on Research and Quality promotes ethically and scientifically sound clinical and translational research to sustain patient care in musculoskeletal disorders. The Council also serves as the primary resource for educating its members, the public, and public policy makers regarding evidenced-based medical practice, orthopaedic devices and biologics, regulatory pathways and standards development, patient safety, occupational health, technology assessment, and other related important errors.

The Council is comprised of the chairs of the committees on Biological Implants, Biomedical Engineering, Occupational Health and Workers' Compensation, Patient Safety, Research Development, U.S. Bone and Joint Decade, and chair and Appropriate Use Criteria and Clinical Practice Guideline section leaders of the Evidence Based Quality and Value committee. Also on the Council are the second vice-president, three members at large, and representatives of the Diversity Advisory Board, Women's Health Issues Advisory Board, Board of Specialty Societies (BOS), Board of Councilors (BOC), Communications Cabinet, Orthopaedic Research Society (ORS), Orthopedic Research and Education Foundation (OREF).

Board of Directors

The 17 member Board of Directors manage the affairs of the AAOS, set policy, and oversee the Strategic Plan.

APPENDIX III
DETERMINING CRITICAL OUTCOMES
WORK GROUP PARTICIPATION

The first task of the work group is to identify the critical outcomes for the guideline. Members are asked to construct a preliminary list of important outcomes prior to attending the introductory meeting. They participate in three Delphi rounds, completing the "Critical Outcomes Form" shown below.

CRITICAL OUTCOMES FORM

DETERMINING OUTCOMES

The first task as a guideline work group member is to determine outcomes. List the variables you think are relevant and rank them in order of importance. Appropriate outcomes are patient-centered and consider the benefits and potential harm of the treatments being measured.

Criticality

Some outcomes are more important than others. The *most* important ones are considered critical. Critical outcomes are vital for determining whether or not you should offer a treatment or diagnostic test to a patient. Without knowing what the essential outcomes are and how the treatment or test influences them, efficacy cannot be determined.

Patient-Oriented Outcomes

In general, good practice and good evidence-based medicine give priority to the outcomes that patients care about. Patient-oriented outcomes:

- Help the patient live longer or better
- Are typically something the patient experiences
- Are often the patient's diagnostic or treatment goal(s)
- Do not require extrapolation or interpolation to determine their importance to the patient

Examples of patient-oriented outcomes are:

- Survival/mortality
- Pain relief
- Fracture prevention
- Functional status
- Quality of life

Surrogate Outcomes
Patient-oriented outcomes contrast surrogate ones in that the latter:

- Substitute measures for patient-oriented outcomes
- Are typically not experienced by the patient
- Are typically not the patient's goals for treatment
- Require extrapolation or interpolation to determine their relationship to (or effect on) patient-oriented outcomes

Examples of surrogate outcomes are:

- Blood cholesterol (a surrogate for survival)
- Bone mineral density (a surrogate for fractures)
- All imaging results (often surrogates for pain or functional status but they can also be surrogates for other patient-oriented outcomes)

Benefit versus Harm
Potential benefit to patients is based on the patient-oriented outcomes that they desire and potential harm can be thought of as patient-oriented outcomes unwanted to them. For example, avoiding harm (e.g. fractures or death) is considered a benefit.

For Consideration
Not taking the time to develop appropriate critical outcomes has been known to detrimentally affect the strength of the final recommendations, and on occasion prevent being able to make a recommendation for a treatment or diagnostic test of clinical importance.

Rating Outcomes
In addition to identifying patient outcomes, work group members rated the importance of each one using a scale of 1 to 9. The rating categories are shown in the table below:

Rating	*Importance*
9	
8	**Critical**
7	
6	
5	**Important**
4	
3	
2	**Not Important**
1	

Work group members were advised to note that:

1. **Unless you are interested in measures of diagnostic test performance (i.e., sensitivity and specificity), surrogate outcomes may not be rated as "Critical" (7-9).**

2. **If all outcomes are rated as critically important, then it will not be possible to prioritize the ones that are more likely to generate a comprehensive list of initial recommendations.**

Final Determinations
To determine which outcomes to include and designate as critical, three rounds of the Delphi method were used.

The form below was used by the work group.

Please list up to 10 outcomes that you think this guideline should address, and rate them in order of importance on a scale from 1-9. Do not consult with other members of the work group during this step.

Outcome Number	Outcome	Rating
1		
2		
3		
4		
5		
6		
7		
8		
9		
10		

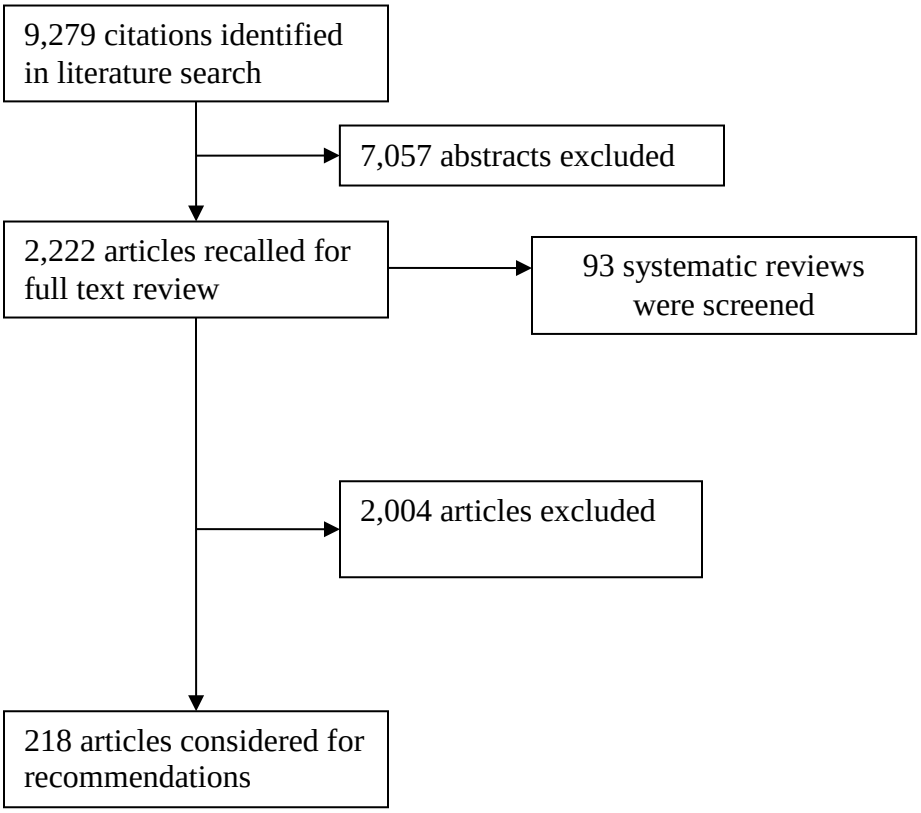
This form was circulated <u>three times.</u>

In the present guideline, the work group identified six critical outcomes: knee pain, activities of daily living, quality of life, functional status, activity tolerance, and self-reported physical function.

The work group identified the following outcomes as important: performance based physical function, serious GI bleed, ability to perform recreational activities, survival, treatment side effects, surgical complications, night time pain affecting sleep, major surgery complications, revision surgery, ability to earn income, ability to drive, social role function, joint stiffness, stability, range of motion, minor GI bleed, avoidance of need for knee replacement, strength, limpness, prevention of disease progression, deformity, joint alignment and stability, and joint swelling/effusion.

The work group identified the following outcomes as unimportant: radiographic improvement, MRI findings, and biomarker improvement.

APPENDIX IV
STUDY ATTRITION FLOWCHART
Attrition chart



APPENDIX V
LITERATURE SEARCH STRATEGIES
PUBMED/MEDLINE

Search Strategy

#1
"Osteoarthritis, Knee"[mh] OR gonitis[tiab] OR gonarthritis[tiab] OR gonarthros*[tiab]

#2
"Knee Joint"[mh] OR "Knee"[mh] OR knee*[tiab]

#3
Osteoarthritis[mh:noexp] OR Arthritis[mh:noexp] OR osteoarthrit*[tiab]

#4
(#1 OR (#2 AND #3)) NOT arthroplasty[majr]

#5
"1966"[PDat]:"2012"[PDat] AND English[lang] AND "2011/4/22"[edat]:"2012"[edat]

#6
(animal[mh] NOT human[mh]) OR cadaver[mh] OR cadaver*[titl] OR comment[pt] OR editorial[pt] OR letter[pt] OR "historical article"[pt] OR addresses[pt] OR news[pt] OR "newspaper article"[pt] OR "in vitro"[pt] OR "case report"[title]

#7
#4 AND #5 NOT #6

#8
Nonarthroplasty[tiab] OR nonsurgical[tiab] OR non-surgical[tiab] OR ((conservative[tiab] OR medical[tiab]) AND management[tiab])

#9
Walking[mh] OR "Exercise therapy"[mh:noexp] OR "Exercise"[mh:noexp] OR "Exercise Movement Techniques"[mh] OR "Muscle Stretching Exercises"[mh] OR exercise*[tiab] OR yoga[tiab] OR aerobic*[tiab] OR fitness[tw] OR conditioning[tiab] OR reconditioning[tiab] OR "tai chi" OR "tai ji" OR aquatic[tiab] OR ((balanc*[tiab] OR flexib*[tiab] OR gait[tiab] OR proprioception OR sensorimotor[tiab] OR endurance[tiab]) AND training[tiab]) OR "Self care" OR "self-management" OR strengthen*[tiab] OR isokinetic[tiab] OR isotonic[tiab] OR isometric[tiab] OR stretch*[tiab]

#10
"weight loss" OR "Diet, reducing"[mh] OR BMI OR "Body mass index"[mh] OR Obesity[mh:noexp] OR "Obesity, morbid"[mh] OR "Overweight"[mh:noexp] OR overweight[tiab] OR obese[tiab] OR obesity[tiab]

#11
"Musculoskeletal Manipulations"[mh] OR "manual therapy" OR mobiliz*[tiab] OR chiropract* OR manipulation*[tiab] OR physiotherap*[tiab] OR "physical therapy modalities"[mh:noexp] OR taping[tiab] OR "Transcutaneous Electric Nerve Stimulation" OR "Transcutaneous Electric Nerve Stimulation"[mh] OR TENS[tiab] OR "neuromuscular electrical stimulation" OR NMES[tiab] OR laser*[tiab] OR "Laser Therapy, Low-Level"[mh] OR "Acupuncture therapy"[mh] OR acupunctur* OR "dry needling" OR electroacupunctur*[tiab] OR ultrasound[tiab] OR ultrasonography[tw] OR Ultrasonography[mh] OR phonophoresis[tw] OR cryotherapy[tw] OR ice[tiab] OR "cold pack" OR heat[tiab] OR "Hot temperature"[mh] OR "hot pack" OR hydrotherapy[tw] OR electromagnet*[tiab] OR balneology[tw] OR iontophoresis[tw]

#12
"Orthotic devices"[mh] OR brace[tiab] OR bracing[tiab] OR orthotic*[tiab] OR wedge[tiab] OR wedges[tiab] OR viscoelastic*[tiab] OR shoes[tw] OR shoe[tw]

#13
"dietary supplements" OR neutraceutic*[tiab] OR vitamin*[tw] OR herbal[tiab] OR "Plant extracts"[mh] OR methylsulfonylmethane[tiab] OR "omega 3" OR "Fish oils"[mh] OR "fish oil" OR "fatty acids" OR glucosamine OR chondroitin OR gelatin[tiab] OR "vitamin d" OR "dimethyl sulfoxide" OR Antioxidants[pa] OR antioxidant*[tiab] OR "coenzyme q"[tiab] OR "coenzyme q10"[tiab] OR CoQ10[tiab] OR Ubiquinone[mh]

#14
"Osteoarthritis, knee/drug therapy"[mh] OR NSAID*[tiab] OR "Anti-Inflammatory Agents"[mh] OR "Anti-Inflammatory Agents, Non-Steroidal"[pa] OR "Analgesics, Non-Narcotic"[mh] OR "Analgesics, Non-Narcotic"[pa] OR opiod*[tiab] OR "Analgesics, Opioid"[mh] OR "Analgesics, Opioid"[pa] OR analges*[tiab] OR narcotics[pa] OR "Cyclooxygenase 2 Inhibitors"[pa] OR Cox-2[tiab] OR Celecoxib OR "Phenylpropionates"[mh] OR patch*[tiab] OR gel[tiab] OR cream[tiab] OR lidocaine[tw] OR Acetaminophen[tw] OR naprox*[tw] OR tramadol[tiab]

#15
"Injections, Intraarticular"[mh] OR corticosteroid*[tiab] OR glucocorticoid*[tw] OR hyaluron*[tw] OR viscosupplement* OR "platelet-rich plasma" OR "Fibroblast Growth Factors"[mh] OR fibroblast*[tw] OR "growth factor" OR "Stem cells"[mh] OR "stem cells" OR mesenchymal OR prolotherap*[tiab] OR "Hypertonic Solutions"[mh]

#16
lavage[tiab] OR irrigat* OR debridement OR meniscectom* OR (loose[tiab] AND (body[tiab] OR bodies[tiab])) OR ((torn[tiab] OR tear[tiab]) AND menisc*[tiab])

#17
Osteotomy[mh:noexp] OR osteotom*[tiab]

#18
unispacer[tiab] OR (interpositional[tiab] AND device[tiab])

#19
#8 OR #9 OR #10 OR #11 OR #12 OR #13 OR #14 OR #15 OR #16 OR #17 OR #18

#20
#7 AND #19

#21
Medline[tw] OR systematic review[tiab] OR Meta-analysis[pt]

#22
#7 AND #21

#23
"Clinical Trial"[pt] OR (clinical[tiab] AND trial[tiab]) OR random*[tw] OR "Therapeutic use"[sh]

#24
(#20 AND #23) NOT #21

#25
#20 NOT (#21 OR #23)

EMBASE

Search strategy

#1
'knee osteoarthritis'/de OR 'knee arthritis'/de OR gonitis OR gonarthritis OR gonarthros*

#2
Knee/de OR 'knee meniscus'/de OR knee*:ti OR (joint*:ti AND knee*)

#3
arthritis/de OR osteoarthrit* OR arthriti*:ti

#4
(#1 OR (#2 AND #3)) NOT arthroplasty/exp

#5
English:la AND [humans]/lim AND [embase]/lim AND [22/4/2011]/sd

#6

cadaver/de OR 'in vitro study'/exp OR 'abstract report'/de OR book/de OR editorial/de OR note/de OR letter/de OR 'case report':ti

#7
#4 AND #5 NOT #6

#8
Nonarthroplasty OR nonsurgical OR non-surgical OR 'conservative treatment'/exp

#9
Walking/de OR exercise/exp OR kinesiotherapy/exp OR 'muscle stretching'/de OR stretching/de OR conditioning OR fitness/de OR ((balanc* OR flexib* OR gait OR proprioception OR sensorimotor OR endurance) AND training) OR 'self care'/de OR 'self-management' OR 'muscle training'/de

#10
'body weight'/de OR 'weight reduction'/de OR 'weight control'/de OR 'body mass'/de OR BMI:ti,ab OR obesity/de OR 'morbid obesity'/de OR overweight

#11
'physical medicine'/de OR balneotherapy/exp OR balneology OR cryotherapy/exp OR 'electrostimulation therapy'/exp OR 'hyperthermic therapy'/exp OR 'manipulative medicine'/exp OR magnetotherapy/de OR physiotherapy/de OR 'joint mobilization'/de OR ultrasound therapy/exp OR 'athletic tape'/de OR taping OR 'cold pack' OR 'hot pack' OR 'electromagnetic radiation'/exp OR iontophoresis/de OR 'neuromuscular electrical stimulation'/de OR ultrasound/de

#12
Orthotics/de OR 'heel wedge' OR brace/de OR viscoelastic* OR 'orthopedic shoe'/de OR shoe/de

#13
'diet supplementation'/de OR neutraceutic* OR vitamin/exp OR 'medicinal plant'/exp OR 'plant extract'/exp OR 'dimethyl sulfone'/de OR methylsulfonylmethane OR 'dimethyl sulfoxide'/de OR 'dimethyl sulfoxide reductase'/de OR 'omega 3 fatty acid'/de OR 'fish oil'/de OR glucosamine/de OR 'chondroitin sulfate'/de OR 'chondroitin 4 sulfate'/de OR 'chondroitin 6 sulfate'/de OR gelatin/de OR antioxidant/exp OR ubiquinone/de OR 'coenzyme q'

#14
'nonsteroid antiinflammatory agent'/exp OR NSAID*:ti,ab OR Paracetamol /de OR Acetaminophen OR 'analgesic agent'/exp OR 'cyclooxygenase 2 inhibitor'/exp OR 'transdermal patch'/de OR cream/de OR gel/exp lidocaine/de OR opiod*

#15

'intraarticular drug administration'/de OR corticosteroid/exp OR 'hyaluronic acid'/de OR viscosupplementation/de OR 'thrombocyte rich plasma'/de OR 'platelet rich plasma' OR 'growth factor'/exp OR 'mesenchymal stem cell transplantation'/de OR 'stem cell transplantation'/de OR prolotherap* OR 'hypertonic solution'/de

#16
lavage/de OR 'needle lavage' OR 'arthroscopic debridement'/de OR debridement/de OR meniscectomy/de OR 'loose bodies' OR 'loose body' OR 'knee meniscus rupture'/de

#17
Osteotomy/de OR 'tibia osteotomy'/de OR 'tibia proximal osteotomy'/de

#18
Unispacer OR uni-spacer OR 'interpositional device'

#19
#8 OR #9 OR #10 OR #11 OR #12 OR #13 OR #14 OR #15 OR #16 OR #17 OR #18

#20
#7 AND #19

#21
'meta analysis':ti,ab,de OR 'systematic review':ti,ab,de OR medline:ti,ab,de

#22
#7 AND #21

#23
random*:ti,ab,de OR 'clinical trial':ti,ab,de OR 'health care quality'/exp

#24
(#20 AND #23) NOT #21

#25
#20 NOT (#21 OR #23)

COCHRANE LIBRARY (WILEY INTERFACE)

Search strategy
Knee*:ti,ab AND osteoarthriti*:ti,ab AND (nonsurgical OR non-surgical OR exercise OR walking OR 'gait training' OR conditioning OR 'self care' OR 'self-management' OR obesity OR BMI OR 'weight loss' OR manipulation* OR chiropract* OR 'manual therapy' OR physiotherapy* OR taping OR 'transcutaneous electric nerve stimulation' OR 'neuromuscular electrical stimulation' OR laser OR acupuncture OR electroacupuncture OR 'dry needling' OR ultrasound OR ultrasonography OR phonophoresis OR cryotherapy OR 'cold pack' OR 'hot pack' OR 'heat therapy' OR hydrotherapy OR electromagnet* OR

balneology OR iontophoresis OR orthotic OR brace OR 'heel wedge' OR 'heel wedges' OR supplement OR vitamin OR neutraceutic* OR herbal OR methylsulfonylmethane OR 'omega 3' OR 'fish oil' OR glucosamine OR chondroitin OR gelatin OR 'dimethyl sulfoxide' OR antioxidant* OR 'coenzyme q' OR CoQ10 OR ubiquinone OR NSAID* OR 'Non-steroidal anti-inflammatory drugs' OR 'anti-inflammatory' OR analgesic* OR opiod* OR 'cyclooxygenase 2 inhibitors' OR 'Cox-2' OR lidocaine OR 'pain patch' OR Acetaminophen OR Paracetamol OR Tramadol OR corticosteroid* OR glucocorticoid* OR hyaluron* OR viscosupplement* OR 'platelet rich plasma' OR 'growth factor' OR 'stem cells' OR prolotherapy OR 'hypertonic solution' OR lavage OR debridement OR meniscectom* OR 'loose bodies' OR osteotomy* OR unispacer OR uni-spacer OR 'interpositional device') NOT (arthroplasty OR replacement):ti

APPENDIX VI
QUALITY AND APPLICABILITY APPRAISAL

QUALITY

Quality questions are asked for every outcome reported in a study. They vary according to the rigor of a study's research design. Different questions are asked depending on if a study uses a controlled design with a no-treatment comparison group, is a crossover or historically controlled study, or case series. A total of 20 questions are asked for each type of research design and are described below:

Quality Questions and Domains for Four Designs of Studies of Treatment Studies

Domain	Question:	Parallel, Contemporary Controls	Crossover Trials	Historical Controls	Case Series
Group Assignment	Stochastic	Yes	Yes	No	No
Group Assignment	Quasi-random Assignment	No	No	No	*NA
Group Assignment	Matched Groups	No	No	Yes	No
Group Assignment	Consecutive Enrollment	NA	NA	NA	Yes
Prospective	Prospective	Yes	Yes	Yes	Yes
Blinding	Blinded Patients	Yes	Yes	No	No
Blinding	Blinded Assessors	Yes	Yes	No	No
Blinding	Blinding Verified	Yes	Yes	No	No
Group Comparability	Allocation Concealment	Yes	Yes	No	No
Group Comparability	>80% Follow-up	Yes	Yes	No	Yes
Group Comparability	<20% Completion Difference	Yes	Yes	No	No
Group Comparability	Similar Baseline Outcome Values	Yes	NA	Yes	No
Group Comparability	Comparable Pt. Characteristics	Yes	NA	Yes	No
Group Comparability	Same Control Group Results	NA	Yes	NA	NA
Group Comparability	Same Experimental Group Results	NA	Yes	NA	NA
Treatment Integrity	Same Centers	Yes	Yes	Yes	No
Treatment Integrity	Same Treatment Duration in and across All Groups	Yes	Yes	Yes	No
Treatment Integrity	Same Concomitant Treatment to All Groups (controlled studies only)	Yes	Yes	Yes	NA
Treatment Integrity	No Confounding Treatment (case series only)	NA	NA	NA	Yes
Measurement	Same Instruments	Yes	Yes	Yes	Yes
Measurement	Valid Instrument	Yes	Yes	Yes	Yes

Domain	Question:	Parallel, Contemporary Controls	Crossover Trials	Historical Controls	Case Series
Bias	Article & Abstract Agree	Yes	Yes	Yes	Yes
Bias	All Outcomes Reported	Yes	Yes	Yes	Yes
Bias	A Priori Analysis	Yes	Yes	Yes	Yes
Statistical Power	Statistically Significant	High	High	High	High
Statistical Power	Number of patients in analysis	See below for further information			

*"NA" means "not asked."

The statistical power domain is assessed differently from the other domains. We characterize this domain as free from flaws if any one of the following is true:

- The results of a statistical test on the outcome of interest are statistically significant (statistical significance is indicative of adequate statistical power).
- The results of a statistical test of the outcome of interest are not statistically significant (or it is unclear whether the results are statistically significant), and the study is either an uncontrolled study in which data from 34 or more patients are included in the statistical analysis of the outcome of interest OR a controlled study in which data from 128 or more patients are included in the analysis of the outcome of interest.
- The study's results for the outcome of interest are used in a meta-analysis. We make this assumption because one reason for performing a meta-analysis is to compensate for the low statistical power of individual studies. Implicit in this assumption is a second assumption; that the power of the meta-analysis will be sufficient to detect an effect as statistically significant.

We term the power domain as flawed if all of the following are true:

- The results of a statistical test on the outcome of interest are either not statistically significant or it is unclear whether the results of statistical test on the outcome of interest are statistically significant.
- The study is an uncontrolled study in which data from fewer than 15 patients are included in the analysis of the outcome of interest OR the study is a controlled study in which data from fewer than 52 patients were included in the analysis of the outcome of interest.
- The results on the outcome of interest will not be used in a meta-analysis.

The numbers used to determine whether a study is of sufficient power are based on Cohen's[134] definitions of small, medium, and large effects. To compute the number of patients needed for an uncontrolled study using a pretest/posttest design, we consider a two-tailed paired samples t-test. We then determine whether or not sample size is sufficient to detect a large effect (defined as a standardized mean difference of ≥ 0.8) with alpha = 0.05 significance level and power = 80%. If a study does not have the ability to detect even a large effect as statistically significant, we characterize it as underpowered and the domain flawed.

To compute the number of patients needed for a controlled study, we consider a two-tailed independent samples t-test with equal size groups, and then determine if sample size is adequate for detecting a large effect, again with alpha = 0.05 and power = 80%. Similar to the above, we term a study as underpowered and the domain flawed if it does not enroll enough patients to detect a large effect size. It is viewed as adequately powered if it enrolls enough patients to detect a small effect.

Quality Domains for Incidence and Prevalence studies

#	Domain	Relationship between Quality and Domain Scores for Incident and Prevalence studies
1	Outcome: Whether the study is measuring the incidence/prevalence of a clinically meaningful event.	0 Flawed Domains = High Quality Study 1 Flawed Domain = Moderate Quality Study 2 Flawed Domains = Low Quality Study ≥ 3 Flawed Domains = Very Low Quality Study
2	Measurement: Whether the study measured the disease/disorder/condition in a way that would lead to accurate estimates of incidence or prevalence.	
3	Participant: Whether those who were studied were representative of the population of interest.	
4	Investigator Bias: Whether author biases could have prejudiced the results.	

Quality Domains for Screening & Diagnosis studies

#	Domain	Relationship between Quality and Domain Scores for Screening and Diagnosis studies
1	Participants: Whether the spectrum of disease among the participants enrolled in the study is the same as the spectrum of disease seen in actual clinical practice	0 Flawed Domains = High Quality Study 1 Flawed Domain = Moderate Quality Study 2 Flawed Domains = Low Quality Study ≥ 3 Flawed Domains = Very Low Quality Study
2	Reference Test: Whether the reference test , often a “gold standard” and the way it was employed in the study ensures correct and unbiased categorization of patients as having or not having disease	
3	Index Test: Whether interpretation of the results of the test under study, often called the “index test”, was unbiased	
4	Study Design: Whether the design of the study allowed for unbiased interpretation of test results	
5	Information: Whether the same clinical data were available when test results were interpreted as would be available when the test is used in practice	
6	Reporting: Whether the patients, tests, and study protocol were described well enough to permit its replication	

Quality Domains for Prognostic studies

Domain		**Relationship between Quality and Domain Scores for Prognosis Studies**
1	Prospective: With prospective studies, a variable is specified as a potential prognostic variable a priori. This is not possible with retrospective studies.	0 Flawed Domains = High Quality Study 1 Flawed Domain = Moderate Quality Study 2 Flawed Domains = Low Quality Study ≥ 3 Flawed Domains = Very Low Quality Study
2	Power: Whether the study had sufficient statistical power to detect a prognostic variable as statistically significant.	
3	Analysis: Whether the statistical analyses used to determine that a variable was rigorous to provide sound results.	
4	Model: Whether the final statistical model used to evaluate a prognostic accounted for enough variance to be statistically significant.	
5	Bias: Whether there was evidence of investigator bias.	

Quality Domains for Treatment studies

#	**Domains**	**Relationship between Quality and Domain Scores for Treatment studies**
1	The study addressed a hypothesis	0 Flawed Domains = High Quality Study 1 – 2 Flawed Domain = Moderate Quality Study 3 – 4 Flawed Domains = Low Quality Study ≥ 5 Flawed Domains = Very Low Quality Study
2	The assignment of patients to groups was unbiased	
3	There was sufficient blinding to mitigate against a placebo effect	
4	The patient groups were comparable at the beginning of the study	
5	The treatment was delivered in such a way that any observed effects could reasonably be attributed to that treatment	
6	Whether the instruments used to measure outcomes were valid	
7	Whether there was evidence of investigator bias	

APPLICABILITY

We determine the applicability of a study using the PRECIS instrument.[135] This instrument consists of 10 questions. The domains that each question applies to are shown in the table below.

Applicability Questions and the Domains for Studies of Treatment

Question	Domain
All Types of Patients Enrolled	Participants
Flexible Instructions to Practitioners	Interventions and Expertise
Full Range of Expt'l Practitioners	Interventions and Expertise
Usual Practice Control	Interventions and Expertise
Full Range of Control Practitioners	Interventions and Expertise
No Formal Follow-up	Interventions and Expertise
Usual and Meaningful Outcome	Interventions and Expertise
Compliance Not Measured	Compliance and Adherence
No Measure of Practitioner Adherence	Compliance and Adherence
All Patients in Analysis	Analysis

Applicability Domains for Incident and Prevalence studies

Domain	Relationship between Applicability and Domain Scores for Incidence and Prevalence studies
Participants (i.e. whether the participants in the study were like those seen in the population of interest)	0 Flawed Domains = High Quality Study 1 – 2 Flawed Domain = Moderate Quality Study ≥ 3 Flawed Domains = Low Quality Study
Analysis (i.e., whether participants were appropriately included and excluded from the analysis)	
Outcome (i.e., whether the incidence/prevalence estimates being made were of a clinically meaningful outcome)	

Applicability Questions and Domains for Screening and Diagnostic Studies

Domain	**Relationship between Applicability and Domain Scores for Screening and Diagnosis studies**
Participants: whether the patients in the study are like those seen in actual clinical practice	0 Flawed Domains = High Quality Study 1 – 3 Flawed Domain = Moderate Quality Study ≥ 4 Flawed Domains = Low Quality Study
Index Test: whether the test under study could be used in actual clinical practice and whether it was administered in a way that reflects its use in actual practice	
Directness: whether the study demonstrated that patient health is affected by use of the diagnostic test under study	
Analysis: whether the data analysis reported in the study was based on a large enough percentage of enrolled patients to ensure that the analysis was not conducted on "unique" or "unusual" patients	

Applicability Domains for Prognostic studies

Domain		**Relationship between Applicability and Domain Scores for Prognostic Studies**
1	Patients: Whether the patients in the study and in the analysis were like those seen in actual clinical practice.	0 Flawed Domains = High Quality Study 1 – 2 Flawed Domain = Moderate Quality Study ≥ 3 Flawed Domains = Low Quality Study
2	Analysis: Whether the analysis was not conducted in a way that was likely to describe variation among patients that might be unique to the dataset the authors used.	
3	Outcome: Whether the prognostic was a predictor of a clinically meaningful outcome.	

Applicability Domains for Treatment studies

Domain		Relationship between Applicability and Domain Scores for Treatment Studies
1	Patients: whether the patients in the study are like those seen in actual clinical practice	0 Flawed Domains = High Quality Study 1 – 3 Flawed Domain = Moderate Quality Study ≥ 4 Flawed Domains = Low Quality Study
2	Interventions and Expertise: whether the treatments are delivered as they would be in actual clinical practice and whether the clinicians providing then are like those in actual clinical practice	
3	Compliance and Adherence (i.e., whether the steps taken in the study to ensure patient compliance and adherence to treatment regimens would make the compliance/adherence in the study different from that seen in actual clinical practice)	
4	Analysis: whether the data analysis reported in the study was based on a large enough percentage of enrolled patients to ensure that the analysis was not conducted on “unique” or “unusual” patients.	

APPENDIX VII

FORM FOR ASSIGNING STRENGTH OF RECOMMENDATION

GUIDELINE RECOMMENDATION_____

PRELIMINARY GRADE OF RECOMMENDATION: _____

STEP 1: LIST BENEFITS AND HARMS

Please list the benefits (as demonstrated by the systematic review) of the intervention.

Please list the harms (as demonstrated by the systematic review) of the intervention.

Please list the benefits for which the systematic review is not definitive.

Please list the harms for which the systematic review is not definitive.

STEP 2: IDENTIFY CRITICAL OUTCOMES

Please circle the above outcomes that are critical for determining whether the intervention is beneficial and whether it is harmful.

Are data about critical outcomes lacking to such a degree that you would lower the preliminary strength of the recommendation?

What is the resulting strength of recommendation?

STEP 3: EVALUATE APPLICABILITY OF THE EVIDENCE

Is the applicability of the evidence for any of the critical outcomes so low that substantially worse results are likely to be obtained in actual clinical practice?

Please list the critical outcomes backed by evidence of doubtful applicability.

Should the strength of recommendation be lowered because of low applicability?

What is the resulting strength of recommendation?

STEP 4: BALANCE BENEFITS AND HARMS

Are there tradeoffs between benefits and harms that alter the strength of recommendation obtained in STEP 3?

What is the resulting strength of recommendation?

STEP 5 CONSIDER STRENGTH OF EVIDENCE

Does the strength of the existing evidence alter the strength of recommendation obtained in STEP 4?

What is the resulting strength of recommendation?

NOTE: Because we are not performing a formal cost analyses, you should only consider costs if their impact is substantial.

APPENDIX VIII
OPINION BASED RECOMMENDATIONS
RULES FOR MAKING OPINION BASED RECOMMENDATIONS

A guideline can contain recommendations for which there is no evidence. Work groups might make the decision to issue opinion-based recommendations. Although expert opinion is a form of evidence, it is also important to avoid liberal use in a guideline since research shows that expert opinion can be incorrect.

Opinion-based recommendations are developed only if they address a vitally important aspect of patient care. For example, constructing an opinion-based recommendation in favor of taking a history and physical is warranted. Constructing an opinion-based recommendation in favor of a specific modification of a surgical technique is less commonly warranted. To ensure that an opinion-based recommendation is absolutely necessary, the AAOS has adopted rules to guide the content of the rationales that are based on those outlined by the U.S. Preventive Services Task Force (USPSTF).[136] Specifically, rationales based on expert opinion must:

- Not contain references to or citations from articles not included in the systematic review.
- Not contain the AAOS guideline language "We Recommend", "We suggest" or "The practitioner might."
- Contain an explanation of the potential preventable burden of disease. This involves considering both the incidence and/or prevalence of the disease, disorder, or condition and the associated burden of suffering. To paraphrase the USPSTF, when evidence is insufficient, provision of a treatment (or diagnostic) for a serious condition might be viewed more favorably than provision of a treatment (or diagnostic) for a condition that does not cause as much suffering. The AAOS understands that evaluating the "burden of suffering" is subjective and involves judgment. This evaluation should be informed by patient values and concerns. It is not appropriate for a guideline to recommend widespread use of a technology backed by little data and for which there is limited experience. Such technologies are addressed in the AAOS' Technology Overviews.
- Address potential harms.
- Address apparent discrepancies in the logic of different recommendations. If there are no relevant data for several recommendations and the work group chooses to issue an opinion-based recommendation in some cases but not in other cases, the rationales must explain why.
- Consider current practice. The USPSTF specifically states that clinicians justifiably fear not providing a service that is practiced on a widespread basis will lead to litigation.[136] Not providing a service that is not widely available or commonly used has less serious consequences than not providing a treatment accepted by the medical profession that patients expect. The patient's "expectation of treatment" must be tempered by the treating physician's guidance about the reasonable outcomes that the patient can expect.
- Justify when applicable why a more costly device, drug, or procedure is being recommended.

Work group members write the rationales for opinion based recommendations on the first day of the final work group meeting. When the work group reconvenes on the second day, members approve the rationales. If the work group cannot adopt a rationale after three votes, the rationale and the opinion-based recommendation will be withdrawn, and a "recommendation" stating that the group can neither recommend for or against the recommendation in question will appear in the guideline.

Sometimes work group members change their views. At any time during the discussion of the rationales, any member of the work group can make a motion to withdraw a recommendation. The guideline will state that the work group can neither recommend for or against the recommendation in question.

CHECKLIST FOR VOTING ON OPINION BASED RECOMMENDATIONS

When voting on the rationale, please consider the following:

1. Does the recommendation affect a substantial number of patients or address treatment (or diagnosis) of a condition that causes death and/or considerable suffering?

2. Does the recommendation address the potential harms that will be incurred if it is implemented and, if these harms are serious, does the recommendation justify:

   a. why the potential benefits outweigh the potential harm

   b. why an alternative course of treatment (or diagnostic workup) that involves less serious or fewer harms is not being recommended

3. Does the rationale explain why the work group chose to make a recommendation when presented with minimal evidence when it might not have in other cases?

4. Does the rationale explain that the recommendation is consistent with current practice?

5. If applicable, does the rationale justify why a less costly device, drug, or procedure is not being recommended?

VOTING BY THE NOMINAL GROUP TECHNIQUE

Voting on guideline recommendations will be conducted using a modification of the nominal group technique (NGT), a method previously used in guideline development.[137] Each work group member ranks his or her agreement with a recommendation or performance measure on a scale of 1 to 9 (where 1 = "extremely inappropriate" and 9 = "extremely appropriate"). Consensus is obtained if the number of individuals who do not rate a measure as 7, 8, or 9 is statistically non-significant (as determined using the binomial distribution). Because the number of work group members who are allowed to dissent with the recommendation depends on statistical significance, the number of permissible dissenters varies with the size of the work group. The number of permissible dissenters for several work group sizes is given in the table below:

Work Group Size	Number of Permissible Dissenters
≤3	Not allowed. Statistical significance cannot be obtained
4-5	0
6-8	1
9	1 or 2

The NGT is conducted by first having members vote on a given recommendation/performance measure without discussion. If the number of dissenters is "permissible", the recommendation/measure is adopted. If the number of dissenters is not permissible, then there is discussion to see if the disagreement(s) can be resolved. Three rounds of voting are held to attempt to resolve differences. If agreement is not reached after three voting rounds, the recommendation is not adopted.

APPENDIX IX
STRUCTURED PEER REVIEW FORM

Review of any AAOS confidential draft allows us to improve the overall guideline but does not imply endorsement by any given individual or any specialty society who participates in our review processes. The AAOS review process may result in changes to the documents; therefore, endorsement cannot be solicited until the AAOS Board of Directors officially approves the final guideline.

Reviewer Information:

Name of Reviewer_____

Address_____

City_____ State_____ Zip Code_____

Phone _____Fax _____E-mail_____

Specialty Area/Discipline: _____

Work setting: _____Credentials: _____

May we list you as a Peer Reviewer in the final Guidelines (GL)? ☐ Yes ☐ No
If you do not wish to be listed, your name will be removed for identification purposes. However, your COI will still be available for review with the comments you have made.

Are you reviewing this guideline as a representative of a professional society? ☐ Yes ☐ No

If yes, may we list your society as a reviewer of this guideline? ☐ Yes ☐ No

Society Name: _____
(Listing the specialty society as a reviewing society does not imply or otherwise indicate endorsement of this guideline.)

Conflicts of Interest (COI): All Reviewers must declare their conflicts of interest.

If the boxes below are not checked and/or the reviewer does not attach his/her conflicts of interest, the reviewer's comments will not be addressed by the AAOS nor will the reviewer's name or society be listed as a reviewer of this GL. If a committee reviews the guideline, only the chairperson/or lead of the review must declare their relevant COI.

☐ **I have declared my conflicts of interest on page 2 of this form.**

☐ **I have declared my conflicts of interest in the AAOS database; my customer # is** _____

☐ **I understand that the AAOS will post my declared conflicts of interest with my comments concerning review of this guideline or technology overview on the AAOS website.**

REVIEWER CONFLICT OF INTEREST - The Orthopaedic Disclosure Program

Each item below requires an answer. Please report information for the last 12-months as required by the Accreditation Council for Continuing Medical Education (ACCME) guidelines.

Do you or a member of your immediate family receive royalties for any pharmaceutical, biomaterial or orthopaedic product or device? If YES, please identify product or device:	☐ Yes ☐ No
Within the past twelve months, have you or a member of your immediate family served on the speakers bureau or have you been paid an honorarium to present by any pharmaceutical, biomaterial or orthopaedic product or device company? If YES, please identify company:	☐ Yes ☐ No
Are you or a member of your immediate family a PAID EMPLOYEE for any pharmaceutical, biomaterial or orthopaedic device or equipment company, or supplier? If YES, please identify company or supplier:	☐ Yes ☐ No
Are you or a member of your immediate family a PAID CONSULTANT for any pharmaceutical, biomaterial or orthopaedic device or equipment company, or supplier? If YES, please identify company or supplier:	☐ Yes ☐ No
Are you or a member of your immediate family an UNPAID CONSULTANT for any pharmaceutical, biomaterial or orthopaedic device or equipment company, or supplier? If YES, please identify company or supplier:	☐ Yes ☐ No
Do you or a member of your immediate family own stock or stock options in any pharmaceutical, biomaterial or orthopaedic device or equipment company, or supplier (excluding mutual funds) If YES, please identify company or supplier:	☐ Yes ☐ No
Do you or a member of your immediate family receive research or institutional support as a principal investigator from any pharmaceutical, biomaterial or orthopaedic device or equipment company, or supplier? If YES, please identify company or supplier:	☐ Yes ☐ No
Do you or a member of your immediate family receive any other financial or material support from any pharmaceutical, biomaterial or orthopaedic device and equipment company or supplier? If YES, please identify company or supplier:	☐ Yes ☐ No
Do you or a member of your immediate family receive any royalties, financial or material support from any medical and/or orthopaedic publishers? If YES, please identify publisher:	☐ Yes ☐ No
Do you or a member of your immediate family serve on the editorial or governing board of any medical and/or orthopaedic publication? If YES, please identify:	☐ Yes ☐ No
Do you or a member of your immediate family serve on the Board of Directors or a committee of any medical and/or orthopaedic professional society? If YES, please identify:	☐ Yes ☐ No

Guidelines Peer Review Form

Reviewer Instructions

Please read and review this Draft Clinical Practice Guideline and its associated Technical Report with particular focus on your area of expertise. Your responses are confidential and will be used only to assess the validity, clarity and accuracy of the interpretation of the evidence. If applicable, please specify the draft page and line numbers in your comments. Please feel free to also comment on the overall structure and content of the guideline and Technical Report. If you need more space than is provided, please attach additional pages.

Please indicate your level of agreement with each of the following statements by placing an "X" in the appropriate box.

	Disagree	Somewhat Disagree	Somewhat Agree	Agree
1. The recommendations are clearly stated	☐	☐	☐	☐
2. There is an explicit link between the recommendations and the supporting evidence	☐	☐	☐	☐
3. Given the nature of the topic and the data, all clinically important outcomes are considered	☐	☐	☐	☐
4. The guideline's target audience is clearly described	☐	☐	☐	☐
5. The patients to whom this guideline is meant to apply are specifically described	☐	☐	☐	☐
6. The criteria used to select articles for inclusion are appropriate	☐	☐	☐	☐
7. The reasons why some studies were excluded are clearly described	☐	☐	☐	☐
8. All important studies that met the article inclusion criteria are included	☐	☐	☐	☐
9. The validity of the studies is appropriately appraised	☐	☐	☐	☐
10. The methods are described in such a way as to be reproducible.	☐	☐	☐	☐
11. The statistical methods are appropriate to the material and the objectives of this guideline	☐	☐	☐	☐
12. Important parameters (e.g., setting, study population, study design) that could affect study results are systematically addressed	☐	☐	☐	☐
13. Health benefits, side effects, and risks are adequately addressed	☐	☐	☐	☐
14. The writing style is appropriate for health care professionals.	☐	☐	☐	☐
15. The grades assigned to each recommendation are appropriate	☐	☐	☐	☐

COMMENTS

Please provide a brief explanation of both your positive and negative answers in the preceding section. If applicable, please specify the draft page and line numbers in your comments. Please feel free to also comment on the overall structure and content of the guideline and Technical Report

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OVERALL ASSESSMENT

Would you recommend these guidelines for use in practice? (check one)

☐ Strongly recommend

☐ Recommend (with provisions or alterations)

☐ Would not recommend

☐ Unsure

APPENDIX X
PARTICIPATING PEER REVIEW ORGANIZATIONS

Peer review of the guideline is completed by interested external organizations. The AAOS solicits reviewers for each guideline. They consist of experts in the topic area and represent professional societies other than AAOS. Review organizations are nominated by the work group at the introductory meeting. For this guideline, nineteen organizations were invited to review the full guideline. Fifteen societies participated in the review of the guideline on treatment of osteoarthritis of the knee and have given consent to be listed below:

American Academy of Family Physicians (AAFP)

American Association of Hip and Knee Surgeons (AAHKS)

Arthroscopy Association of North America (AANA)

American Orthopaedic Society for Sports Medicine (AOSSM)

American Academy of Physical Medicine and Rehabilitation (AAPMR)

American Physical Therapy Association (APTA)

Eastern Orthopaedic Association (EOA)

Orthopaedic Trauma Association (OTA)

Arthritis Foundation

Knee Society

American College of Sports Medicine (ACSM)

Southern Orthopaedic Association (SOA)

Mid-America Orthopaedic Association

Western Orthopaedic Association (WOA)

Peer review comments will be available on aaos.org.

Participation in the AAOS guideline peer review process does not constitute an endorsement nor does it imply that the reviewer supports this document.

APPENDIX XI

INTERPRETING THE FOREST PLOTS

We use descriptive diagrams known as forest plots to present data from studies comparing the differences in outcomes between two treatment groups when a meta-analysis has been performed (combining results of multiple studies into a single estimate of overall effect). The overall effect is shown at the bottom of the graph as a diamond to illustrate the confidence intervals. The standardized mean difference or odds ratio are measures used to depict differences in outcomes between treatment groups. The horizontal line running through each point represents the 95% confidence interval for that point estimate. The solid vertical line represents "no effect" and is where the standardized mean difference = 0 or odds ratio = 1.

ABBREVIATIONS USED IN THIS REPORT

Abbreviation	Term
95% CI	95% Confidence interval
AAOS	American Academy of Orthopaedic Surgeons
AIMS	Arthritis Impact Management Scale
ASES	Arthritis Self-Efficacy Scale
BMI	Body mass index
BOC	AAOS Board of Councilors
BOD	AAOS Board of Directors
BOS	AAOS Board of Specialty Societies
COI	Conflict of interest
CORQ	AAOS Council on Research and Quality
Cox-2	Cyclooxygenase-2
CPG	Clinical practice guidelines
Da	Daltons
EBM	Evidence-based medicine
EBP	Evidence-based practice
EBPC	AAOS Evidence-Based Practice Committee
FDA	United States Food and Drug Administration
GI	Gastrointestinal
GOC	AAOS Guidelines Oversight Committee
GRADE	Grading of Recommendations, Assessment, Development, and Evaluation
HA	Hyaluronic Acid
HAD	Hospital Anxiety and Depression
HAQ	Health Assessment Questionnaire
HMW	High Molecular Weight
HSS	Hospital for Special Surgery
IOM	Institute of Medicine
kDa	Kilo-Daltons
KOOS	Knee Injury and Osteoarthritis Outcome Score

KSS	Knee Society Score
LMW	Low Molecular Weight
MACTAR	McMaster Toronto Arthritis Patient Preference Disability questionnaire
MCII	Minimal Clinically Important Improvement
MR	Magnetic resonance
NR	Not reported
NRS	Numerical Rating Scale
NS	Not significant
NSAID	Non-steroidal anti-inflammatory drug
OARSI	Osteoarthritis Research Society International
OR	Odds ratio
OREF	Orthopaedic Research and Education Foundation
ORS	Orthopaedic Research Society
PQLC	Profile of Quality of Life in the Chronically Ill
PRECIS	Pragmatic-explanatory continuum indicator summary
QUADAS	Quality Assessment of Diagnostic Accuracy Studies instrument
SF	Short Form
SMD	Standardized Mean Difference
TKA	Total knee arthroplasty
VAS	Visual Analogue Scale
WMD	Weighted Mean Difference
WOMAC	Western Ontario and McMaster Universities Index

APPENDIX XII
CONFLICT OF INTEREST

Prior to the development of this guideline, work group members disclose conflicts of interest. They disclose COIs in writing to the American Academy of Orthopaedic Surgeons via a private on-line reporting database and also verbally at the recommendation approval meeting.

Disclosure Items: (n) = Respondent answered 'No' to all items indicating no conflicts. 1= Royalties from a company or supplier; 2= Speakers bureau/paid presentations for a company or supplier; 3A= Paid employee for a company or supplier; 3B= Paid consultant for a company or supplier; 3C= Unpaid consultant for a company or supplier; 4= Stock or stock options in a company or supplier; 5= Research support from a company or supplier as a PI; 6= Other financial or material support from a company or supplier; 7= Royalties, financial or material support from publishers; 8= Medical/Orthopaedic publications editorial/governing board; 9= Board member/committee appointments for a society.

David S. Jevsevar, MD, MBA, Work Group Chair: 2 (Medacta USA); 4 (Omni Life Sciences); 5 (Medacta USA); Submitted on: 04/03/2013.

Gregory Alexander Brown, MD, PhD, Work Group Vice-Chair: 4 (KareMetrix LLC, Orthopaedic Solutions LLC); 5 (Smith & Nephew); 9(AAOS, ASTM, International Standards Organization); Submitted on: 04/06/2013.

Dina L. Jones, PT, PhD: 8 (Arthritis Care & Research (Member, Committee on Journal Publications)). Submitted on 04/05/2013.

Elizabeth G. Matzkin, MD: (n); Submitted on 04/03/2013.

Paul Manner, MD, FRCSC: 8 (Journal of Bone and Joint Surgery – American, Orthopedics). Submitted on 05/08/2013.

Pekka A. Mooar, MD: 5 (Baxter); 8 (Web MD); 9 (AAOS); Submitted on 04/03/2013.

John T. Schousboe, MD, PhD: (n); Submitted on 08/23/2012.

Steven Stovitz, MD: 8 (British Journal of Sports Medicine); Submitted on 06/28/2013.

James O. Sanders, MD: 2 (DePuy, A Johnson & Johnson Company); 4 (Abbott, Abbvie, GE Heathcare, Hospira); 8 (Journal of Pediatric Orthopedics); 9 (AAOS, Pediatric Orthopaedic Society of North America, Scoliosis Research Society); Submitted on 04/26/13).

Kevin J. Bozic, MD, MBA: 9 (AAOS, American Association of Hip and Knee Surgeons, American Joint Replacement Registry, American Orthopaedic Association, California Joint Replacement Registry Project, California Orthopaedic Association, Orthopaedic Research and Education Foundation); Submitted on 04/05/2013.

Michael J. Goldberg, MD: 3B (BioMarin Pharmaceutical), 8 (Journal Children's Orthopaedics); 9 (AAOS); Submitted on 04/02/2013.

William Robert Martin, III, MD: 9 (National Board of Medical Examiners); Submitted on 03/12/2010.

Deborah S. Cummins, PhD: (n); Submitted on 04/26/13.

Patrick Donnelly, MA: (n); Submitted on 04/08/13.

Anne Woznica, MLIS: (n); Submitted on 04/05/13.

Leeaht Gross, MPH: (n); Submitted on 04/01/13.

APPENDIX XIII
NETWORK META ANALYSIS CHECKS FOR CONSISTENCY

Table 229. Network Meta-Analysis Consistency Check: WOMAC Pain

Comparison	MTC Mean Difference	MTC SD	Direct Weighted Mean Difference	Direct Effect SD	Omega (Direct Minus Indirect Effect)	Z	p-value (For Omega)
Celecoxib versus Placebo	-6.665	1.663	-6.31	58.31655	0.355289	0.00609	0.995141
Diacerein versus Placebo	-6.122	3.458	-4.4	41.94362	1.733785	0.041195	0.96714
Diclofenac versus Placebo	-8.824	2.655	-9.5	42.4978	-0.67865	-0.01594	0.987284
Lumiracoxib versus Placebo	-6.552	2.021	-5.02	43.89235	1.535255	0.034941	0.972127
Naproxen versus Piroxicam	1.271	3.652	2	44.09972	0.734034	0.016588	0.986766
Naproxen versus Placebo	-9.29	2.813	-10.24	32.95406	-0.95697	-0.02893	0.976918
Naproxinod versus Placebo	-8.87	3.866	-10.71	53.3577	-1.84971	-0.03458	0.972419
Piroxicam versus Diclofenac	-1.737	4.073	-0.44	49.16689	1.305962	0.026471	0.978882
Piroxicam versus Tenidap	-0.1768	3.947	-0.2	43.75281	-0.02339	-0.00053	0.999575
Rofecoxib versus Placebo	-12.4	2.867	-14.12	40.93851	-1.72848	-0.04212	0.966405
Topical Diclofenac versus Placebo	-8.218	3.161	-8.17	45.51421	0.048233	0.001057	0.999157
Topical Eltenac versus Placebo	-3.099	5.568	-3.13	46.37836	-0.03145	-0.00067	0.999463
Tramadol versus Diclofenac	1.075	6.142	-0.2	49.14379	-1.29523	-0.02615	0.979138
Valdecoxib versus Placebo	-8.433	3.68	-6.73	46.67269	1.713654	0.036602	0.970802
Diclofenac versus Tramadol	-0.2052	3.966	-0.2	43.75281	0.005243	0.000119	0.999905
Tenoxicam versus Placebo	-1.805	3.347	-1.8	8.532672	0.005909	0.000637	0.999492

Comparison	MTC Mean Difference	MTC SD	Direct Weighted Mean Difference	Direct Effect SD	Omega (Direct Minus Indirect Effect)	Z	p-value (For Omega)
Acetaminophen versus Aceclofenac	7.656	4.979	7.64	73.5249	-0.01607	-0.00022	0.999826
Topical Ketoprofen versus Placebo	-7.361	3.814	-7	41.19538	0.364121	0.008801	0.992978
Topical Ketoprofen versus Celecoxib	-0.6956	4.161	0.6	43.92958	1.307329	0.029626	0.976365
Tramadol versus Placebo	-8.619	3.929	-9.7	64.54882	-1.08502	-0.01678	0.986614

Table 230. Network Meta-Analysis Consistency Check: WOMAC Function

Comparison	MTC Mean Difference	MTC SD	Direct Weighted Mean Difference	Direct Effect SD	Omega	Z	p
Lumiracoxib versus Celecoxib	-0.1848	0.7628	-0.45	24.76538	-0.13283	-0.00536	0.837689
Celecoxib versus Diclofenac	2.405	1.486	1.9	26.66777	0.816794	0.030581	0.923854
Tramadol versus Diclofenac	1.294	2.412	1.07	34.52125	0.852826	0.024644	0.87909
Celecoxib versus Lumiracoxib	0.1848	0.7628	0.2	1416.932	-0.1176	-8.3E-05	0.909168
Naproxen versus Naproxcinod	-2.222	2.014	-2.21	35.80515	-1.66921	-0.04655	0.995723
Diacerein versus Piroxicam	3.004	2.323	3.01	25.76558	2.477993	0.095783	0.975604
Tenidap versus Piroxicam	-1.026	1.828	-1.02	29.44944	-0.71691	-0.0243	0.980339
Celecoxib versus Placebo	-4.009	0.6665	-3.79	25.53272	5.232178	0.204851	0.999934
Diacerein versus Placebo	-3.315	2.567	-3.32	29.62268	-2.84205	-0.09558	0.962875
Diclofenac versus Placebo	-6.414	1.466	-7	26.49743	-4.03707	-0.15212	0.923693
Lumiracoxib versus Placebo	-4.193	0.7906	-3.79	25.53509	2.914644	0.114088	0.980616
Naproxcinod versus Placebo	-7.137	2.031	-7.15	35.82434	-5.44286	-0.15169	0.837689
Naproxen versus Placebo	-9.359	2.026	-9.36	35.81259	-7.10997	-0.19821	0.923854

Comparison	MTC Mean Difference	MTC SD	Direct Weighted Mean Difference	Direct Effect SD	Omega	Z	p
Rofecoxib versus Placebo	-3.914	1.654	-5.4	27.69695	-3.98862	-0.14375	0.87909
Topical Diclofenac versus Placebo	-5.806	1.594	-5.75	30.02551	-3.48118	-0.11578	0.909168
Celecoxib versus Placebo	-0.09485	1.626	-1.1	27.51334	-1.06798	-0.03875	0.879433
Tramadol versus Placebo	-5.12	2.308	-4.97	29.58248	-4.03927	-0.13613	0.842877
Topical Ketoprofen versus Placebo	-2.816	1.801	-2.99	28.15572	-2.13411	-0.07564	0.885696
Topical Ketoprofen versus Celecoxib	1.193	1.806	1.36	28.42009	0.999747	0.035106	0.907829

Table 231. Network Meta-Analysis Consistency Check: WOMAC Stiffness

Comparison	MTC Mean Difference	MTC SD	Direct Weighted Mean difference	Direct Effect SD	Omega	Z	p
Lumiracoxib versus Celecoxib	0.01963	-0.11	3.736156	3.009356	-0.13042	-0.03480101	0.972238
Celecoxib versus Diclofenac	0.3448	0.3	3.562489	3.866677	-0.04565	-0.01269421	0.989872
Tramadol versus Diclofenac	0.7592	0.43	4.346562	3.465048	-0.33706	-0.07663726	0.938912
Valdecoxib versus Naproxen	0.081	0.08	3.491004	3.663208	-0.00102	-0.00028997	0.999769
Diacerein versus Piroxicam	0.2447	0.24	2.913194	3.508201	-0.00488	-0.00164401	0.998688
Tenidap versus Piroxicam	-0.03978	-0.04	4.121328	3.654279	-0.00022	-5.3858E-05	0.999957
Celecoxib versus Placebo	-0.6101	-0.49	3.009357	4.005223	0.120964	0.040052235	0.968051
Diacerein versus Placebo	-0.4014	-0.4	3.866677	3.317778	0.001434	0.000366376	0.999708
Diclofenac versus Placebo	-0.9549	-1	3.465048	3.495311	-0.046	-0.01314553	0.989512
Lumiracoxib versus Placebo	-0.5905	-0.39	3.663208	3.736156	0.202042	0.054943476	0.956183
Naproxen versus Placebo	-0.419	-0.42	3.508201	3.562489	-0.00102	-0.00028847	0.99977
Rofecoxib versus Placebo	-1.017	-1.09	3.654279	4.346562	-0.07376	-0.02007989	0.98398
Topical Diclofenac versus Placebo	-0.6398	-0.61	4.005223	3.491004	0.030108	0.007478655	0.994033
Tramadol versus Placebo	-0.1957	-0.68	3.317778	2.913194	-0.49347	-0.1473462	0.882859
Valdecoxib versus Placebo	-0.338	-0.34	3.495311	4.121328	-0.00205	-0.00057914	0.999538

Comparison	MTC Mean Difference	MTC SD	Direct Weighted Mean difference	Direct Effect SD	Omega	Z	p
Celecoxib versus Rofecoxib	0.4069	-0.1	2.781132	2.781132	-0.51756	-0.1841701	0.85388

Table 232. Network Meta-Analysis Consistency Check: WOMAC Total

Comparison	MTC Mean Difference	MTC SD	Direct Weighted Mean Difference	Direct Effect SD	Omega	Z	p
Lumiracoxib versus Celecoxib	-0.4188	1.111	-0.47	34.0524	-0.05125	-0.0015	0.9988
Diclofenac versus Diacerein	-0.1763	1.818	-0.42	17.27515	-0.63141	-0.03635	0.971006
Celecoxib versus Diclofenac	2.502	2.031	2.6	36.43917	0.098305	0.002694	0.997851
Valdecoxib versus Naproxen	1.041	3.395	0.82	37.78499	-0.2228	-0.00587	0.995314
Diacerein versus Piroxicam	2.513	3.079	2.53	32.56303	0.017153	0.000524	0.999582
Tenidap versus Piroxicam	-0.4035	2.635	-0.38	41.27031	0.023596	0.000571	0.999545
Celecoxib versus Placebo	-5.996	1.09	-6.2	47.90869	-0.20411	-0.00426	0.996602
Diacerein versus Placebo	-8.321	2.303	-5.92	41.48486	2.408422	0.057966	0.953776
Diclofenac versus Placebo	-8.498	1.965	-9.9	36.68875	-1.40603	-0.03827	0.969474
Lumiracoxib versus Placebo	-6.414	1.29	-4.7	34.83313	1.716354	0.04924	0.960728
Naproxcinod versus Placebo	-6.069	2.835	-8.43	47.669	-2.36938	-0.04962	0.960428
Naproxen versus Placebo	-7.109	1.948	-7.74	86.35239	-0.63132	-0.00731	0.994168
Valdecoxib versus Placebo	-5.028	2.38	-3.74	37.7288	1.293146	0.034207	0.972712

Comparison	MTC Mean Difference	MTC SD	Direct Weighted Mean Difference	Direct Effect SD	Omega	Z	p
Tramadol versus Placebo	-8.453	3.993	-8.448	41.28798	0.005047	0.000122	0.999903

Table 233. Network Meta-Analysis Consistency Check: Adverse Events

Comparison	MTC LN Odds Ratio	MTC SD	Direct Effect LN Odds Ratio	Direct Effect SD	Omega	Z	p
Lumiracoxib 100mg versus Placebo	0.3026	0.3692	0.23	4.002017	-0.14039	-0.03493	0.972134
Lumiracoxib 100mg WLD versus Placebo	0.3403	0.37	0.27	4.076128	-0.10083	-0.02463	0.980346
Naproxcinod 750mg versus Placebo	0.2079	0.4476	-0.08	4.248963	-0.53352	-0.12487	0.90063
Naproxen 500mg versus Placebo	0.1992	0.4479	0.21	5.219101	-0.23967	-0.04575	0.963508
Celecoxib 100mg versus Placebo	-0.07778	0.2717	0.08	4.167209	-0.19252	-0.0461	0.963231
Celecoxib 200mg versus Placebo	0.1848	0.1959	0.35	4.146549	0.154445	0.037205	0.970322
High Dose Diflunisal versus Placebo	0.2966	0.4752	0.29	4.634799	-0.18717	-0.04017	0.967957
Low Dose Diflunisal versus Placebo	0.1956	0.478	0.19	4.669442	-0.29105	-0.062	0.95056
Lumiracoxib 200mg versus Placebo	-0.2919	0.2712	0.13	4.330409	-0.14176	-0.03267	0.973937
Lumiracoxib 400mg versus Placebo	0.1176	0.2718	0.09	8.483219	-0.18199	-0.02144	0.982893

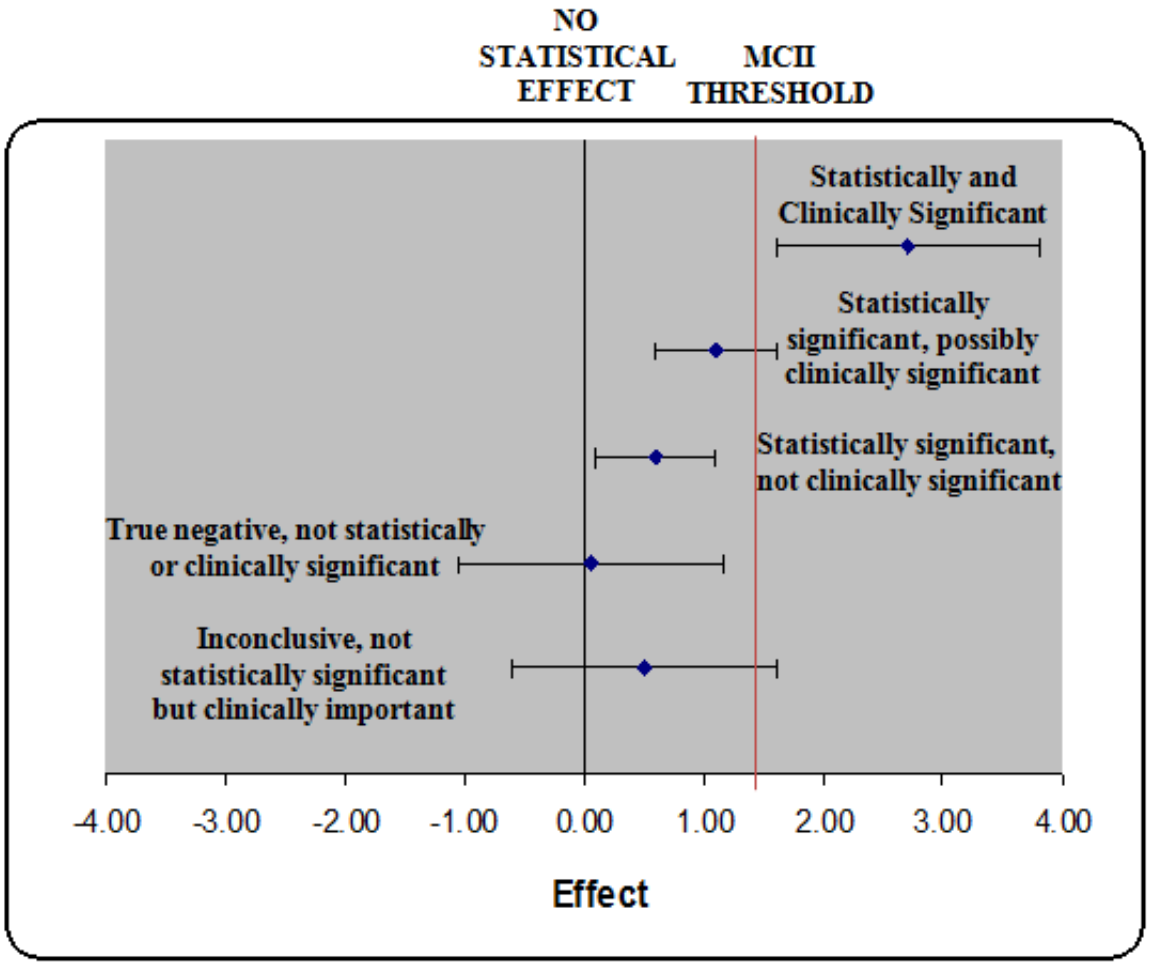
Comparison	MTC LN Odds Ratio	MTC SD	Direct Effect LN Odds Ratio	Direct Effect SD	Omega	Z	p
Rofecoxib 12.5mg versus Placebo	0.16	0.3016	0	4.232689	-0.30314	-0.07144	0.94305
Rofecoxib 25mg versus Placebo	0.2956	0.3019	0.52	4.491048	0.21909	0.048673	0.96118
Rofecoxib 12.5mg versus Nabumetone	0.1536	0.3865	0.08	3.978238	-0.30942	-0.07741	0.938297
Naproxcinod 750mg versus Naproxen 500mg	0.008678	0.4152	0.01	4.398402	-0.40884	-0.09254	0.926271
Acetaminophen versus Aceclofenac	-0.124	0.5135	-0.12	4.331515	-0.64253	-0.14729	0.882901
Lumiracoxib 100mg WLD versus Celecoxib 200mg	0.1555	0.3692	0.23	3.992522	-0.1404	-0.03502	0.972068
Celecoxib 100mg versus Celecoxib 200mg	-0.2626	0.2901	-0.17	3.990409	-0.46254	-0.11561	0.907964
Lumiracoxib 200mg versus Celecoxib 200mg	-0.4767	0.2906	0.08	4.787857	-0.21138	-0.04407	0.964851
Lumiracoxib 400mg versus Celecoxib 200mg	-0.06717	0.291	-0.04	4.112072	-0.33267	-0.0807	0.935683
High dose diflunisal versus low dose diflunisal	0.101	0.4724	0.1	4.516707	-0.37652	-0.0829	0.933928
Celecoxib 100mg versus Lumiracoxib 200mg	0.2141	0.3175	-0.17	4.047825	-0.49052	-0.12081	0.903844

Comparison	MTC LN Odds Ratio	MTC SD	Direct Effect LN Odds Ratio	Direct Effect SD	Omega	Z	p
Lumiracoxib 400mg versus Lumiracoxib 200mg	0.4096	0.2897	0.05	4.06868	-0.24092	-0.05906	0.952902
Celecoxib 100mg versus Lumiracoxib 400mg	-0.1954	0.3179	-0.22	3.976647	-0.54136	-0.1357	0.892059
Acetaminophen versus Rofecoxib 12.5mg	0.1747	0.3989	0.09	4.044641	-0.31193	-0.07675	0.938825
Celecoxib 200mg versus Rofecoxib 12.5mg	0.02484	0.305	-0.13	3.029447	-0.43945	-0.14432	0.885245
Acetaminophen versus Rofecoxib 25mg	0.03899	0.388	0.04	4.318388	-0.35083	-0.08091	0.935511
Celecoxib 200mg versus Rofecoxib 25mg	-0.1108	0.2803	-0.12	3.554488	-0.4028	-0.11297	0.910054
Rofecoxib 12.5mg versus Rofecoxib 25mg	-0.1357	0.3395	0.12	4.195686	-0.22095	-0.05249	0.95814

APPENDIX XIV

CONFIDENCE INTERVALS OF TREATMENT EFFECTS THAT RANGE IN STATISTICAL AND CLINICAL SIGNFICANCE

- Treatment effects that do not contain zero, i.e. are higher than the black line, are statistically significant
- Treatment effects that contain zero, i.e. cross the black line, are not statistically significant
- Treatment effects that are higher than the red line are clinically significant
- If only a portion of the confidence interval lies above the minimum threshold for clinical significance, its impact on patients cannot be determined
- If the entire confidence interval lies below the minimum threshold for clinical significance, i.e. is below the red line, it is not meaningful to patients
- Inconclusive treatment effects are not consistent in statistical and clinical significance
- True negative treatment effects are neither statistically or clinically significant



APPENDIX XV
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