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OARSI guidelines for the non-surgical management of knee osteoarthritis

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SUMMARY

Objective: To develop concise, up-to-date, patient-focused, evidence-based, expert consensus guidelines for the management of knee osteoarthritis (OA), intended to inform patients, physicians, and allied healthcare professionals worldwide.

Method: Thirteen experts from relevant medical disciplines (primary care, rheumatology, orthopedics, physical therapy, physical medicine and rehabilitation, and evidence-based medicine), three continents and ten countries (USA, UK, France, Netherlands, Belgium, Sweden, Denmark, Australia, Japan, and Canada) and a patient representative comprised the Osteoarthritis Guidelines Development Group (OAGDG). Based on previous OA guidelines and a systematic review of the OA literature, 29 treatment modalities were considered for recommendation. Evidence published subsequent to the 2010 OARSI guidelines was based on a systematic review conducted by the OA Research Society International (OARSI) evidence team at Tufts Medical Center, Boston, USA. Medline, EMBASE, Google Scholar, Web of Science, and the Cochrane Central Register of Controlled Trials were initially searched in first quarter 2012 and last searched in March 2013. Included evidence was assessed for quality using Assessment of Multiple Systematic Reviews (AMSTAR) criteria, and published criticism of included evidence was also considered. To provide recommendations for individuals with a range of health profiles and OA burden, treatment recommendations were stratified into four clinical sub-phenotypes. Consensus recommendations were produced using the RAND/UCLA Appropriateness Method and Delphi voting process. Treatments were recommended as Appropriate, Uncertain, or Not Appropriate, for each of four clinical sub-phenotypes and accompanied by 1–10 risk and benefit scores.

Results: Appropriate treatment modalities for all individuals with knee OA included biomechanical interventions, intra-articular corticosteroids, exercise (land-based and water-based), self-management and education, strength training, and weight management. Treatments appropriate for specific clinical sub-

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phenotypes included acetaminophen (paracetamol), balneotherapy, capsaicin, cane (walking stick), duloxetine, oral non-steroidal anti-inflammatory drugs (NSAIDs; COX-2 selective and non-selective), and topical NSAIDs. Treatments of uncertain appropriateness for specific clinical sub-phenotypes included acupuncture, avocado soybean unsaponfiables, chondroitin, crutches, diacerein, glucosamine, intra-articular hyaluronic acid, opioids (oral and transdermal), rosehip, transcutaneous electrical nerve stimulation, and ultrasound. Treatments voted not appropriate included risedronate and electrotherapy (neuromuscular electrical stimulation).

Conclusion: These evidence-based consensus recommendations provide guidance to patients and practitioners on treatments applicable to all individuals with knee OA, as well as therapies that can be considered according to individualized patient needs and preferences.

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Introduction

Osteoarthritis (OA) of the knee is a major cause of pain and locomotor disability worldwide. In January 2010, the OA Research Society International (OARSI) published an update to their evidence-based, consensus recommendations for the treatment of OA of the hip and knee[1]. The 2010 guidelines update followed two previous OARSI guidelines statements[2,3] and included systematic reviews (SRs) of the evidence for relevant therapies and critical appraisals of existing guidelines. Since the publication of the 2010 OARSI guidelines, the evidence base on knee OA treatment has evolved. This guidelines statement aims to incorporate evidence from these recent publications, in addition to the best-available previously published research, to assess where previous treatment recommendations should be modified or expanded to include new OA treatments. Because clinical considerations and availability of evidence between knee OA and hip OA treatments differ, the present guidelines sought to focus specifically on treatment of primary OA of the knee.

For the present guidelines, we endeavored to enhance the applicability of treatment recommendations by stratifying for relevant co-morbidities, and for the presence of OA in joints other than the knee(s). To synthesize the scientific literature and expert opinion, we adopted the RAND/University of California, Los Angeles Appropriateness method[4] and used a modified Delphi method to achieve expert consensus closely integrated with empirical evidence.

This statement updates the previous OARSI recommendations, incorporating literature published between January 2009 and March 2013, to scrutinize the safety and efficacy of new therapies for OA and reexamine existing therapies in light of recent evidence. These recommendations are intended to be used in conjunction with individual patient and physician's values and judgments to optimize OA treatment for different needs. These guidelines are intended for use by practitioners internationally, based on expert views of the relative safety and efficacy of available treatments for OA, irrespective of healthcare reimbursement policies or popular treatment practices.

Methodology

Literature search

Our strategy was to build on the prior OARSI literature review and guidelines by searching for meta-analyses, SRs and randomized controlled trials (RCTs) in the period subsequent to the 2010 guidelines search. The initial literature search was conducted in the first quarter of 2012, and was based on treatments from the OARSI 2010 guidelines in addition to new treatments proposed by the Osteoarthritis Guidelines Development Group (OAGDG). The search was last updated in March 2013.

We deployed electronic searches in Medline, EMBASE, Google Scholar, Web of Science, and the Cochrane Central Register of Controlled Trials using relevant subject headings and keywords and then hand-searched the reference lists of all retrieved studies and abstracts presented at pertinent scientific meetings. Publications eligible for inclusion in our literature summary were (1) the most current SRs and/or meta-analyses and (2) any randomized clinical trials published subsequent to those SRs. If multiple SRs were published in a similar time period, all were included. If no SRs or meta-analyses were available, all published RCTs were included.

Literature summary

Our approach to summation of the evidence was to update the literature summary for the prior recommendations with high-quality evidence that emerged subsequent to its publication in 2010. We selected the best-available evidence to inform guidelines development. Meta-analyses, SRs and RCTs were considered to be the highest level of evidence. The value of meta-analyses for a literature synthesis is that they provide insight across the range of available RCTs on a topic as well as forest plots, sensitivity analyses and pooled results. The data extraction team produced a summary for each intervention that included description of the study methodology with full citations, any reported safety information, and relevant outcomes including effect sizes.

The quality and level of evidence available for each treatment modality was graded according to the following:

Level/type of evidence: The highest level of available evidence used (e.g., SR and/or most current RCT).

Quality of evidence: The methodological rigor of the highest level of evidence used. Meta-analyses and SRs were assigned a quality rating of "Good", "Fair", or "Poor" using the Assessment of Multiple Systematic Reviews Tool (AMSTAR). The Cochrane Risk of Bias Assessment Method was used to rate RCTs.

Estimated Effect Sizes: If the level of evidence listed above included a meta-analysis, the Estimated Effect Size for pain *versus* control was stated from that meta-analysis. Only pooled effect sizes reported as a standardized mean difference (SMD) were reported.

Thus, the expert panel was informed with the prior OARSI guideline publications, subsequent publications generated by the literature search, and a literature summary (Bibliography available as supplement). We provided the literature summary to the OAGDG in August of 2012.

Composition of the expert panel

The OAGDG expert panel was composed of 13 voting members and a patient advocate. This group was selected for its diverse expertise and experience in OA management. The panel included seven rheumatologists (NA, FB, GH, DH, KK, TM, FR), two orthopedic surgeons (HK, SL), two physical therapists (SBZ, ER), one primary care practitioner and clinical guidelines methodologist (MU), and one physical therapy and rehabilitation specialist (YH). These

members have experience in both academic medicine and private practice, and also have expertise in clinical epidemiology and other research methodology (Appendix 1).

Management of conflict of interest (COI)

At the request of the OARSI Ethics Committee, all members of the OAGDG were required to complete a COI questionnaire to report any potential conflicts including consulting, grant support, practice revenue, intellectual property, etc. for each treatment (Appendix 1). During initial rounds of voting, OAGDG members were instructed to recuse themselves from voting on potentially conflicted treatment modalities. At the April 2013 OARSI meeting, OAGDG members updated disclosures and discussed these conflicts in person with an ethics committee member prior to the final round of voting. The Ethics Committee representative made a final determination regarding the level at which a potential conflict would disqualify an OAGDG member from voting on each treatment. Final disclosure and voting recusal results were twice distributed among the OAGDG to verify their accuracy.

Role of funding source

This project was commissioned and funded by OARSI, yet was developed independently by the OARSI Treatment Guidelines Committee. The funding source did not participate in the literature search; determination of study eligibility criteria; voting process; data analysis or interpretation; or manuscript preparation. The manuscript was reviewed and approved by OARSI's Executive Committee prior to release for public comment.

OARSI receives sponsorship from Bioiberica, EMD Serono, Expanscience, Rottapharm/Madaus, Abbvie, Astellas, Bioventus, Boston Imaging Core Lab (BICL), Chondrometrics, Fidia Pharma USA, Flexion, Perceptive Informatics, Merck, Seikagaku, Servier, and Zimmer. No direct medical industry support was used or requested for guideline development. Guidelines development was a budgeted item in OARSI's annual budget.

Formulation of recommendations

Role of the expert panel

The literature summary was released to the OAGDG in August of 2012. An updated literature summary was released in October 2012 to inform subsequent rounds of voting (Bibliography available in supplement). Their role was to use the evidence base along with their expert knowledge, to provide votes on the appropriateness of each treatment modality, according to RAND/UCLA methodology[4], and also an assessment of benefit and risk. The RAND/UCLA methodology is a highly-established approach that was explicitly developed to leverage expert opinion about interventions in situations where the evidence may be incomplete.

After an initial round of voting that occurred after viewing the evidence, but prior to any discussion, the results were scrutinized by the OAGDG using an online forum to generate discussion and clarifications. Subsequent rounds of voting were performed to with further stratifications of treatment modalities (e.g., non-steroidal anti-inflammatory drugs (NSAIDs) were split into non-selective, selective COX-2 inhibitors, and topical) in October of 2012, March of 2013, and during the OAGDG's face-to-face meeting in April of 2013.

OA clinical sub-phenotypes. In order to enhance the specificity of the treatment recommendations for individuals with varying health profiles and OA burden, we defined four clinical sub-phenotypes (Table I). The rationale for these stratifications was that co-morbidities and the presence of OA in other joints might influence treatment choices. However, in all situations the voting was focused on treatment of the knees, and not on treatment of the non-knee joints. The OAGDG also decided on treatments that might merit separate evaluation of symptomatic and structural outcomes.

Voting and scoring. For each treatment modality, the OAGDG voted on appropriateness using a nine-point scale (1–9), therapeutic benefit on a 10-point scale (1–10), and overall risk on a 10-point scale (1–10).

According to the RAND/UCLA Appropriateness Method[4], the panelists ranked the appropriateness of each treatment on a nine-point scale, in which a score in the range 1–3 is considered 'inappropriate', 4–6 'uncertain', and 7–9 'appropriate'. We then pooled these scores to generate a median appropriateness score for each treatment according to patient sub-phenotype. In addition, according to RAND/UCLA methodology, we classified the presence of 'disagreement' among the votes for a treatment modality if greater than one-third fell in the opposite tertile to the median score [e.g., a vote was considered in "Disagreement" if it received an "Appropriate" median vote ($\geq$7) with five of 13 members voting "Not appropriate" ($\leq$3)]. Finally, we classified a treatment as "Appropriate" if it received a median score of $\geq$7 without disagreement. A treatment was classified as "Not appropriate" if it received a median vote of $\leq$3 or lower without disagreement. A treatment receiving a score between 3 and 6, or a treatment with disagreement, was classified as "Uncertain". An "Uncertain" recommendation can reflect either the ambiguous state of current evidence or equivocal appropriateness either due to a moderately unfavorable risk profile or to limited efficacy. However, the 'uncertain' classification is not intended to be a negative recommendation or preclude use of that therapy. Rather it indicates a role for physician–patient interaction in determining whether this treatment may have merit in the context of their individual characteristics, co-morbidities and preferences.

Each OAGDG member also voted separately on the level of risk and the level of benefit associated with each treatment. Risk was

Table I
Stratification into sub-phenotypes

OA joint type	**Knee-only OA**: Symptomatic OA in one or both knees only. **Multiple-joint OA***: Symptomatic OA of the knee(s) in addition to other joints (e.g., hip, hand, spine, etc).
Co-morbidities	**No co-morbidities**: The individual with OA has no pertinent co-morbid health concerns. **Co-morbidities**: The individual with OA has any of the following pertinent co-morbid health concerns: diabetes; hypertension; CV disease; renal failure; gastrointestinal (GI) bleeding; depression; or physical impairment limiting activity, including obesity. • **Moderate co-morbidity risk**†: The individual with OA has any of the following pertinent co-morbid health concerns: diabetes; advanced age; hypertension; CV disease; renal failure; GI complications; depression; or physical impairment limiting activity, including obesity. • **High co-morbidity risk**†: The individual with OA has risk factors such as history of GI bleed, myocardial infarction, chronic renal failure, etc.

* Defines a clinical sub-phenotype. Recommendations refer to treatment of the knee(s) in such individuals.

† For Oral NSAIDs (both non-selective and selective COX-2 inhibitors). Further stratification of risk categories was considered necessary for these treatments given the important safety implications and substantial availability of safety data.

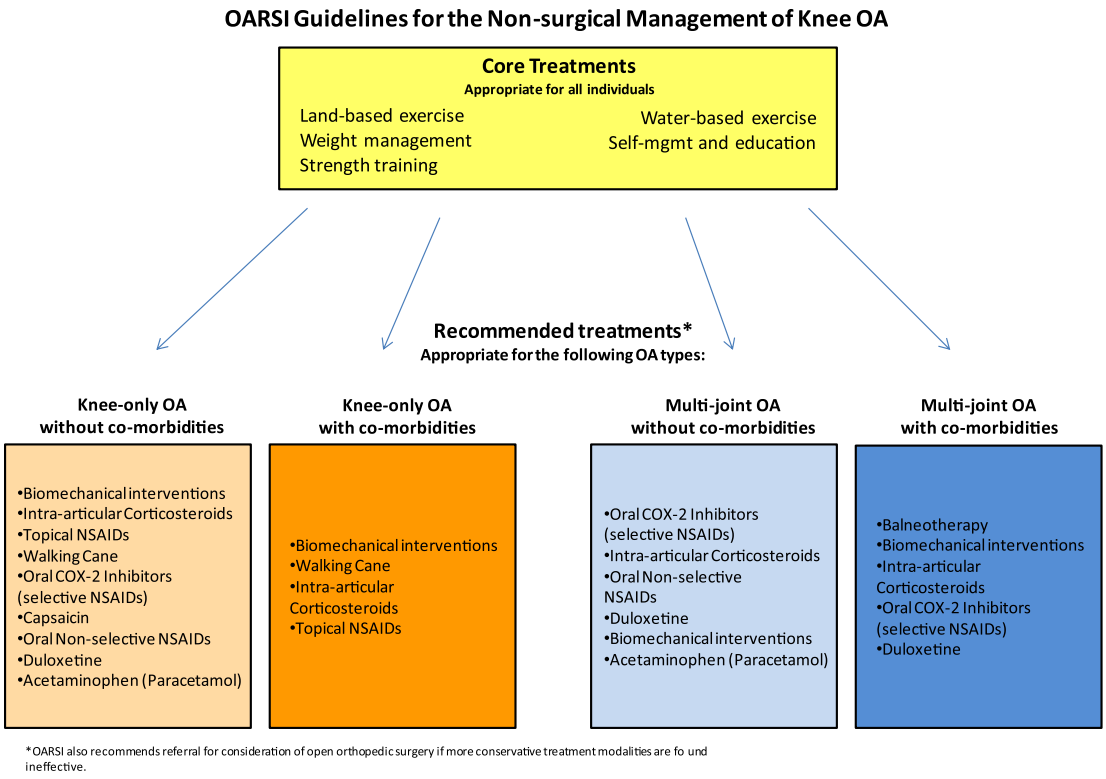


Fig. 1. Appropriate treatments summary.

scored from 1 (least risk) to 10 (most risk) and benefit was scored from 1 (no benefit) to 10 (most beneficial). The group's mean risk and benefit scores [along with 95% confidence intervals (CIs)] for each treatment are plotted separately as bar graphs within the guidelines statement (Appendix 2: Annotated Figure).

The OARSI guidelines report was drafted after a face-to-face meeting and re-vote at the OAGDG meeting at the April 2013 OARSI World Congress. These guidelines provide recommendations according to the median "appropriateness" scores voted upon by a panel of expert physicians and researchers based on their knowledge and the literature summary.

Figure 1 provides a summary of all treatments voted "Appropriate," organized by clinical sub-phenotype. The OAGDG's median voting scores for appropriateness, upon which the recommendations are based, are appended in a summary table (Appendix 3). Also included are the OAGDG's mean risk scores, benefit scores, and composite benefit and risk scores for each treatment and clinical sub-phenotype. The composite benefit and risk score is the product of the benefit score (1–10) and the transposed risk score (where 1 = highest and 10 = safety) yielding a range of 1 (worst) to 100 (best).

Public comment. The guidelines report draft was disseminated for public comment between September 4th and 18th, 2013. At the conclusion of the public comment period, public responses to the guidelines report were distributed among the OAGDG in order to formulate an appropriate response. Consistent with the OAGDG's prior procedures, it was determined that omission of any research within the committee's original literature summary criteria would necessitate a re-vote on the treatment for which evidence was omitted. Additional evidence for balneotherapy and chondroitin was brought to the attention of the OAGDG during public comment, resulting in an update of the evidence report and a re-vote on each of these interventions by the OAGDG expert panel. To incorporate the new chondroitin evidence, pooled analyses of pain and function outcomes were conducted for randomized clinical trials of chondroitin in knee OA. The balneotherapy evidence was considered too heterogeneous to permit pooled analysis. The finalized guidelines report draft was submitted for publication following approval of the OARSI Executive Committee.

Recommendations

Non-pharmacological interventions

Acupuncture

Recommendation:

- **Uncertain**

Rationale:

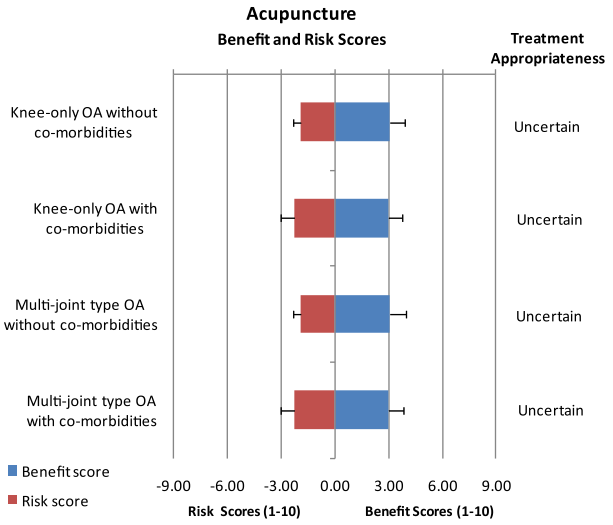
The efficacy of acupuncture for peripheral joint OA has been tested in numerous clinical trials. Trials using waiting list- or usual care control groups, have generally found a clinically relevant benefit, but those using a sham-acupuncture have been less positive[5]. A recent pooled analysis of 16 RCTs found statistically significant benefit of acupuncture in sham-controlled trials, though this did not reach the investigators' threshold for clinical significance[5].

Quality assessment:

Level of evidence: SR and meta-analysis of RCTs.
Quality of evidence: Good.

Estimated Effect Size for

Pain (SMD): 0.28 (0.11–0.45)[5].
Function (SMD): 0.28 (0.09–0.46)[5].



Balneotherapy/spa therapy

Recommendation:

- **Appropriate**: individuals with multiple-joint OA and relevant co-morbidities
- **Uncertain**: individuals without relevant co-morbidities
- **Uncertain**: individuals with knee-only OA

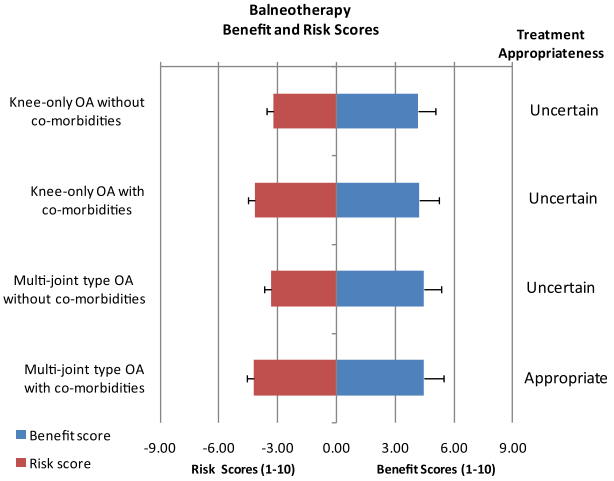
Rationale:

Balneotherapy (defined as the use of baths containing thermal mineral waters) includes practices such as Dead Sea salt or mineral baths, sulfur baths, and radon-carbon dioxide baths. Two 2009 SRs and a 2009 RCT demonstrated benefit of balneotherapy for pain when compared with controls, but the methodologic quality of trials was poor and both reviews concluded that additional large and well-designed RCTs are needed[6–8]. No significant safety concerns were found to be associated with balneotherapy, though reporting of adverse events was patchy among included trials[7,9]. In the voting, balneotherapy was considered appropriate only for the sub-phenotype with multiple-joint OA and co-morbidities, due to paucity of treatment alternatives for that group.

Quality assessment:

Level of evidence: SR and meta-analysis of RCTs.
Quality of evidence: Fair.

Estimated Effect Size for Pain or Function: Not available.



Biomechanical interventions

Recommendation:

- **Appropriate**

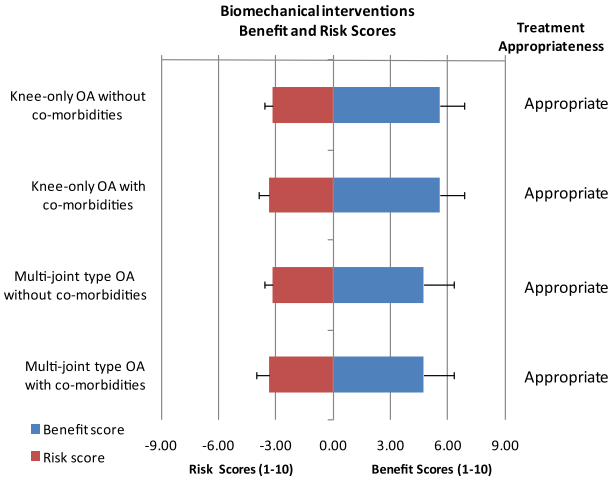
Rationale:

We recommend use of biomechanical interventions as directed by an appropriate specialist. A 2011 SR and three recent RCTs evaluated the effectiveness of knee braces, knee sleeves, and foot orthoses in conservative management of knee OA[10–13]. One review suggested that knee braces and foot orthoses were effective in decreasing pain, joint stiffness, and drug dosage and also improved physical function, with insignificant adverse events[10]. The conclusions were limited due to the heterogeneity and poor quality of available evidence. Results regarding lateral wedge insoles varied, with one RCT demonstrating no symptomatic or structural benefits[11] and another asserting their appropriateness as a possible alternative to valgus bracing for conservative medial knee OA treatment[12]. One recent RCT found that variable-stiffness walking shoes reduced adduction movement and pain and improved function after 6 months of wear, though this benefit was not statistically significant when compared to constant-stiffness footwear[13].

Quality assessment:

Level of evidence: SR of RCTs and non-randomized clinical trials.
Quality of evidence: Fair.

Estimated Effect Size for Pain or Function: Not available.



Cane (walking stick)

Recommendation:

- **Appropriate**: knee-only OA
- **Uncertain**: multiple-joint OA

Rationale:

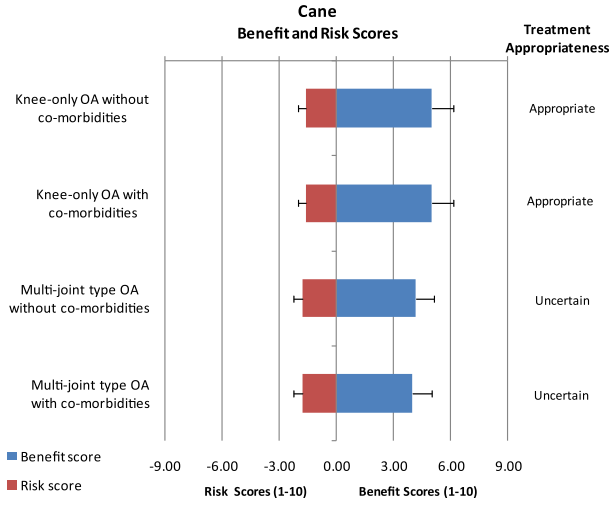
A single-blind RCT concluded that canes, in comparison with usual disease management, could be used to diminish pain and improve function and some aspects of quality of life in participants with knee OA[14]. A substantial increase in energy expenditure in the first month of cane use was no longer a factor for concern by the end of the second month. There was a lack of evidence regarding

cane use for individuals with multiple-joint type OA. This treatment could be inappropriate for some such individuals, as cane use to relieve knee pain may increase weight-bearing load on other affected joints (e.g., contralateral hand and hip joints), though further research is needed to confirm this.

Quality assessment:

Level of overall evidence: Single-blind RCT.
Quality of overall evidence: Fair.

Estimated Effect Size for Pain or Function: Not available.



Crutches

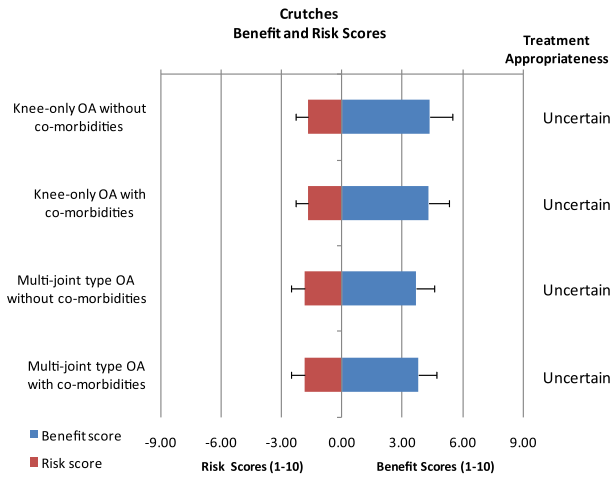
Recommendation:

- **Uncertain**

Rationale:

There is insufficient evidence at this time to support the use of crutches as an appropriate alternative to cane use.

Level of Evidence: Expert consensus of OAGDG.
Quality of evidence: No available trials.
Estimated Effect Size for Pain or Function: Not available.



Electrotherapy/neuromuscular electrical stimulation

Recommendation:

- **Not appropriate**

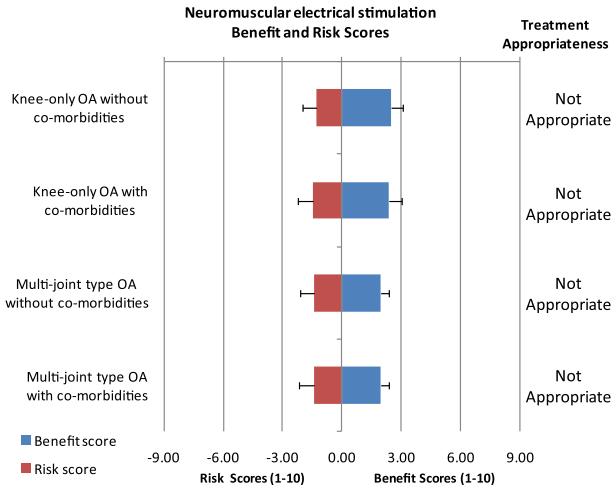
Rationale:

A 2012 SR and meta-analysis demonstrated conflicting efficacy data for neuromuscular electrical stimulation and concluded that additional studies were needed to determine the efficacy of this intervention[15]. A recent RCT showed no significant additive effect of electromyograph (EMG) biofeedback to strengthening exercise for pain, function and muscle strength in 40 participants with knee OA[16].

Quality assessment:

Level of evidence: SR and meta-analysis of RCTs.
Quality of evidence: Fair.

Estimated Effect Size for Pain or Function: Not available.



Exercise (land-based)

Recommendation:

- **Appropriate**

Rationale:

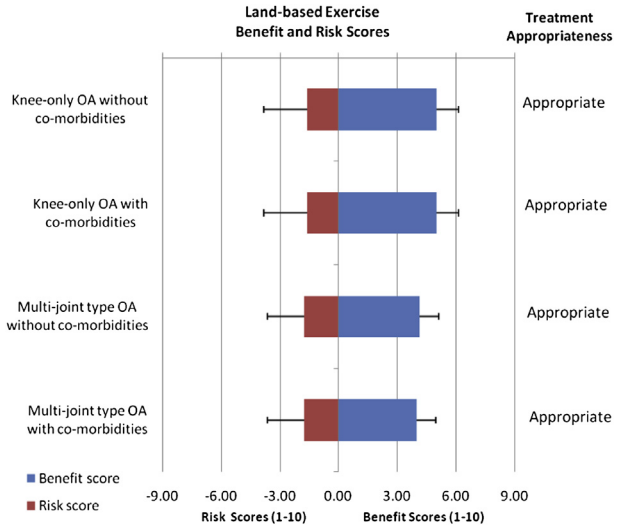
Four recent meta-analyses found small but clinically relevant short-term benefits of land-based exercise for pain and physical function in knee OA[17–20]. Meta-analyses investigating t'ai chi found strong favorable benefits of t'ai chi for improving pain and physical function in individuals with knee OA[21,22]. The duration and type of exercise programs included in these meta-analyses varied widely, but interventions included a combination of elements including strength training, active range of motion exercise, and aerobic activity. Results were generally positive among land-based exercise type, and did not significantly favor any specific exercise regimens[17–20].

Quality assessment:

Level of evidence: SR and meta-analysis of RCTs.
Quality of evidence: Good.

Estimated Effect Size for

Pain (SMD): Ranges from 0.34 (0.19–0.49)[17] to 0.63 (0.39–0.87)[21].
Function (SMD): 0.25 (0.03–0.48)[17].



Exercise (water-based)

Recommendation:

- **Appropriate**

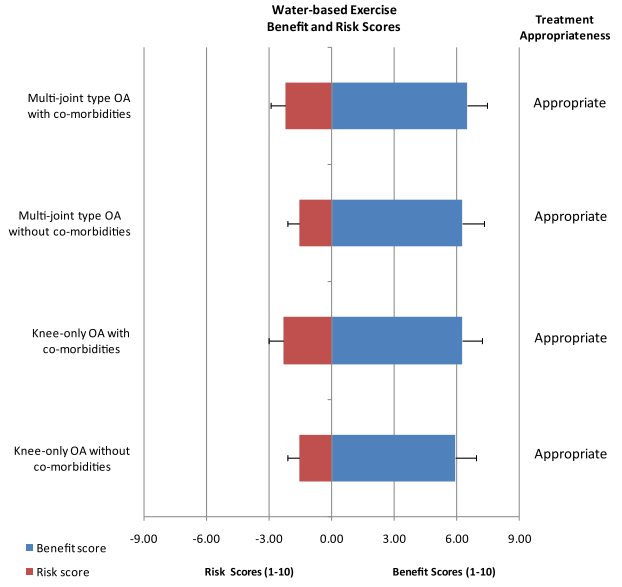
Rationale:

A 2007 SR investigating water-based exercise in knee and hip OA found small to moderate short-term benefits for function and quality of life, but only minor benefits for pain[23].

Quality assessment:

Level of evidence: SR and meta-analysis of RCTs and quasi-randomized trials.
Quality of evidence: Good.

Estimated Effect Size for Pain or Function: Not available.



Strength training

Recommendation:

- **Appropriate**

Rationale:

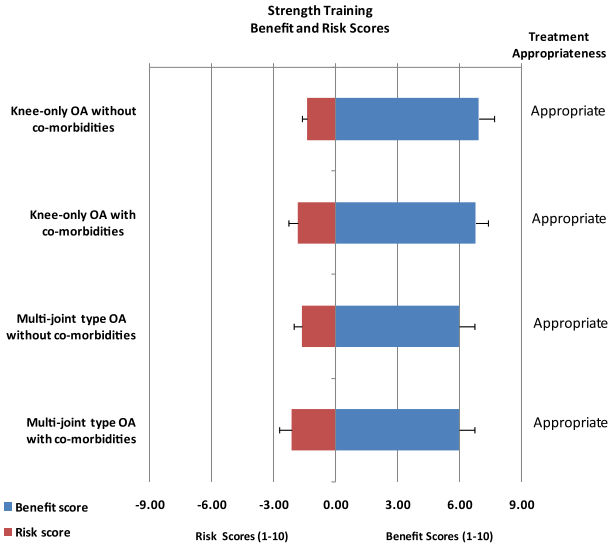
A 2011 meta-analysis and SR demonstrated moderate effect sizes of strength training for reducing pain and improving physical function compared with controls[17]. Strength training programs primarily incorporate resistance-based lower limb and quadriceps strengthening exercises. Both weight-bearing and non-weight-bearing interventions were included, as well as group and individual programs. Participants experienced similarly significant improvement with each of these programs.

Quality assessment:

Level of evidence: SR and meta-analysis of RCTs.
Quality of evidence: Good.

Estimated Effect Size for

Pain (SMD): 0.38 (0.23–0.54)[17].
Function (SMD): 0.41 (0.17–0.66)[17].



Self-management and education

Recommendation:

- **Appropriate**

Rationale:

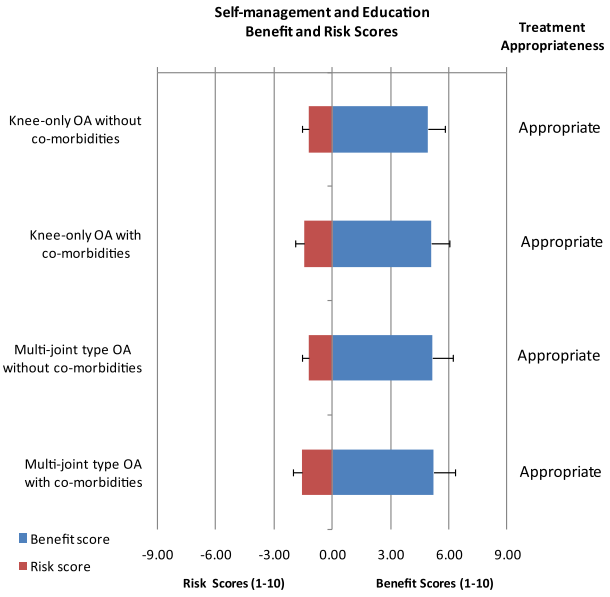
A 2011 meta-analysis and a 2005 meta-analysis found moderate benefits of self-management programs for chronic musculoskeletal pain conditions on measures of pain and disability[24,25]. Analysis of arthritis-related disability showed only modest benefit. Recent randomized clinical trials indicated significant clinical benefits of self-management[26,27] and suggested feasibility of implementation in primary care by means of group sessions[28] and telephone-based sessions[29]. Another RCT expressed reservations about the efficacy and practicality of such interventions[30].

Quality assessment:

Level of evidence: SR and meta-analysis of RCTs.
Quality of evidence: Good.

Estimated Effect Sizes for

Pain (SMD): Ranges from 0.06 (0.02–0.10)[25] to 0.29 (0.17–0.41)[24].



Transcutaneous electrical nerve stimulation (TENS)

Recommendation:

- **Uncertain**: knee-only OA
- **Not appropriate**: multiple-joint OA

Rationale:

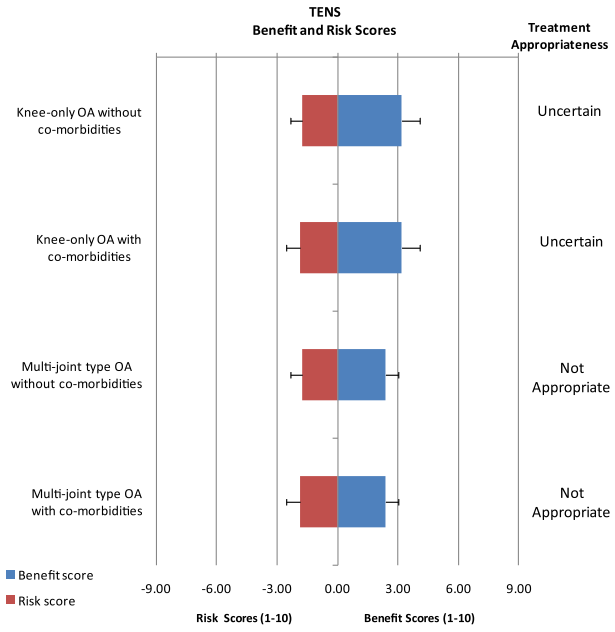
A 2009 SR found inconclusive results regarding the effect of TENS for pain relief in knee OA[31]. Due to the low methodological quality and high heterogeneity of included trials, no effect size was reported as a primary result. The review found no evidence to suggest that TENS was unsafe. A recent RCT revealed no statistically significant difference for pain between TENS and a sham TENS procedure[32].

Quality assessment:

Level of evidence: SR of randomized or quasi-randomized clinical trials.
Quality of evidence: Good.

Estimated Effect Size for

Pain (SMD): 0.07 (−0.32–0.46)[31].
Function (SMD): 0.34 (0.14–0.54)[31].



Weight management

Recommendation:

- **Appropriate**

Rationale:

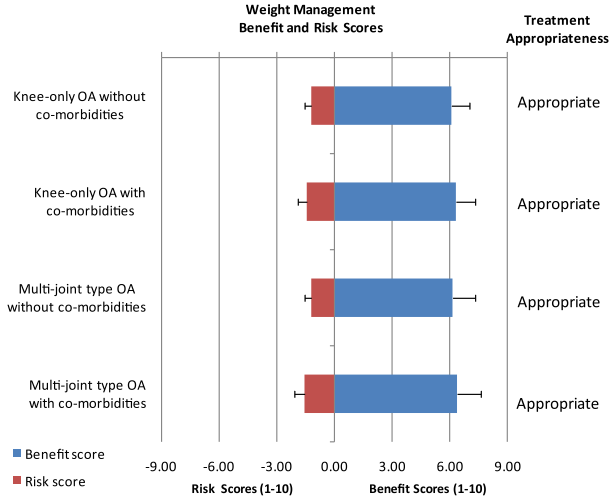
A 2007 SR and meta-analysis found reductions in pain and physical disability for overweight participants with knee OA after a moderate weight reduction regime[33]. The analysis supported the notion that a weight loss of 5% should be achieved within a 20-week period—that is, 0.25% per week—for the treatment to be efficacious.

Quality assessment:

Level of overall evidence: SR and meta-analysis of RCTs.
Quality of overall evidence: Good.

Estimated Effect Size for

Pain (SMD): 0.20 (0.0–0.39)[33].
Function (SMD): 0.23 (0.04–0.42)[33].



Ultrasound

Recommendation:

- **Uncertain**: knee-only OA
- **Not appropriate**: multiple-joint OA

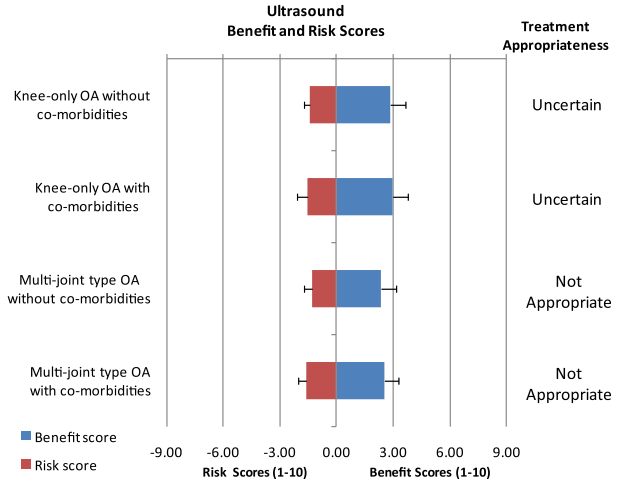
Rationale:

Two 2010 SRs suggested a possible beneficial effect of ultrasound for knee OA; however, the quality of the analyzed evidence was low[34,35]. No safety risks were reported to be associated with ultrasound. A 2012 RCT found no significant differences between the groups for pain or function[36].

Quality assessment:

Level of evidence: SR and meta-analysis of RCTs.
Quality of evidence: Good.

Estimated Effect Size for Pain (SMD): Ranges from 0.49 (0.18–0.79)[35] to 0.49 (0.23–0.76)[34].



Pharmacological interventions

Acetaminophen (paracetamol)

Recommendation:

- **Appropriate**: individuals without relevant co-morbidities
- **Uncertain**: individuals with relevant co-morbidities

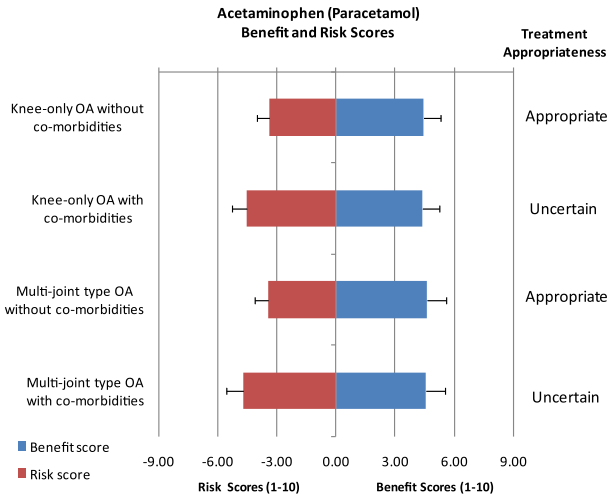
Rationale:

A 2010 SR and meta-analysis abstract found a low-level effect of acetaminophen for OA pain, suggesting usefulness as a short-term analgesic[37]. However, both this review and a 2012 safety review indicated increased risk of adverse events associated with acetaminophen use, including GI adverse events and multi-organ failure[38]. These recent findings suggest greater risk associated with acetaminophen use (particularly when used for extended durations) than previously thought. Thus, we recommend conservative dosing and treatment duration consistent with approved prescribing limits.

Quality assessment:

Level of evidence: SR and meta-analysis of RCTs.
Quality of evidence: Good.

Estimated Effect Size for Pain (SMD): 0.18 (0.11–0.25)[37].



Avocado soybean unsaponfiables (ASU)

Recommendation:

- **Uncertain**

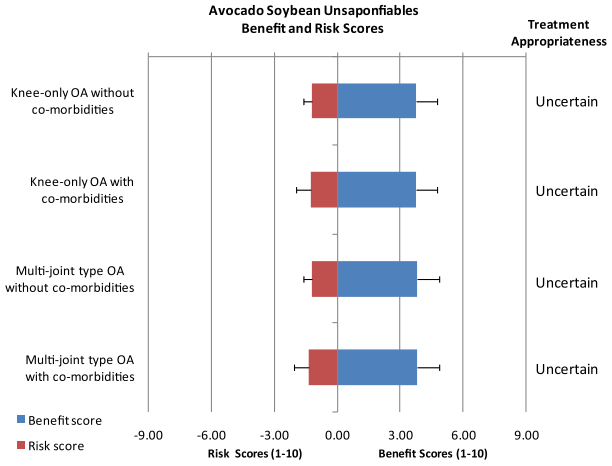
Rationale:

A 2008 SR and meta-analysis comparing ASU with oral placebo in 644 patients with knee and hip OA demonstrated a small benefit for pain in favor of ASU that was more evident in knee OA[39].

Quality assessment:

Level of evidence: SR and meta-analysis of RCTs.
Quality of evidence: Good.

Estimated Effect Size for Pain (SMD): 0.39 (0.01–0.76)[39].



Capsaicin

Recommendation:

- **Appropriate**: knee-only OA without relevant co-morbidities
- **Uncertain**: multi-joint OA and individuals with relevant co-morbidities

Rationale:

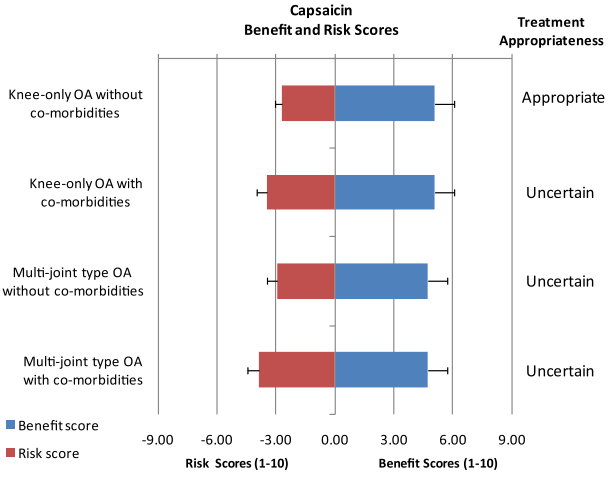
Citing a previous SR[40] and RCT[41], a 2011 comparative efficacy review concluded that topical capsaicin was superior to placebo for

50% pain reduction (number needed to treat 8.1) but associated with increased local adverse events [54% vs 15%; relative risk (RR) 3.6 (95% CI: 2.6–5.0)] and withdrawals due to adverse events [13% vs 3%; RR 4.0 (95% CI: 2.3–6.8)][42].

Quality assessment:

Level of evidence: SR of RCTs.
Quality of evidence: Good.

Estimated Effect Size for Pain and Physical function: Not available.



Corticosteroids (intra-articular injection)

Recommendation:

- **Appropriate**

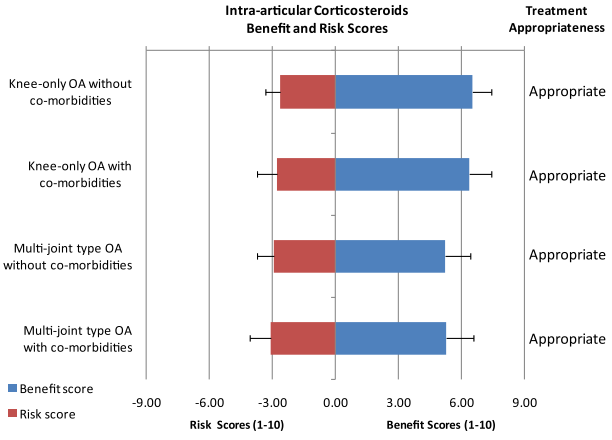
Rationale:

Two recent SRs demonstrated clinically significant short-term decreases in pain[43,44]. Short-term effects were found to be significantly greater than those of intra-articular hyaluronic acid. The reviews concluded that for longer duration of pain relief, clinicians should consider other treatment options.

Quality assessment:

Level of evidence: SR and meta-analysis of RCTs.
Quality of evidence: Good.

Estimated Effect Size for Pain: Not available.



Chondroitin (for symptom relief)

Recommendation:

- **Uncertain**

Chondroitin (for disease modification)

Recommendation:

- **Not appropriate**

Rationale:

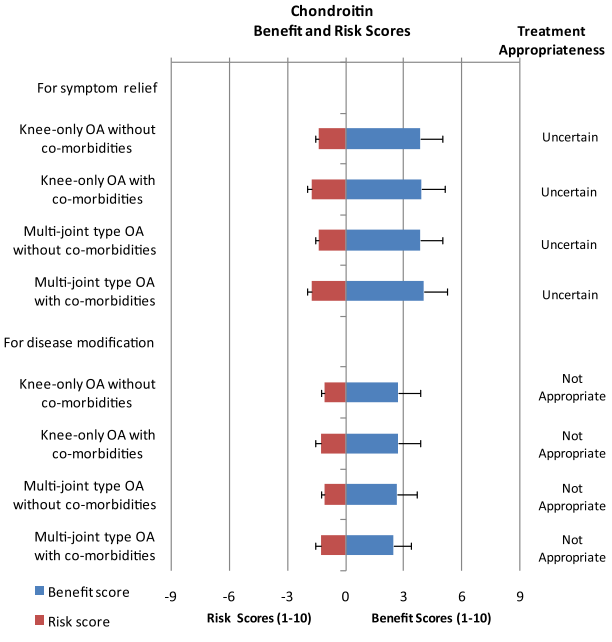
Four SRs examined the efficacy of chondroitin for knee OA[45–48]. Results differed regarding symptom relief, with some reviews finding no significant benefit of chondroitin over placebo for pain and others finding large effect sizes in favor of chondroitin. A high degree of heterogeneity and small, poor quality included trials in one meta-analysis made definitive assessment difficult[46]. Effect sizes for pain were small to non-existent [e.g., 0.01 (95% CI: −0.07–0.13)] in stratified analyses of large-scale, high-quality trials[46]. Another meta-analysis showed no statistically significant benefit of chondroitin when compared with placebo[45]. Results were also mixed regarding disease modification, with only some studies showing statistically significant decreases in joint-space narrowing (JSN) over longer (2-year) follow-up[47,48].

Quality assessment:

Level of evidence: SR and meta-analysis of RCTs.
Quality of evidence: Good.

Estimated Effect Size for Pain (SMD): Ranges from 0.13 (0.00–0.27)[45] to 0.75 (0.50–0.99)[46].

Estimated Effect Size for reduction in rate of decline of minimum joint-space width (SMD): Ranges from 0.26 (0.14–0.38)[47] to 0.30 (0.00–0.59)[48].



Diacerein

Recommendation:

- **Uncertain**

Rationale:

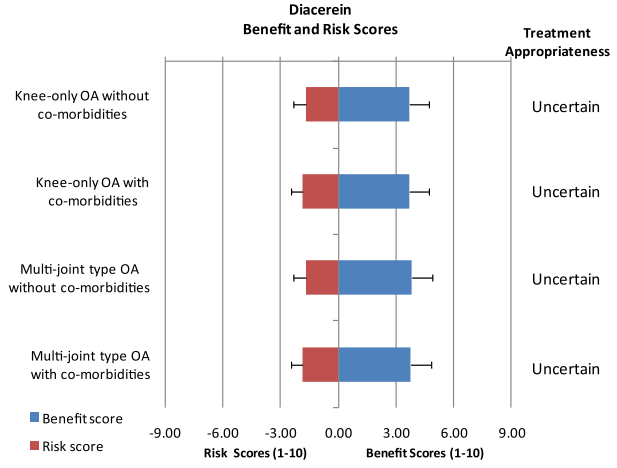
A 2010 SR and meta-analysis found a small but statistically significant short-term benefit of diacerein for pain compared with placebo, despite a large degree of heterogeneity among included trials[49]. The review also found a significantly increased risk of diarrhea among those receiving diacerein [RR = 3.51 (95% CI: 2.55–4.83, $P < 0.001$)]. The study authors suggested that diacerein may still be a safer alternative to NSAIDs, which are associated with more severe adverse events, but also concluded that more high-quality trials are needed to confirm the efficacy of diacerein and rule out publication bias.

Quality assessment:

Level of evidence: SR and meta-analysis of RCTs.
Quality of evidence: Good.

Estimated Effect Size for

Pain (SMD): 0.24 (0.08–0.39)[49].
Function (SMD): 0.14 (0.03–0.25)[49].



Duloxetine

Recommendation:

- **Appropriate**: individuals without co-morbidities
- **Appropriate**: individuals with multiple-joint OA and relevant co-morbidities
- **Uncertain**: knee-only OA with relevant co-morbidities

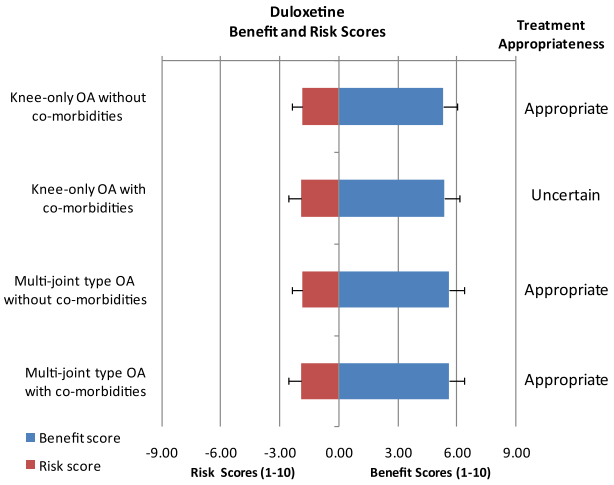
Rationale:

A 2012 SR and a 2011 RCT comparing duloxetine with oral placebo found duloxetine efficacious and tolerable for chronic pain associated with OA[50,51]. Pooled analysis found that 16.3% of the patients who received duloxetine withdrew due to adverse events compared with 5.6% of those receiving placebo[50]. The most commonly reported adverse events included nausea, dry mouth, somnolence, fatigue, constipation, decreased appetite, and hyperhidrosis. While duloxetine was considered appropriate for most clinical sub-phenotypes, associated adverse events and availability of more targeted therapies predicated uncertain appropriateness for individuals with knee-only OA and co-morbidities.

Quality assessment:

Level of evidence: SR and meta-analysis of RCTs.
Quality of evidence: Fair.

Estimated Effect Size for Pain: Not available.



Glucosamine (for symptom relief)

Recommendation:

- **Uncertain**

Glucosamine (for disease modification)

Recommendation:

- **Not appropriate**

Rationale:

Two SRs comparing glucosamine with placebo for OA found mixed results regarding the efficacy of glucosamine for pain relief and physical function[45,52]. One review found no statistically significant benefit of glucosamine for pain[45] and the other found a positive effect for pain that did not reach statistical significance when confined to studies with adequate allocation concealment[52]. The most recent meta-analysis[45] included a large, NIH-funded RCT (GAIT study) that had a null result for glucosamine for pain relief[53]. Regarding disease modification, a SR found no statistically significant differences in minimum JSN between glucosamine and placebo at 1-year follow-up, though a moderate effect was detected at 3 years[48]. A 2011 safety review found that long-term use of glucosamine was not associated with cardiovascular (CV) safety risks[54]. Two more meta-analyses found no increase in overall adverse events relative to placebo[45,52]. Small pooled effect sizes (especially for the large high-quality studies), inconsistency in results between industry-sponsored and independent trials, and heterogeneity among studies generated uncertainty as to the appropriateness of glucosamine.

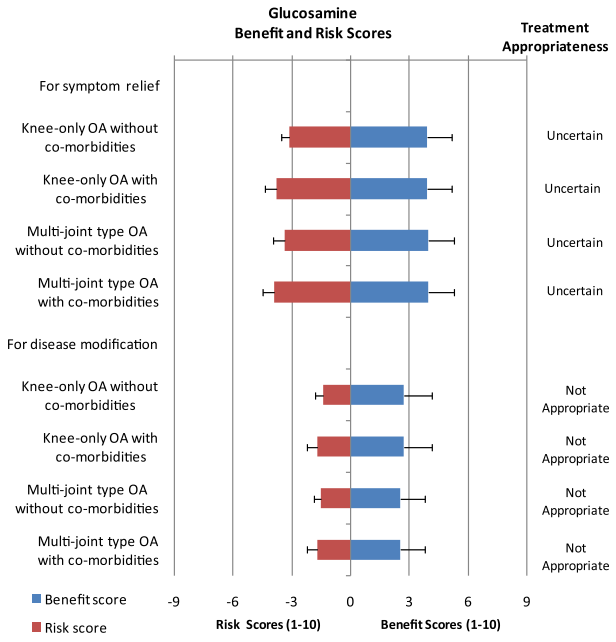
Quality assessment:

Level of evidence: SR and meta-analysis of RCTs.

Quality of evidence: Good.

Estimated Effect Size for Pain (SMD): Ranges from 0.17 (0.05, 0.28)[45] to 0.47 (0.23–0.72)[52].

Estimated Effect Size for reduction in rate of decline of minimum joint-space width (SMD): 0.08 (−0.12–0.27)[48].



Hyaluronic acid (intra-articular injection)

Recommendation:

- **Uncertain**: knee-only OA
- **Not appropriate**: multiple-joint OA

Rationale:

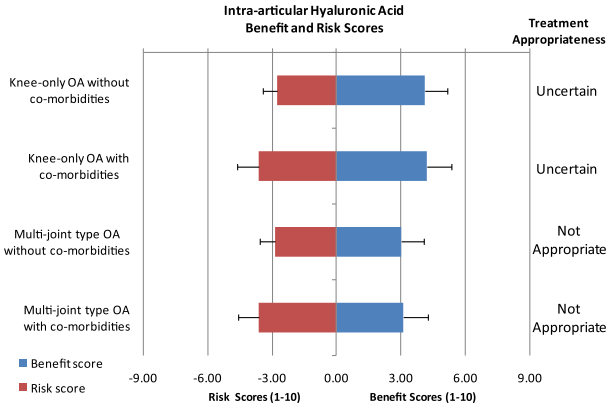
A recent SR demonstrated small but significant efficacy of intra-articular hyaluronic acid for knee OA pain by week 4 with a peak at week 8 (reaching moderate clinical significance) and residual benefit until 24 weeks[55]. Another review found moderate benefits of IAHA for pain and physical function in knee OA, though sensitivity analyses including larger trials or trials with adequate blinding found only small effect size for pain[56]. A third review comparing IAHA with intra-articular corticosteroids (IACS) found that while IACS provided greater benefit for pain 2 weeks after injection, IAHA provided greater benefit at 12 and 26 weeks[43]. Inconsistent conclusions among the meta-analyses and conflicting results regarding IAHA's safety influenced panel votes.

Quality assessment:

Level of evidence: SR and meta-analysis of RCTs.
Quality of evidence: Good.

Estimated Effect Size for

Pain (SMD): Ranges from 0.37 (0.28–0.46)[56] to 0.46 (0.28–0.65)[55].
Physical function: 0.33 (0.22–0.43)[56] to 0.31 (0.11–0.51)[55].



NSAIDs (oral non-selective NSAIDs)

Recommendation:

- **Appropriate**: individuals without co-morbidities
- **Uncertain**: individuals with moderate co-morbidity risk
- **Not appropriate**: individuals with high co-morbidity risk

Gastroprotection:

- We do not recommend proton-pump inhibitor (PPI) co-prescription with non-selective oral NSAIDs for those with no co-morbidity risk. For those with moderate or high co-morbidity risk receiving oral non-selective NSAIDs, we recommend PPI co-prescription, though we strongly advise against using oral NSAIDs altogether for individuals with high co-morbidity risk.

Rationale:

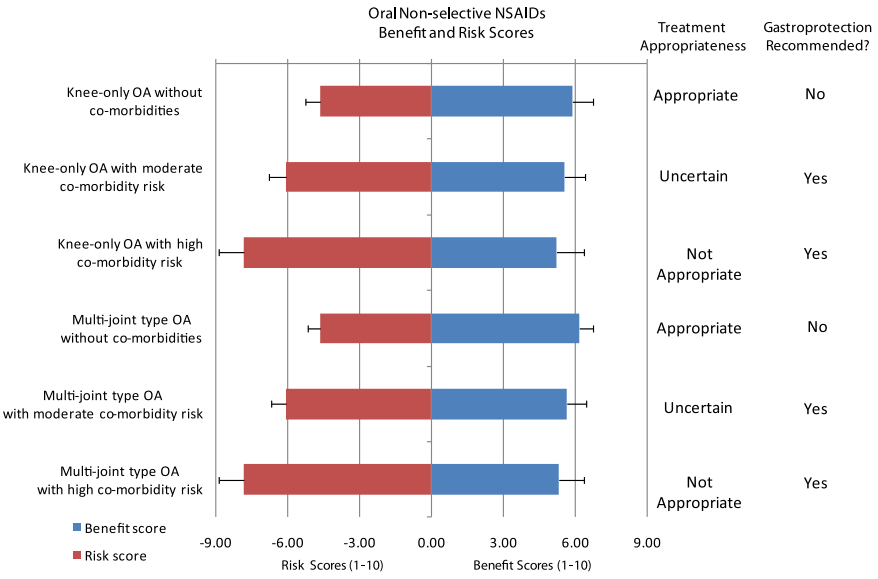
A 2011 comparative effectiveness review indicated that NSAIDs are associated with increased risk of serious GI, CV, and renal harms compared with placebo[42]. Nevertheless, the CV safety of naproxen appeared moderately superior to that of any COX-2 selective NSAID in two SRs of RCTs. Among currently marketed NSAIDs, diclofenac is associated with the highest rate of hepatic laboratory abnormalities. Due to serious safety risks associated with oral NSAID use, we recommend conservative dosing and treatment duration consistent with approved prescribing limits.

The 2011 Cochrane review found that co-prescribing of PPIs, misoprostol, and H2-antagonists reduced the risk of endoscopically detected gastroduodenal ulcers compared with placebo in persons prescribed non-selective NSAIDs[42].

Quality assessment:

Level of evidence: SR and meta-analysis of RCTs.
Quality of evidence: Good.

Estimated Effect Size for Pain (SMD): 0.37 (0.26–0.49)[57].



NSAIDs (oral COX-2 inhibitors)

- **Appropriate**: individuals without co-morbidities
- **Appropriate**: multiple-joint OA with moderate co-morbidity risk
- **Uncertain**: knee-only OA with moderate co-morbidity risk
- **Not appropriate**: individuals with high co-morbidity risk

Gastroprotection:

- We do not recommend PPI co-prescription with COX-2 selective oral NSAIDs for those with no co-morbidity risk. For individuals with moderate co-morbidity risk, we advocate neither for nor against PPI co-prescription. For individuals with high co-morbidity risk receiving oral COX-2 selective NSAIDs, we recommend PPI co-prescription, though we strongly advise against using oral NSAIDs altogether for such individuals.

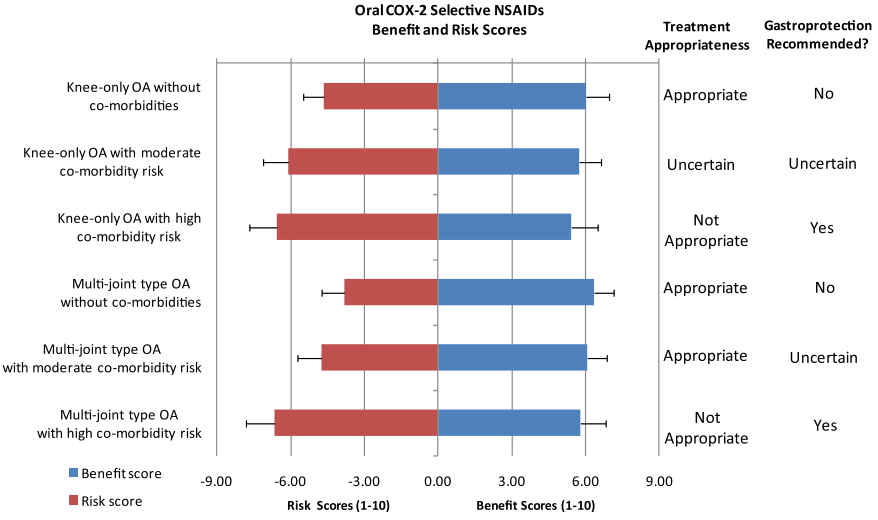
Rationale:

A 2011 comparative effectiveness review found that relative to non-COX-2 selective NSAIDs, selective COX-2 inhibitors were better or comparably tolerated, though rates of serious adverse events were similar[42]. Celecoxib was associated with a lower risk of ulcer complications (RR 0.23, 95% CI: 0.07–0.76) compared with non-selective NSAIDs but a moderately higher risk of CV complications. Due to serious safety risks associated with oral NSAID use, we recommend conservative dosing and treatment duration consistent with US approved prescribing limits.

Quality assessment based on Chou *et al.*[42] and Lee *et al.*[57]:

Level of evidence: SR and meta-analysis of RCTs.
Quality of evidence: Good.

Estimated Effect Size for Pain: 0.44 (0.33–0.55)[57].



NSAIDs (topical)

Recommendation:

- **Appropriate**: individuals with knee-only OA
- **Uncertain**: individuals with multiple-joint OA

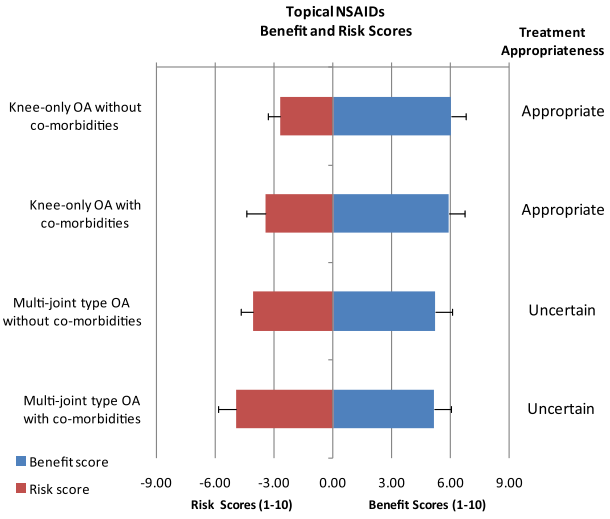
Rationale:

A 2011 Cochrane comparative effectiveness review found comparable efficacy of topical and oral NSAIDs for knee OA[42]. Topical NSAIDs were associated with lower risk of GI adverse events but higher risk of dermatological adverse events compared with oral NSAIDs. Overall, topical NSAIDs were considered to be safer and better tolerated compared with oral NSAIDs.

Quality assessment:

Level of evidence: SR and meta-analysis of RCTs.
Quality of evidence: Good.

Estimated Effect Size for Pain: Not available.



Opioids (transdermal)

Recommendation:

- **Uncertain**

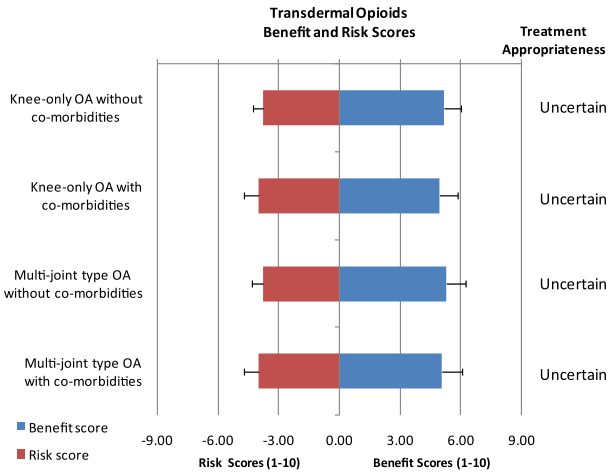
Rationale:

A 2009 SR and meta-analysis examining the efficacy of opioids for knee and hip OA found small effect sizes for pain and physical function for transdermal fentanyl[58]. Patients receiving some form of opioid therapy were four times as likely as patients receiving placebo to withdraw due to adverse events (RR 4.05, 95% CI: 3.06–5.38) and more than three times as likely to experience a serious adverse event (RR 3.35, 95% CI: 0.83–13.56). Thus, the study concluded that opioids offered limited usefulness in the long term.

Quality assessment:

Level of evidence: SR and meta-analysis of RCTs.
Quality of evidence: Good.

Estimated Effect Size for Pain (SMD): Ranges from 0.22 (0.03–0.42) to 0.36 (0.26–0.47)[58].



Opioids (oral)

Recommendation:

- **Uncertain**

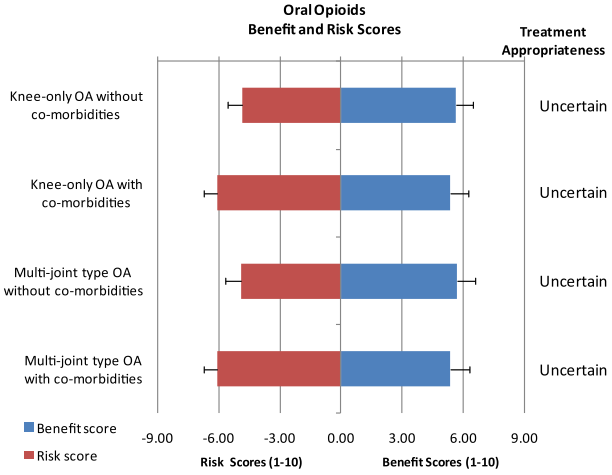
Rationale:

Analyses of pain relief from a 2009 SR found a moderate effect size for codeine over placebo, a small to moderate benefit for oxycodone, and a small benefit for morphine in patients with OA of the knee or hip[58]. A 2006 review also found a small but statistically significant benefit for tramadol over placebo[59]. However, patients receiving some form of opioid therapy were four times as likely as patients receiving placebo to withdraw due to adverse events (RR 4.05, 95% CI: 3.06–5.38) and more than three times as likely to experience a serious adverse event (RR 3.35, 95% CI: 0.83–13.56)[58].

Quality assessment:

Level of evidence: SR and meta-analysis of RCTs.
Quality of evidence: Good.

Estimated Effect Size for Pain: Ranges from 0.36 (0.26–0.47) to 0.51 (0.01–1.01)[58].



Risedronate

Recommendation:

- **Not appropriate**

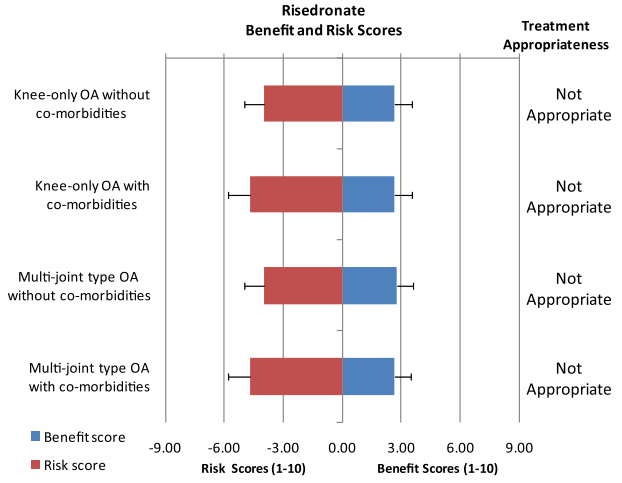
Rationale:

Risedronate was evaluated primarily on its disease-modifying efficacy, as the majority of available evidence targets this outcome. A 2012 SR found that higher doses of risedronate (15 mg/d) did not reduce the signs or symptoms of OA, but did reduce the marker of cartilage degradation (CTX-II), which may contribute to attenuation of radiological progression of OA[60]. The review concluded that further RCTs would be needed to assess the efficacy of risedronate for symptoms, function, and progression of knee OA.

Quality assessment:

Level of evidence: SR and meta-analysis of RCTs.
Quality of evidence: Poor.

Estimated Effect Size for Pain: Not available.



Rosehip

Recommendation:

- **Uncertain**

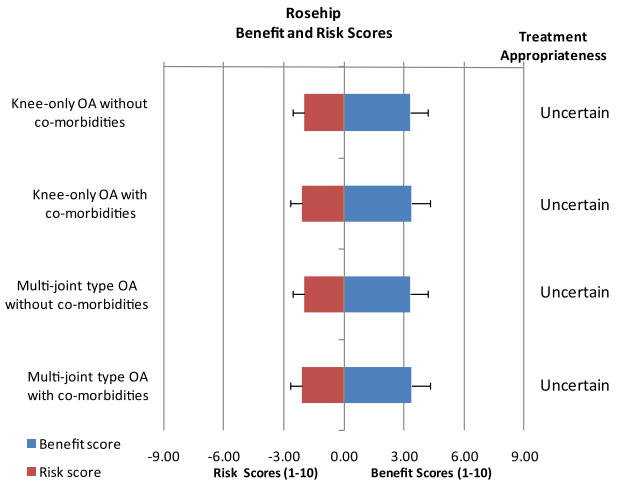
Rationale:

A 2008 SR and meta-analysis of three small trials found a positive effect of rosehip powder for pain when compared with placebo, but the reviewers concluded that further evaluation in larger-scale trials is necessary due to the paucity of available data[61]. Safety results from one included study did not provide conclusive results.

Quality assessment:

Level of evidence: SR and meta-analysis of RCTs.
Quality of evidence: Good.

Estimated Effect Size for Pain: 0.37 (0.13–0.60)[61].



Discussion

These OARSI 2013 guidelines for the management of knee OA represent an update to the previous OARSI publications in 2010 and 2008[1,2] and used the original evidence and set of evaluated treatments as the base for a literature update. Their purpose is to disseminate a framework for treatment of knee OA to professionals involved in the management of this disorder, as well as patients, provider organizations and regulatory bodies. The guidelines were also developed for an International context, reflecting the constituency and perspective of OARSI, the sponsoring organization. These guidelines should be used in conjunction with individual patients' values and clinical judgment.

We used the RAND/UCLA approach as a methodology for measuring expert opinion and reaching a classification for appropriateness of each treatment modality[4]. This well-established approach leverages expert opinion in relation to their synthesis of contemporary evidence. One advantage for the field of OA treatment is that it was explicitly developed to measure expert opinion in situations where the evidence may be incomplete. The outcome of the voting process, according to this methodology, is a designation for each putative therapy of "Appropriate," "Uncertain" or "Inappropriate." Among these, the implication of the term "Uncertain" was viewed as unclear by reviewers. To clarify, the "Uncertain" classification is not intended here to be a negative recommendation or to preclude use of that therapy. Rather it requires a role for physician–patient interaction in determining whether this treatment may have merit in the context of its risk-benefit profile and the individual characteristics, co-morbidities and preferences of the patient.

Our guidelines diverge from the previous OARSI guidelines in 2010 and 2008 as well as from recent American College of Rheumatology (ACR) and European League Against Rheumatism (EULAR) guidelines by focusing specifically on treatment of OA of the knee. The decision was made to examine knee OA separately due to disparities in available evidence between hip OA and knee OA and differences in best treatment practices between these conditions. The current guidelines aim to identify the best-available treatment practices for knee OA, irrespective of differing healthcare policies and treatment standards internationally. Thus, this update of the OARSI guidelines also excluded cost effective analysis, evaluating treatments solely based upon their safety and efficacy profiles.

Our guidelines also provide separate recommendations for each of four clinical sub-phenotypes. These were assessed separately in order to best capture heterogeneous health profiles and OA disease types. One limitation of this method is that the research literature was not surveyed for OA sites beyond the knee and hip. Thus, recommendations for individuals with multiple-joint OA may not take into account all evidence regarding other joint sites. Expert opinion of the OAGDG panel was used to support recommendations in these instances. However, these guidelines' recommendations pertain to treatment of knee OA specifically, even when making recommendations for individuals with OA in multiple-joint sites. For all considered treatments, best-available evidence of efficacy and safety in knee OA was evaluated.

Our expert panel (OAGDG) represented a range of clinical disciplines that included rheumatologists (NA, FB, GH, DH, KK, TM, FR), orthopedic surgeons (HK, SL), a primary care physician (MU), physical therapists (SBZ, ER), a physiatrist (YH), and a clinical epidemiologist (TM) (Appendix 1). The OAGDG also solicited ongoing input from a patient advocate (RK), who attended the April 2013 OAGDG meeting and provided continuing feedback and oversight *via* the development group's online discussion forum. Our team also included an evidence-based methodologist (RB) who organized the development of the evidence report used by the OAGDG panel. Panel voting was conducted with oversight from OARSI's Ethics Committee. OAGDG members with perceived financial conflicts of interest were recused from voting following written and oral disclosures, with final decisions made by an Ethics Committee representative present at the OAGDG's April 2013 face-to-face meeting. Despite recusals, a majority of practicing clinicians were present within the voting at all times. Thus, the results of voting are unlikely to have lacked sufficient voter expertise for any treatment.

The present statement also incorporated treatments not addressed in the prior OARSI guidelines such as risedronate and duloxetine. Treatments such as ASU, rosehip, electrotherapy, and ultrasound were not included in the 2008 OARSI recommendations but have since been discussed in the 2010 evidence update and assessed within our current guidelines. The present guidelines focused primarily on the non-surgical management of knee OA, though we recommend referral for consideration of orthopedic surgical interventions after more conservative treatment options have been exhausted. To examine the symptomatic slow-acting drug for OA (SYSDOA) effect, glucosamine and chondroitin were assessed separately for disease modification and for symptom relief. Other treatments received one score for overall efficacy, as other treatments were judged to lack sufficient evidence to merit separate assessment for disease modification effect and symptomatic effect.

In comparison to the previous OARSI guidelines published in 2008, recommendations for some treatments have changed. Though the method of assessing treatment appropriateness has changed between guidelines versions, complicating straightforward comparison, it nevertheless appears that recent evidence has increased safety concerns regarding use of treatments such as acetaminophen and opioids (both oral and transdermal), while evidence for use of treatments such as duloxetine, balneotherapy, and land-based exercises such as t'ai chi has strengthened. These differences are updates to previous OARSI guidelines following the development of new treatment options and greater available evidence for existing treatments.

While many of the recommendations in this guidelines statement agree with those published in other OA guidelines, our recommendations differ notably from others in a number of ways. Although our recommendations are based on best-available evidence, the current evidence contains some areas of inconsistency. With regard to non-pharmaceutical treatments, our recommendations were largely similar to other recent guidelines published by the American Academy of Orthopaedic Surgeons (AAOS), ACR, and EULAR, consistently recommending exercise programs for individuals with knee OA as well as weight loss programs for overweight individuals with knee OA. For this guidelines statement, exercise modalities were divided into three groups (land-based, water-based, and strength training) to provide greater specificity than other OA guidelines in assessing their distinct benefits and risks and to evaluate their relative appropriateness for different clinical sub-phenotypes. In other areas of non-pharmacological treatment, our guidelines differed more substantially from others. For electrotherapeutic modalities, AAOS provided an "Inconclusive" recommendation, while these guidelines recommend against the use of TENS and provide an "Uncertain" recommendation for EMG-biofeedback. While ACR conditionally recommends acupuncture for knee OA, and AAOS does not recommend acupuncture, our guidelines provide an "Uncertain" recommendation regarding acupuncture, highlighting the lack of strong available evidence regarding its use. Recommendations regarding biomechanical interventions were also mixed; AAOS provided an inconclusive recommendation regarding force braces, and both AAOS and EULAR recommended against the use of wedged insoles, while ACR conditionally recommended the use of medially wedged insoles. Rather than providing recommendations individually for specific biomechanical modalities, these guidelines recommend the use of biomechanical interventions as directed by an appropriate specialist.

With regard to pharmaceutical treatment modalities, our guidelines also differ from others in several areas. AAOS's 2013 guidelines provided "Inconclusive" recommendations for both acetaminophen and intra-articular corticosteroids, citing for IACS a "lack of compelling evidence that has resulted in an unclear balance between benefits and potential harm." In contrast, our guidelines coincide with ACR's 2012 guidelines in recommending both APAP (for those without relevant co-morbidities) and IACS as appropriate, finding the potential benefits to outweigh associated risks in certain clinical scenarios. Regarding glucosamine and chondroitin, AAOS recommended against use of both treatments and ACR recommended against chondroitin and conditionally against glucosamine. Our guidelines provide greater specificity than previous guidelines by evaluating these treatments separately for symptomatic relief and disease modification. Our group responded more favorably (voting "Uncertain") for the symptomatic efficacy of each of these two treatments than for the disease-modifying use of each (voting "Not appropriate"). The contrasting assessments of glucosamine and chondroitin's symptomatic *versus* disease-modifying efficacy may indicate the source of some of the inconsistency in the perceived value of these treatments among other recent guidelines. Regarding hyaluronic acid treatment, AAOS recommended against the use of IAHA, citing a lack of efficacy. Our guidelines offer a stance similar to that of ACR, providing an "Uncertain" recommendation for IAHA for individuals with knee-only OA. Despite safety and efficacy concerns of IAHA raised by one meta-analysis, a number of analyses revealed positive effect sizes for pain. Oral NSAIDs (both non-selective and COX-2 selective) were conditionally recommended by ACR, which was also reflected in our guidelines through the use of clinical sub-phenotypes. Conversely, AAOS strongly recommended both oral and topical NSAIDs. ACR guidelines conditionally recommend against topical capsaicin use, while we considered it appropriate in patients without relevant co-morbidities. Finally, the ACR provided negative or uncertain recommendations for the use of duloxetine, while these guidelines considered duloxetine appropriate for those without co-morbidities and those with multiple-joint OA and provided an "Uncertain" recommendation for duloxetine in individuals with knee-only OA and co-morbidities.

Limitations of our guidelines include the scope of treatments addressed. These guidelines were developed based on the previous guidelines report and expanded where the OAGDG felt sufficient new evidence was available to merit inclusion (based on number and quality of available trials). Our guidelines did not consider treatments included in the previous OARSI 2010 guidelines such as vitamin E and calcitonin, as well as interventions included in the AAOS guidelines, such as platelet-rich plasma therapy and growth factor injections. Treatment duration and duration of benefit were not voted on separately for limited *versus* extended course for pharmaceutical treatments due to the lack of clarity in available evidence. Other treatments not included in our guidelines include lavage and debridement (considered for inclusion but removed due to consistent evidence of ineffectiveness), strontium (recently received a recommendation to restrict use by the European Medicines Agency and not approved by US FDA)[62], and licofelone (not currently approved by the European Medicines Agency or US FDA). Manual therapy was not included in these guidelines due to insufficient available evidence. Unlike ACR, we did not include patellar taping or psychosocial intervention for knee OA. However, our guidelines also contain many treatment modalities not addressed by other (ACR) guidelines, such as ASU, risedronate, diacerein, and rosehip. In addition, these guidelines divided various treatments (e.g., NSAIDs, opioids, and exercise) into sub-categories to better assess considerations such as delivery method, drug mechanism or other factors, aiming to provide specific and actionable treatment recommendations. Our guidelines are also unique in that the recommendations considered the risk, benefit, and appropriateness of each treatment individually for the specific sub-phenotypes described in our methods. One limitation of these categories is that not every treatment had available research for all clinical sub-phenotypes. In such cases, expert consensus was relied upon *via* the RAND/UCLA voting method. The role of expert opinion and voters' enthusiasm for treatment modalities may also explain some instances where the panel's voting diverged from effect sizes presented in the evidence. The four clinical sub-phenotypes were assessed separately for every treatment considered in order to best capture heterogeneous health profiles and OA disease types.

Conflict of interest

Full disclosure statements from all members of the OARSI Guidelines Development Group are shown in Appendix 1. These were reviewed by the OARSI Ethics Committee. No potential conflicts of interest were identified that should preclude any member of the committee participating in this critical appraisal. No OAGDG members are employees of any pharmaceutical or medical device company. OAGDG members were recused from voting on select treatments where potential conflicts arose, as described in the report Methodology section. Corporate members of OARSI are also listed in Appendix 1. The data extraction team included five members of the Division of Rheumatology, Tufts Medical Center, Boston, MA, USA: Raveendhara Bannuru MD, FAGE, Elizaveta Vaysbrot, MD, Matthew Sullivan, BA, Elena Manning, BS, and Bryan Bourdeau, BS. Dr Bannuru is supported by a F32 HS021396 grant from the Agency for Healthcare Research and Quality. The content is solely the responsibility of the authors and does not necessarily represent the official views of the Agency for Healthcare Research and Quality. Elizaveta Vaysbrot, Matthew Sullivan, Elena Manning, and Bryan Bourdeau have no conflicts of interest to disclose.

Role of the funding source

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Appendix 1

Disclosure of potential conflicts of interest

Name & specialty (in author-list order)	Consulting fees, honoraria, research or institutional support, educational grants, equipment, services or expenses	Research grants/contracts	Service with organization with interests comparable to OARSI	Recused from voting on the following treatment modalities
T. McAlindon Rheumatologist; Epidemiologist	Flexion Therapeutics|Consulting, Samumed|Consulting, Abbvie|Consulting, Sanofi|Consulting, Myrtus|Licensing fee	NIH, Croma	Co-editor for Arthritis & Rheumatism	Hyaluronic acid
R. Bannuru	None	AHRQ|F32 HS021396 grant	None	Not a voter
M. Sullivan	None	None	None	Not a voter
N. Arden* Rheumatologist	Merck|Consultancy, Roche|Consultancy, Smith and Nephew|Consultancy, Pfizer|Speaker Bureau, Flexion|Consultancy, Bioiberica|Consultancy, Speaker bureau	NIHR|Outcomes of Arthroplasty and Biomedical Research Unit, NIH|Hip morphology, ARUK|VIDEO, project and equipment grants	None	Chondroitin Hyaluronic acid All surgery
F. Berenbaum* Rheumatologist	Pfizer|Advisory board, Expanscience|Advisory board, UCB|Advisory board, Servier|Advisory board, research support,	Agence Nationale Recherche	French Society of Rheumatology	NSAIDs

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Appendix 1 (*continued*)

Name & specialty (in author-list order)	Consulting fees, honoraria, research or institutional support, educational grants, equipment, services or expenses	Research grants/contracts	Service with organization with interests comparable to OARSI	Recused from voting on the following treatment modalities
	symposium, TRB Chemedica|research support, Sanofi|Advisory board, Abbott|Advisory board			
S. Bierma-Zeinstra* Physical therapist; Epidemiologist	None	Dutch Arthritis Association|research in corticosteroids for OA, OA vascular pathology, early OA diagnosis, brace vs osteotomy treatment, & OA stepped care; The Netherlands Organization for Health Research and Development|research in identification, prevention of knee OA, OA phenotyping, treatment cost-effectiveness (ACL rupture, viscosupplementation, surgery vs conservative treatment in lumbar stenosis), corticosteroids for trochanteric pain syndrome, ankle injury complications, exercise after injury, & exercise therapy for patellofemoral pain syndrome; Nuts Ohra|research in X-ray OA diagnosis, OA pain medication, & statines & OA; EU FP7|markers for early detection & progression of OA	None	Glucosamine
S. Bierma-Zeinstra (disclosure cont'd)				
G. Hawker* Rheumatologist	Women's College Hospital|Physician in Chief of Medicine|Salary Support Award, Women's College Hospital Foundation|FM Hill Chair in Academic Women's Medicine. *Nothing to declare*	Operating grants from the Canadian Institutes of Health Research|Canadian Arthritis Network|Cochrane Collaboration/writing paper with Adelphi, a marketing company who worked for Pfizer on a survey of physicians regarding factors that influence their perceptions of OA severity – unpaid	None	None
Y. Henrotin* Physical therapy & rehabilitation	Bioiberica; BioXtract; Danone; Nestle; Pierre Fabre; Grunenthal; Expanscience; Artialis; Tilman; Merck; Ibsa|Honoraria. Patent ownership: Artialis|Biomarkers; Kit immunoassays| Development & commercialization of biomarkers of cartilage degradation & inflammation	Walloon Government-Belgium|First Post-Doc RW/ 5291 PROMART-Recherche de nouveaux biomarqueurs (2007–2009).165.765; First Post-Doc RW/716609 CARTIMAT: Recherche de nouveaux biomateriaux; FIRST Entreprise - 73.726,4 Euros, European commission|FP7 D-Board, rd; Bioiberica & Expanscience|unrestricted educational grants	None	Chondroitin
D. Hunter* Rheumatologist	DonJoy|Royalties; Merck Serono|Consulting, Flexion Therapeutics|Consulting	Australian Research Council|Future Fellowship, NIH|POMA, NHMRC|project grants	Bone and Joint Decade International Coordinating Council, Advisory editor for Arthritis Care and Research, Associate Editor for International Journal of Rheumatic Diseases	Biomechanical interventions
H. Kawaguchi* Orthopedic surgeon	Teijin Pharma Co., Ltd.|Consulting fee	None	BMC Musculoskeletal Disorders|Associate Editor, Japanese Orthopaedic Association|Committee Member, Japanese Society for Bone and Mineral Metabolism|Committee Member, Journal of	Hyaluronic acid

Appendix 1 (*continued*)

Name & specialty (in author-list order)	Consulting fees, honoraria, research or institutional support, educational grants, equipment, services or expenses	Research grants/contracts	Service with organization with interests comparable to OARSI	Recused from voting on the following treatment modalities
			Orthopaedic Science|Editorial Board, Journal of Bone &Mineral Metabolism|Editorial Board, Japanese Society of Cartilage Metabolism|Comm. Member	
R. Katzanek Patient advocate	Nothing to declare	None	None	N/A
K. Kwoh Rheumatologist	Novartis|Advisory Board and DSMB, NIH|DSMB, Express Scripts|Consulting, Pfizer|RA Quality Measures Roundtable	NIH|NIAMS P60AR054731 PITT-MCRC for rheumatic and musculoskeletal diseases; NIAMS N01AR-2-2260 Clinical centers for the Osteoarthritis Initiative; NHLBI HHSN26820100002 Pivotal OAI MRI Analyses (POMA); NIAMS R01AR056630 Single- vs Double-Bundle ACL Reconstruction: A Prospective Randomized Trial; NINR R01NR010904 Promoting Physical Activity in Older Adults with Co-morbidity; CDC|U48DP001918 Health Promotion and Disease Prevention Research Center	Arthritis Foundation|Public Health Committee	Glucosamine Risedronate
S. Lohmander* Orthopedic surgeon	Merck Serono|Advisory board, Informed Medical Decision Making|Speaker honorarium, Össur Advisory Board, Abbott Consultancy, Flexion Therapeutics Advisory Board, Allergan Consultancy, Medivir Consultancy, Merrimack Pharmaceuticals Consultancy, Servier Consultancy	Swedish Research Council|Lund University, Swedish Rheumatism Association|Lund University, Medical faculty|Lund University	None	Biomechanical interventions
F. Rannou* Rheumatologist	Sanofi Aventis, Pfizer, Rottapharm, Pierre Fabre, Genzyme, Merck, Genévrier, Expanscience, Negma, Servier|Consulting/ Advisory board	AP-HP|Non-pharmacological treatments in rheumatic diseases, GSK|HO-1 inducer molecules in cartilage, Fondation de l'Avenir|Molecular mapping of IVD in scoliosis	Member of the Eular Scientific Committee	NSAIDs Hyaluronic acid ASU Diacerein
E. Roos* Physical therapist	National Welfare Board, Sweden|Reviewer, National board for preventive medicine, Denmark|Board member, Össur|Lecture fees, Finnish Orthopedic Society|Lecture fees, Studentlitteratur|Royalties, Munksgaard|Royalties, Osteoarthritis and Cartilage|Associate Editor	Southern Health Care Region, Denmark|RCT on exercise vs pharma, Danish Rheumatism Association|Knee OA prevention and treatment	None	None
M. Underwood Primary care practitioner; primary care research	Travel, Accommodation and Conference fee waiver from OARSI to attend OAGDG meetings concurrent with annual scientific meeting	NIHR Programme grants|Improving outcomes from the treatment of back pain; Improving self-management of chronic pain, NHS HTA Programme|Prevention of Fall Injury Trial (Pre-FIT); Adherence to strengthening activities in rheumatoid arthritis of the hand (SARAH); Older People's Exercise intervention in Residential and nursing Accommodation	National Institute for Health and Care Excellence (NICE)| Chair of Headache Guideline Development Group (2010–12). Chair NICE Accreditation Advisory Committee (2013) NICE Strategy Board, in attendance (2013)	Acupuncture

(*continued on next page*)

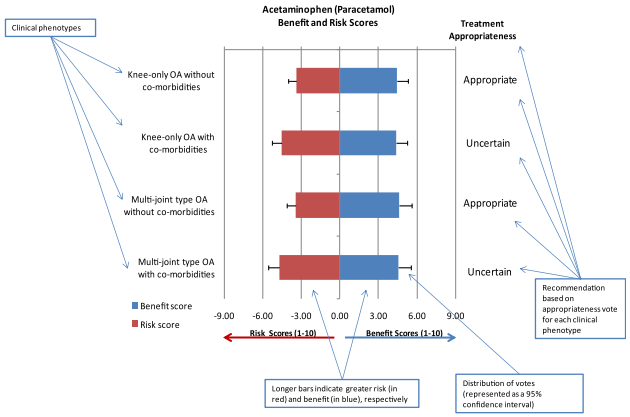
Appendix 1 (*continued*)

Name & specialty (in author-list order)	Consulting fees, honoraria, research or institutional support, educational grants, equipment, services or expenses	Research grants/contracts	Service with organization with interests comparable to OARSI	Recused from voting on the following treatment modalities
		(OPERA), National Centre for Osteopathic Research|Investigating osteopath's attitudes to managing and assessing risk in clinical settings and patient's experiences and responses, Research for Patient Benefit|Improving Patient Choice in Treating Low Back Pain (IMPACT - LBP). NHS Health Technology Assessment Programme. Facet joint feasibility study.		

OARSI's Congress sponsors and corporate members for 2013 include the following: Bioiberica; EMD Serono; Expanscience; Rottapharm/Madaus; Abbvie; Astellas; Bioventus; Boston Imaging Core Lab (BICL); Chondrometrics; Fidia Pharma USA, Inc.; Flexion; Perceptive Informatics; Merck; Seikagaku; Servier; Zimmer. No direct medical industry support was used or requested for guideline development. Guidelines development was a budgeted item in OARSI's annual budget.

* Panel member has an editorial position with the Osteoarthritis and Cartilage journal.

Appendix 2



Appendix 3

Table A
Appropriateness voting data

		Appropriateness scores					
		No co-morbidities			Co-morbidities		
		Median	Appropriate (Y/N/U)	Disagreement?	Median	Appropriate (Y/N/U)	Disagreement?
Non-pharmaceutical treatments							
Acupuncture	Knee	5	Uncertain	No	4.5	Uncertain	No
	Multi-joint	4.5	Uncertain	No	4.5	Uncertain	No
Balneotherapy	Knee	5	Uncertain	No	6	Uncertain	No
	Multi-joint	6	Uncertain	No	7	Yes	No
Biomechanical interventions	Knee	7	Yes	No	7	Yes	No
	Multi-joint	7	Yes	No	7	Yes	No
Cane (walking stick)	Knee	7	Yes	No	7	Yes	No
	Multi-joint	6	Uncertain	No	6	Uncertain	No
Crutches	Knee	6	Uncertain	No	6	Uncertain	No
	Multi-joint	5	Uncertain	No	5.5	Uncertain	No
Electrotherapy/neuromuscular electrical stimulation	Knee	3	No	No	3	No	No

Table A (*continued*)

		Appropriateness scores					
		No co-morbidities			Co-morbidities		
		Median	Appropriate (Y/N/U)	Disagreement?	Median	Appropriate (Y/N/U)	Disagreement?
	Multi-joint	3	No	No	3	No	No
Exercise (land-based)	Knee	8	Yes	No	8	Yes	No
	Multi-joint	8	Yes	No	8	Yes	No
Exercise (water-based)	Knee	7	Yes	No	7	Yes	No
	Multi-joint	8	Yes	No	8	Yes	No
Strength training	Knee	8	Yes	No	8	Yes	No
	Multi-joint	8	Yes	No	7	Yes	No
Self-management and education	Knee	8	Yes	No	9	Yes	No
	Multi-joint	9	Yes	No	9	Yes	No
TENS	Knee	5	Uncertain	No	5	Uncertain	No
	Multi-joint	3	No	No	3	No	No
Weight management	Knee	8	Yes	No	8	Yes	No
	Multi-joint	8	Yes	No	9	Yes	No
Ultrasound	Knee	4	Uncertain	No	4	Uncertain	No
	Multi-joint	3	No	No	3	No	No
Pharmaceutical treatments							
Acetaminophen (paracetamol)	Knee	7	Yes	No	6	Uncertain	No
	Multi-joint	7	Yes	No	6	Uncertain	No
ASU	Knee	4	Uncertain	No	4	Uncertain	No
	Multi-joint	5	Uncertain	No	5	Uncertain	No
Capsaicin	Knee	7	Yes	No	6	Uncertain	No
	Multi-joint	6	Uncertain	No	6	Uncertain	No
Corticosteriods (intra-articular injection)	Knee	7	Yes	No	7	Yes	No
	Multi-joint	7	Yes	No	7	Yes	No
Chondroitin: symptom relief	Knee	5	Uncertain	No	5	Uncertain	No
	Multi-joint	5	Uncertain	No	5	Uncertain	No
Chondroitin: disease modification	Knee	3	No	No	3	No	No
	Multi-joint	3	No	No	3	No	No
Diacerein	Knee	4	Uncertain	No	4	Uncertain	No
	Multi-joint	4	Uncertain	No	4	Uncertain	No
Duloxetine	Knee	7	Yes	No	6	Uncertain	No
	Multi-joint	7	Yes	No	7	Yes	No
Glucosamine: symptom relief	Knee	5.5	Uncertain	No	5.5	Uncertain	No
	Multi-joint	5.5	Uncertain	No	5.5	Uncertain	No
Glucosamine: disease modification	Knee	3	No	No	3	No	No
	Multi-joint	3	No	No	3	No	No
Hyaluronic acid (intra-articular injection)	Knee	5	Uncertain	No	4	Uncertain	No
	Multi-joint	3	No	No	3	No	No
NSAIDs (topical)	Knee	8	Yes	No	7	Yes	No
	Multi-joint	6	Uncertain	No	6	Uncertain	No
Opioids: transdermal	Knee	4	Uncertain	No	4	Uncertain	No
	Multi-joint	5	Uncertain	No	4	Uncertain	No
Opioids: oral	Knee	5	Uncertain	No	4	Uncertain	No
	Multi-joint	5	Uncertain	No	6	Uncertain	No
Risedronate	Knee	3	No	No	3	No	No
	Multi-joint	3	No	No	3	No	No
Rosehip	Knee	5	Uncertain	No	5	Uncertain	No
	Multi-joint	5	Uncertain	No	5	Uncertain	No

For each treatment modality, the OAGDG voted on appropriateness using a nine-point scale (1–9).
Definitions: **No co-morbidities**: The individual with OA has no pertinent co-morbid health concerns. **Co-morbidities**: The individual with OA has any of the following pertinent co-morbid health concerns: diabetes; hypertension; CV disease; renal failure; GI bleeding; depression; or physical impairment limiting activity, including obesity. **Knee**: Symptomatic OA in one or both knees only. **Multi-joint OA**: Symptomatic OA of the knee(s) in addition to other joints (e.g., hip, hand, spine, etc).
Disagreement: An appropriateness vote was considered to be in 'disagreement' if greater than one-third of votes fell in the opposite tertile to the median score [e.g., a vote was considered in "Disagreement" if it received an "Appropriate" median vote ($\geq$7) with five of 13 members voting "Not appropriate" ($\leq$3)].

Table B
Risk scores, benefit scores, and composite risk and benefit scores

		Risk scores		Benefit scores		Benefit and risk scores	
		No co-morbidities	Co-morbidities	No co-morbidities	Co-morbidities	No co-morbidities	Co-morbidities
		Mean (1–10)	Mean (1–10)	Mean (1–10)	Mean (1–10)	(1–100)	(1–100)
Non pharmaceutical treatments							
Acupuncture	Knee	1.9	2.3	3.1	3.0	28.0	26.3
	Multi-joint	1.9	2.3	3.1	3.0	28.0	26.3
Balneotherapy	Knee	1.3	1.5	4.2	4.2	40.3	40.0
	Multi-joint	1.3	1.6	4.5	4.5	43.2	41.9
Biomechanical interventions	Knee	1.5	2.0	5.6	5.6	57.0	50.4

(*continued on next page*)

Table B (*continued*)

		Risk scores		Benefit scores		Benefit and risk scores	
		No co-morbidities	Co-morbidities	No co-morbidities	Co-morbidities	No co-morbidities	Co-morbidities
		Mean (1–10)	Mean (1–10)	Mean (1–10)	Mean (1–10)	(1–100)	(1–100)
	Multi-joint	1.6	2.1	4.7	4.7	37.6	41.8
Cane (walking stick)	Knee	1.6	1.6	5.0	5.0	46.9	46.9
	Multi-joint	1.8	1.8	4.2	4.0	38.3	36.9
Crutches	Knee	1.7	1.7	4.4	4.3	40.8	40.1
	Multi-joint	1.8	1.8	3.7	3.8	33.8	34.5
Electrotherapy/neuromuscular electrical stimulation	Knee	2.0	2.1	2.5	2.4	22.2	21.3
	Multi-joint	2.0	2.1	1.9	1.9	17.3	17.2
Exercise (land-based)	Knee	1.2	1.9	6.6	6.8	64.6	61.4
	Multi-joint	1.3	2.1	6.4	6.5	61.9	58.3
Exercise (water-based)	Knee	1.5	2.3	5.9	6.2	56.0	54.2
	Multi-joint	1.5	2.2	6.2	6.5	59.0	56.7
Strength training	Knee	1.4	1.8	6.9	6.8	66.6	62.0
	Multi-joint	1.6	2.2	6.0	6.0	56.3	53.1
Self management and education	Knee	1.2	1.5	4.9	5.1	48.1	48.4
	Multi-joint	1.2	1.5	5.2	5.2	50.3	49.5
TENS	Knee	1.8	1.8	3.2	3.2	29.1	28.9
	Multi-joint	1.8	1.8	2.4	2.4	22.0	21.8
Weight management	Knee	1.2	1.5	6.1	6.3	59.4	60.2
	Multi-joint	1.2	1.5	6.2	6.4	60.1	60.4
Ultrasound	Knee	1.3	1.5	2.8	3.0	27.6	28.6
	Multi-joint	1.4	1.4	2.4	2.5	22.9	24.4
Pharmaceutical treatments							
Acetaminophen (paracetamol)	Knee	3.4	4.5	4.5	4.4	34.0	28.3
	Multi-joint	3.5	4.7	4.6	4.5	34.8	28.6
Avocado soybean unsaponfiables	Knee	1.6	1.8	3.5	3.5	33.2	32.6
	Multi-joint	1.6	1.8	3.6	3.6	34.0	33.4
Capsaicin	Knee	2.6	2.8	5.1	5.1	42.6	41.8
	Multi-joint	2.9	3.1	4.7	4.7	37.9	37.2
Corticosteriods (intra-articular injection)	Knee	2.8	3.6	6.5	6.4	53.8	47.1
	Multi-joint	2.8	3.6	5.2	5.3	42.7	39.2
Chondroitin: symptom relief	Knee	1.1	1.3	3.8	3.9	37.8	38.0
	Multi-joint	1.1	1.3	3.8	4.0	37.8	38.9
Chondroitin: disease modification	Knee	1.1	1.3	2.7	2.7	27.0	26.5
	Multi-joint	1.1	1.4	2.6	2.5	26.1	23.7
Diacerein	Knee	3.8	4.0	3.7	3.7	26.6	25.7
	Multi-joint	3.8	4.0	3.8	3.8	27.8	26.3
Duloxetine	Knee	4.0	4.7	5.3	5.4	37.2	34.0
	Multi-joint	4.0	4.7	5.6	5.6	39.3	35.4
Glucosamine: symptom relief	Knee	1.4	1.7	3.9	3.9	37.4	36.3
	Multi-joint	1.5	1.7	4.0	4.0	38.0	37.2
Glucosamine: disease modification	Knee	1.4	1.7	2.7	2.7	26.3	25.3
	Multi-joint	1.4	1.7	2.5	2.5	24.5	23.6
Hyaluronic acid (intra-articular injection)	Knee	3.1	3.8	4.1	4.2	32.4	30.5
	Multi-joint	3.3	3.9	3.0	3.1	23.0	22.1
NSAIDs (topical)	Knee	2.7	3.5	6.0	5.9	49.8	44.7
	Multi-joint	2.9	3.8	5.2	5.2	42.2	36.9
Opioids: transdermal	Knee	4.8	6.1	5.2	4.9	31.7	24.2
	Multi-joint	4.9	6.1	5.3	5.1	32.3	25.0
Opioids: oral	Knee	5.5	6.5	5.6	5.4	30.7	24.0
	Multi-joint	5.6	6.5	5.7	5.4	30.7	24.0
Risedronate	Knee	3.2	3.3	2.7	2.7	20.9	20.4
	Multi-joint	3.2	3.3	2.8	2.7	21.5	20.4
Rosehip	Knee	1.8	1.9	3.3	3.4	30.3	30.7
	Multi-joint	1.8	1.9	3.3	3.4	30.3	30.7

For each treatment modality, the OAGDG voted on therapeutic benefit on a 10-point scale (1–10) and overall risk on a 10-point scale (1–10). The composite benefit and risk score is the product of the benefit score (1–10) and the transposed risk score (where 1 = highest and 10 = safety) yielding a range of 1 (worst) to 100 (best).
No co-morbidities: The individual with OA has no pertinent co-morbid health concerns. **Co-morbidities:** The individual with OA has any of the following pertinent co-morbid health concerns: diabetes; hypertension; cardiovascular disease; renal failure; GI bleeding; depression; or physical impairment limiting activity, including obesity. **Knee:** Symptomatic OA in one or both knees only. **Multi-joint:** Symptomatic OA of the knee(s) in addition to other joints (e.g. hip, hand, spine, etc).

Table C
Oral NSAIDs voting data

Treatment	OA type	Appropriateness vote			Voting disagreement?			Percent voting in favor of gastroprotection		
		Co-morbidity risk			Co-morbidity risk			Co-morbidity risk		
		No co-morbidities	Moderate risk	High risk	No co-morbidities	Moderate risk	High risk	No co-morbidities	Moderate risk	High risk
Oral NSAIDs (non-selective)	Knee-only OA	7.0	5.0	2.0	No	No	No	33%	92%	100%
	Multi-joint OA	7.5	4.0	2.0	No	No	No	67%	92%	92%

Table C (*continued*)

Treatment	OA type	Appropriateness vote			Voting disagreement?			Percent voting in favor of gastroprotection		
		Co-morbidity risk			Co-morbidity risk			Co-morbidity risk		
		No co-morbidities	Moderate risk	High risk	No co-morbidities	Moderate risk	High risk	No co-morbidities	Moderate risk	High risk
Oral NSAIDs (COX-2 inhibitors)	Knee-only OA	7.0	6.0	3.0	No	No	No	18%	50%	100%
	Multi-joint OA	7.0	7.0	3.0	No	No	No	36%	50%	91%
Treatment	OA Type	Risk scores			Benefit scores			Benefit and risk scores		
		Co-morbidity risk			Co-morbidity risk			Co-morbidity risk		
		No co-morbidities	Moderate risk	High risk	No co-morbidities	Moderate risk	High risk	No co-morbidities	Moderate risk	High risk
Oral NSAIDs (non-selective)	Knee-only OA	4.6	6.1	7.8	5.9	5.6	5.2	40.7	29.7	17.3
	Multi-joint OA	4.6	6.1	7.8	6.2	5.6	5.3	42.8	30.9	18.6
Oral NSAIDs (COX-2 inhibitors)	Knee-only OA	4.6	6.1	6.6	6.0	5.7	5.4	46.6	38.3	24.7
	Multi-joint OA	3.8	4.7	6.6	6.4	6.1	5.8	46.8	38.8	25.4

For each treatment modality, the OAGDG voted on appropriateness using a nine-point scale (1–9), on therapeutic benefit on a 10-point scale (1–10) and overall risk on a 10-point scale (1–10). The composite benefit and risk score is the product of the benefit score (1–10) and the transposed risk score (where 1 = highest and 10 = safety) yielding a range of 1 (worst) to 100 (best).

Definitions: **No co-morbidities**: The individual with OA has no pertinent co-morbid health concerns. **Co-morbidities**: The individual with OA has any of the following pertinent co-morbid health concerns: diabetes; hypertension; CV disease; renal failure; GI bleeding; depression; or physical impairment limiting activity, including obesity. **Knee-only OA**: Symptomatic OA in one or both knees only. **Multi-joint OA**: Symptomatic OA of the knee(s) in addition to other joints (e.g., hip, hand, spine, etc).

Disagreement: An appropriateness vote was considered to be in 'disagreement' if greater than one-third of votes fell in the opposite tertile to the median score [e.g., a vote was considered in "Disagreement" if it received an "Appropriate" median vote (≥7) with five of 13 members voting "Not appropriate" (≤3)].

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