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OARSI Guidelines for the Non-Surgical Management of Knee Osteoarthritis

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Abstract

OBJECTIVE: To develop concise, up-to-date, patient-focused, evidence-based, expert consensus guidelines for the management of knee osteoarthritis, intended to inform patients, physicians, and allied health care 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 osteoarthritis (OA) literature, twenty-nine treatment modalities were considered for recommendation. Evidence published subsequent to the 2010 OARSI guidelines was based on a systematic review conducted by the 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 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 subphenotypes. 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 subphenotypes 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 subphenotypes included acetaminophen (paracetamol), balneotherapy, capsaicin, cane (walking stick), duloxetine, oral NSAIDs (COX-2 selective and non-selective), and topical NSAIDs. Treatments of uncertain appropriateness for specific clinical subphenotypes included acupuncture, avocado soybean unsaponifiables, 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.
OARSI Guidelines for the Non-Surgical Management of Knee Osteoarthritis

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 (SR) 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 osteoarthritis of the knee.

For the present guidelines, we endeavored to enhance the applicability of treatment recommendations by stratifying for relevant comorbidities, 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, systematic reviews and randomized controlled trials in the period subsequent to the 2010 guidelines search. The initial literature search was conducted in the 1st 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 systematic reviews and/or meta-analyses and 2) any randomized clinical trials published subsequent to those systematic reviews. If multiple systematic reviews were published in a similar time period, all were included. If no systematic reviews 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, systematic reviews and randomized controlled trials 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. Systematic Review and/or most current RCT).

Quality of evidence: The methodological rigor of the highest level of evidence used. Meta-analyses and systematic reviews 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 thirteen 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

At the request of the OARSI Ethics Committee, all members of the OAGDG were required to complete a Conflict of Interest (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, 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., NSAIDs
were split into non-selective NSAIDs, selective or specific COX-2 inhibitors, and topical NSAIDs) in October of 2012, March of 2013, and during the OAGDG’s face-to-face meeting in April of 2013.

**Osteoarthritis 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 1). 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.

<table>
<thead>
<tr>
<th>OA Joint Type</th>
<th>Knee-Only OA: Symptomatic OA in one or both knees only.</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Multiple-joint OA*: Symptomatic OA of the knee(s) in addition to other joints (e.g. hip, hand, spine, etc.).</td>
</tr>
<tr>
<td>Co-Morbidities</td>
<td><strong>No Co-morbidities</strong>: The individual with OA has no pertinent co-morbid health concerns.</td>
</tr>
<tr>
<td></td>
<td><strong>Co-morbidities</strong>: 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.</td>
</tr>
<tr>
<td></td>
<td>• <strong>Moderate co-morbidity risk</strong>: The individual with OA has any of the following pertinent co-morbidity health concerns: diabetes; advanced age; hypertension; cardiovascular disease; renal failure; GI complications; depression; or physical impairment limiting activity, including obesity.</td>
</tr>
<tr>
<td></td>
<td>• <strong>High Co-morbidity Risk</strong>: The individual with OA has risk factors such as history of GI bleed, myocardial infarction, chronic renal failure, etc.</td>
</tr>
</tbody>
</table>

* 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.

**Voting and Scoring**

For each treatment modality, the OAGDG voted on appropriateness using a 9-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, 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 (≥ 7) with 5 of 13 members voting “Not appropriate” (≤ 3)). Finally, we classified a treatment as “Appropriate” if it received a median score of ≥7 without disagreement. A treatment was classified as “Not appropriate” if it received a median vote of ≤ 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, comorbidities and preferences.

Each OAGDG member also voted separately on the level of risk and the level of benefit associated with each treatment. Risk was 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) 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 CS evidence, pooled analyses of pain and function outcomes were conducted for randomized clinical trials of CS 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.
OARSI Guidelines for the Non-surgical Management of Knee OA

Core Treatments
Appropriate for all individuals
- Land-based exercise
- Water-based exercise
- Weight management
- Self-mgmt and education
- Strength training

Recommended treatments*
Appropriate for the following OA types:

**Knee-only OA**
- **without co-morbidities**
  - Biomechanical interventions
  - Intra-articular Corticosteroids
  - Topical NSAIDs
  - Walking Cane
  - Oral COX-2 Inhibitors (selective NSAIDs)
  - Capsaicin
  - Oral Non-selective NSAIDs
  - Duloxetine
  - Acetaminophen (Paracetamol)

- **with co-morbidities**
  - Biomechanical interventions
  - Walking Cane
  - Intra-articular Corticosteroids
  - Topical NSAIDs

**Multi-joint OA**
- **without co-morbidities**
  - Oral COX-2 Inhibitors (selective NSAIDs)
  - Intra-articular Corticosteroids
  - Oral Non-selective NSAIDs
  - Duloxetine
  - Biomechanical interventions
  - Acetaminophen (Paracetamol)

- **with co-morbidities**
  - Balneotherapy
  - Biomechanical interventions
  - Oral COX-2 Inhibitors (selective NSAIDs)
  - Duloxetine

*OARSI also recommends referral for consideration of open orthopedic surgery if more conservative treatment modalities are found ineffective.

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**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:** Systematic review and meta-analysis of RCTs
- **Quality of evidence:** Good

**Estimated Effect Size for**

- **Pain (SMD):** 0.28 (0.11 to 0.45)\(^5\)
- **Function (SMD):** 0.28 (0.09 to 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, sulphur baths, and radon-carbon dioxide baths. Two 2009 systematic reviews 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 comorbidities, due to paucity of treatment alternatives for that group.

**Quality assessment:**

- **Level of evidence:** Systematic review 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 systematic review and three recent RCTs evaluated the effectiveness of knee braces, knee sleeves, and foot orthoses in conservative management of knee osteoarthritis.\textsuperscript{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.\textsuperscript{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\textsuperscript{11} and another asserting their appropriateness as a possible alternative to valgus bracing for conservative medial knee OA treatment.\textsuperscript{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.\textsuperscript{13}

Quality assessment:

**Level of evidence:** Systematic review 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. 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 randomized controlled trial

**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.


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 systematic review 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 EMG-biofeedback to strengthening exercise for pain, function and muscle strength in 40 participants with knee OA.\(^{16}\)

**Quality assessment:**

- **Level of evidence:** Systematic review 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:** Systematic review and meta-analysis of RCTs
- **Quality of evidence:** Good

**Estimated Effect Size for**

- **Pain (SMD):** Ranges from 0.34 (0.19 to 0.49)\(^{17}\) to 0.63 (0.39 to 0.87)\(^{21}\)
- **Function (SMD):** 0.25 (0.03 to 0.48)\(^{17}\)
Exercise (Water-based)

Recommendation:

- **Appropriate**

Rationale:

A 2007 systematic review 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:** Systematic review 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 systematic review 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:** Systematic review and meta-analysis of RCTs
- **Quality of evidence:** Good

**Estimated Effect Size for**

- **Pain (SMD):** 0.38 (0.23 to 0.54)\(^{17}\)
- **Function (SMD):** 0.41 (0.17 to 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:** Systematic review and meta-analysis of RCTs
- **Quality of evidence:** Good

**Estimated Effect Sizes for**

- **Pain (SMD):** ranges from 0.06 (0.02 to 0.10)\(^ {25}\) to 0.29 (0.17 to 0.41)\(^ {24}\)
**Transcutaneous Electrical Nerve Stimulation (TENS)**

**Recommendation:**

- **Uncertain:** Knee-only OA
- **Not appropriate:** Multiple-joint OA

**Rationale:**

A 2009 systematic review found inconclusive results regarding the effect of TENS for pain relief in knee OA.\(^3^1\) 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.\(^3^2\)

**Quality assessment:**

- **Level of evidence:** Systematic review of randomized or quasi-randomized clinical trials
- **Quality of evidence:** Good

**Estimated Effect Size for**

- **Pain (SMD):** 0.07 (-0.32 to 0.46)\(^3^1\)
- **Function (SMD):** 0.34 (0.14 to 0.54)\(^3^1\)
Weight management

Recommendation:

- Appropriate

Rationale:

A 2007 systematic review and meta-analysis found reductions in pain and physical disability for overweight participants with knee OA after a moderate weight reduction regime. 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: Systematic review and meta-analysis of RCTs

Quality of overall evidence: Good

Estimated Effect Size for

Pain (SMD): 0.20 (0.0 to 0.39)

Function (SMD): 0.23 (0.04 to 0.42)
**Ultrasound**

**Recommendation:**

- **Uncertain:** Knee-only OA
- **Not appropriate:** Multiple-joint OA

**Rationale:** Two 2010 systematic reviews 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:** Systematic review and meta-analysis of RCTs
- **Quality of evidence:** Good

**Estimated Effect Size for Pain (SMD):** Ranges from 0.49 (0.18 to 0.79)\(^35\) to 0.49 (0.23 to 0.76)\(^34\)
**Pharmacological Interventions**

**Acetaminophen (Paracetamol)**

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

**Rationale:** A 2010 systematic review 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:** Systematic review and meta-analysis of RCTs
- **Quality of evidence:** Good

**Estimated Effect Size for Pain (SMD):** 0.18 (0.11 to 0.25)\(^{37}\)
Avocado Soybean Unsaponifiables (ASU)

Recommendation:

- Uncertain

Rationale:

A 2008 systematic review 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**: Systematic review and meta-analysis of RCTs
- **Quality of evidence**: Good
- **Estimated Effect Size for Pain (SMD)**: 0.39 (0.01 to 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 systematic review and RCT, a 2011 comparative efficacy review concluded that topical capsaicin was superior to placebo for 50% pain reduction (NNT 8.1) but associated with increased local adverse events (54% vs. 15%; relative risk 3.6 [95% CI 2.6 to 5.0]) and withdrawals due to adverse events (13% vs. 3%; relative risk 4.0 [95% CI 2.3 to 6.8]).

**Quality assessment:**

- **Level of evidence:** Systematic review 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 systematic reviews demonstrated clinically significant short-term decreases in pain.\textsuperscript{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: Systematic review 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 systematic reviews examined the efficacy of chondroitin for knee OA.\textsuperscript{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.\textsuperscript{46} Effect sizes for pain were small to non-existent (e.g., 0.01 [95% CI: -0.07 to 0.13]) in stratified analyses of large-scale, high-quality trials.\textsuperscript{46} Another meta-analysis showed no statistically significant benefit of chondroitin when compared with placebo.\textsuperscript{46} Results were also mixed regarding disease modification, with only some studies showing statistically significant decreases in joint-space narrowing over longer (two-year) follow-up.\textsuperscript{47,48}

**Quality assessment:**

- **Level of evidence:** Systematic review and meta-analysis of RCTs
- **Quality of evidence:** Good

**Estimated Effect Size for Pain (SMD):** Ranges from 0.13 (0.00 to 0.27)\textsuperscript{45} to 0.75 (0.50 to 0.99)\textsuperscript{46}

**Estimated Effect Size for reduction in rate of decline of minimum joint-space width (SMD):** ranges from 0.26 (0.14 to 0.38)\textsuperscript{47} to 0.30 (0.00 to 0.59)\textsuperscript{48}
Diacerein

Recommendation:

- Uncertain

Rationale:

A 2010 systematic review 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. 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: Systematic review and meta-analysis of RCTs

Quality of evidence: Good

Estimated Effect Size for

Pain (SMD): 0.24 (0.08 to 0.39)\textsuperscript{49}

Function (SMD): 0.14 (0.03 to 0.25)\textsuperscript{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 systematic review 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:** Systematic review 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 systematic reviews 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 systematic review found no statistically significant differences in minimum joint-space narrowing (JSN) between glucosamine and placebo at one-year follow-up, though a moderate effect was detected at three-years.\(^ {48}\) A 2011 safety review found that long-term use of glucosamine was not associated with cardiovascular 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:** Systematic review 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 to 0.72)\(^ {52}\)

**Estimated Effect Size for reduction in rate of decline of minimum joint-space width (SMD):** 0.08 (-0.12 to 0.27)\(^ {48}\)
Hyaluronic Acid (Intra-articular Injection)

Recommendation:

- **Uncertain**: Knee-only OA
- **Not appropriate**: Multiple-joint OA

Rationale:

A recent systematic review 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 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**: Systematic review and meta-analysis of RCTs
- **Quality of evidence**: Good
- **Estimated Effect Size for**

  **Pain (SMD)**: ranges from 0.37 (0.28 to 0.46)\(^{56}\) to 0.46 (0.28 to 0.65)\(^{55}\)

  **Physical Function**: 0.33 (0.22 to 0.43)\(^{56}\) to 0.31 (0.11 to 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 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 gastrointestinal (GI), cardiovascular (CV), and renal harms compared with placebo. Nevertheless, the CV safety of naproxen appeared moderately superior to that of any COX-2 selective NSAID in two systematic reviews 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.

**Quality assessment:**

- **Level of evidence:** Systematic review and meta-analysis of RCTs
- **Quality of evidence:** Good

**Estimated Effect Size for Pain (SMD):** 0.37 (0.26 to 0.49)
**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. Celecoxib was associated with a lower risk of ulcer complications (Relative risk 0.23, 95% CI 0.07 to 0.76) compared with nonselective NSAIDs but a moderately higher risk of cardiovascular 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., 2011** and Lee et al., 2005:

- **Level of evidence:** Systematic review and meta-analysis of RCTs
- **Quality of evidence:** Good

**Estimated Effect Size for Pain:** 0.44 (0.33 to 0.55)
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 osteoarthritis. 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:** Systematic review and meta-analysis of RCTs
- **Quality of evidence:** Good

**Estimated Effect Size for Pain:** Not available
Opioids (transdermal)

Recommendation:
• Uncertain

Rationale:
A 2009 systematic review 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. Patients receiving some form of opioid therapy were four times as likely as patients receiving placebo to withdraw due to adverse events (relative risk 4.05, 95% CI 3.06 to 5.38) and more than three times as likely to experience a serious adverse event (relative risk 3.35, 95% CI 0.83 to 13.56). Thus, the study concluded that opioids offered limited usefulness in the long term.

Quality assessment:

Level of evidence: Systematic review and meta-analysis of RCTs

Quality of evidence: Good

Estimated Effect Size for Pain (SMD): Ranges from 0.22 (0.03 to 0.42) to 0.36 (0.26 to 0.47)
Opioids (oral)

Recommendation:

- Uncertain

Rationale:

Analyses of pain relief from a 2009 systematic review 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.\(^5\) A 2006 review also found a small but statistically significant benefit for tramadol over placebo.\(^5\) 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 to 5.38) and more than three times as likely to experience a serious adverse event (RR 3.35, 95% CI 0.83 to 13.56).\(^5\)

Quality assessment:

**Level of evidence:** Systematic review and meta-analysis of RCTs

**Quality of evidence:** Good

**Estimated Effect Size for Pain:** Ranges from 0.36 (0.26 to 0.47) to 0.51 (0.01 to 1.01)\(^5\)
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 systematic review 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.\(^6^0\) 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:** Systematic review and meta-analysis of RCTs

**Quality of evidence:** Poor

**Estimated Effect Size for Pain:** Not available
Rosehip

Recommendation:

- Uncertain

Rationale: A 2008 systematic review 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. Safety results from one included study did not provide conclusive results.

Quality assessment:

Level of evidence: Systematic review and meta-analysis of RCTs

Quality of evidence: Good

Estimated Effect Size for Pain: 0.37 (0.13 to 0.60)
Discussion

These OARSI 2013 guidelines for the management of knee OA represent an update to the previous OARSI publications in 2010 and 2008 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. 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, comorbidities 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 (OA Guideline Development Group) 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 avocado soybean unsaponifiables, 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 SYSDOA (symptomatic slow-acting drug for OA) 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 AAOS, ACR, 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 comorbidities) 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 vs. 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), 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 Methods. 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.
Acknowledgments:
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These guidelines were commissioned by the Osteoarthritis Research Society International and sponsored by a grant from OARSI. This report is endorsed by the Board of Directors of OARSI; it was developed independently by the OARSI Guidelines Development Group.
## Appendix 1: Disclosure of Potential Conflicts of Interest

<table>
<thead>
<tr>
<th>Name &amp; Specialty (In author-list order)</th>
<th>Consulting fees, honoraria, research or institutional support, educational grants, equipment, services or expenses</th>
<th>Research grants/contracts</th>
<th>Service with organization with interests comparable to OARSI</th>
<th>Recused from voting on the following treatment modalities</th>
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<tr>
<td><strong>T. McAlindon</strong> Rheumatologist; Epidemiologist</td>
<td>Flexion Therapeutics</td>
<td>NIH, Croma</td>
<td>Co-editor for Arthritis &amp; Rheumatism</td>
<td>Hyaluronic acid</td>
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<td><strong>R. Bannuru</strong> None</td>
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<td>None</td>
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<tr>
<td><strong>M. Sullivan</strong> None</td>
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<tr>
<td><strong>N. Arden</strong> Rheumatologist</td>
<td>Merck</td>
<td>NIH</td>
<td>None</td>
<td>Chondroitin</td>
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<tr>
<td><strong>F. Berenbaum</strong> Rheumatologist</td>
<td>Pfizer</td>
<td>Agence Nationale Recherche</td>
<td>French Society of Rheumatology</td>
<td>NSAIDs</td>
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<tr>
<td>S. Bierma-Zeinstra* – Physical Therapist; Epidemiologist</td>
<td>None</td>
<td>Dutch Arthritis Association</td>
<td>None</td>
<td>Glucosamine</td>
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<tr>
<td>S. Bierma-Zeinstra (disclosure cont'd)</td>
<td>Operating grants from the Canadian Institutes of Health Research</td>
<td>None</td>
<td>None</td>
<td>None</td>
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<tr>
<td>G. Hawker* – Rheumatologist</td>
<td>Nothing to declare</td>
<td>Operating grants from the Canadian Institutes of Health Research</td>
<td>None</td>
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| **Y. Henrotin***  
Physical Therapy & Rehabilitation | Bioiberica; BioXtract; Danone; Nestle; Pierre Fabre; Grunenthal; Expanscience; Artialis; Tilman; Merck; Ibsa  
| **D. Hunter***  
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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 | Hyaluronic acid |
## Appendix 1: Disclosure of Potential Conflicts of Interest

<table>
<thead>
<tr>
<th>Name &amp; Specialty</th>
<th>Consulting fees, honoraria, research or institutional support, educational grants, equipment, services or expenses</th>
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<td><strong>K. Kwoh</strong></td>
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<td>DSMB, Express Scripts</td>
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## Appendix 1: Disclosure of Potential Conflicts of Interest

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<td>Speaker honorarium, Össur Advisory Board, Abbott Consultancy, Flexion Therapeutics Advisory Board, Allergan Consultancy, Medivir Consultancy, Merrimack Pharmaceuticals Consultancy, Servier Consultancy</td>
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<td>F. Rannou* Rheumatologist</td>
<td>Sanofi Aventis, Pfizer, Rottapharm, Pierre Fabre, Genzyme, Merck, Genévrier, Expanscience, Negma, Servier</td>
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<td>Reviewer, National board for preventive medicine, Denmark</td>
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## Appendix 1: Disclosure of Potential Conflicts of Interest

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<td><strong>M. Underwood</strong>&lt;br&gt;Primary Care Practitioner; Primary Care Research</td>
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<td>Travel, Accommodation and Conference fee waiver from OARSI to attend OAGDG meetings concurrent with annual scientific meeting.</td>
<td>NIHR Programme grants</td>
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*Panel member has an editorial position with the Osteoarthritis and Cartilage journal.*
Appendix 1: Disclosure of Potential Conflicts of Interest

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.
Appendix 2: Annotated Risk and Benefit Scores Visual Diagram

Clinical phenotypes

Knee-only OA without co-morbidities
Knee-only OA with co-morbidities
Multi-joint type OA without co-morbidities
Multi-joint type OA with co-morbidities

Acetaminophen (Paracetamol) Benefit and Risk Scores

Benefit score
Risk score

Risk Scores (1-10)
Benefit Scores (1-10)

Treatment Appropriateness
Appropriate
Uncertain
Appropriate
Uncertain

Recommendation based on appropriateness vote for each clinical phenotype

Longer bars indicate greater risk (in red) and benefit (in blue), respectively

Distribution of votes (represented as a 95% confidence interval)
References


50. Citrome L, Weiss-Citrome A. A systematic review of duloxetine for osteoarthritic pain: what is the number needed to treat, number needed to harm, and likelihood to be helped or harmed? Postgraduate medicine 2012; 124(1): 83-93.
62. European Medicines Agency. Recommendation to restrict the use of Protelos / Osseor (strontium ranelate) [press release].
# Appendix 3 - Table A: Appropriateness Voting Data

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For each treatment modality, the OAGDG voted on appropriateness using a 9-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; 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 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 5 of 13 members voting ”Not appropriate” (≤ 3)).
### Appendix 3 - Table B: Risk Scores, Benefit Scores, and Composite Benefit and Risk Scores

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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).
### Appendix 3 - Table C: Oral NSAIDs Voting Data

<table>
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<tr>
<th>Treatment</th>
<th>OA Type</th>
<th>Appropriateness Vote</th>
<th>Voting Disagreement?</th>
<th>Percent Voting in Favor of Gastroprotection</th>
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<td>Moderate Risk</td>
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</tr>
<tr>
<td></td>
<td></td>
<td>No Comorbidities</td>
<td>Moderate Risk</td>
<td>High Risk</td>
</tr>
<tr>
<td>Oral NSAIDs (Non-selective)</td>
<td>Knee-Only OA</td>
<td>7.0 5.0 2.0</td>
<td>No No No</td>
<td>33% 92% 100%</td>
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<tr>
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<td>Multi-Joint OA</td>
<td>7.5 4.0 2.0</td>
<td>No No No</td>
<td>67% 92% 92%</td>
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<td>Oral NSAIDs (COX-2 Inhibitors)</td>
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<td>No No No</td>
<td>18% 50% 100%</td>
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<td>Multi-Joint OA</td>
<td>7.0 7.0 3.0</td>
<td>No No No</td>
<td>36% 50% 91%</td>
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</table>

### Treatment | OA Type | Risk scores | Benefit scores | Benefit and Risk Scores |
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<td></td>
<td>No Comorbidities</td>
<td>Moderate Risk</td>
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<td>Oral NSAIDs (Non-selective)</td>
<td>Knee-Only OA</td>
<td>4.6 6.1 7.8</td>
<td>5.9 5.6 5.2</td>
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<td>4.6 6.1 7.8</td>
<td>6.2 5.6 5.3</td>
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<tr>
<td>Oral NSAIDs (COX-2 Inhibitors)</td>
<td>Knee-Only OA</td>
<td>4.6 6.1 6.6</td>
<td>6.0 5.7 5.4</td>
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<td></td>
<td>Multi-Joint OA</td>
<td>3.8 4.7 6.6</td>
<td>6.4 6.1 5.8</td>
<td>46.8 38.8 25.4</td>
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</tbody>
</table>
For each treatment modality, the OAGDG voted on appropriateness using a 9-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; cardiovascular 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 5 of 13 members voting ”Not appropriate” (≤ 3)).