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OARSI guidelines for the non-surgical management of knee, hip, and polyarticular osteoarthritis

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SUMMARY

Objective: To update and expand upon prior Osteoarthritis Research Society International (OARSI) guidelines by developing patient-focused treatment recommendations for individuals with Knee, Hip, and Polyarticular osteoarthritis (OA) that are derived from expert consensus and based on objective review of high-quality meta-analytic data.

Methods: We sought evidence for 60 unique interventions. A systematic search of all relevant databases was conducted from inception through July 2018. After abstract and full-text screening by two independent reviewers, eligible studies were matched to PICO questions. Data were extracted and meta-analyses were conducted using RevMan software. Grading of Recommendations Assessment, Development, and Evaluation (GRADE) Evidence Profiles were compiled using the GRADEpro web application. Voting for Core Treatments took place first. Four subsequent voting sessions took place via anonymous online survey, during which Panel members were tasked with voting to produce recommendations for all joint locations and comorbidity classes. We designated non-Core treatments to Level 1A, 1B, 2, 3, 4A, 4B, or 5, based on the percentage of votes in favor, in addition to the strength of the recommendation.

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Results: Core Treatments for Knee OA included arthritis education and structured land-based exercise programs with or without dietary weight management. Core Treatments for Hip and Polyarticular OA included arthritis education and structured land-based exercise programs. Topical non-steroidal anti-inflammatory drugs (NSAIDs) were strongly recommended for individuals with Knee OA (Level 1A). For individuals with gastrointestinal comorbidities, COX-2 inhibitors were Level 1B and NSAIDs with proton pump inhibitors Level 2. For individuals with cardiovascular comorbidities or frailty, use of any oral NSAID was not recommended. Intra-articular (IA) corticosteroids, IA hyaluronic acid, and aquatic exercise were Level 1B/Level 2 treatments for Knee OA, dependent upon comorbidity status, but were not recommended for individuals with Hip or Polyarticular OA. The use of Acetaminophen/Paracetamol (APAP) was conditionally not recommended (Level 4A and 4B), and the use of oral and transdermal opioids was strongly not recommended (Level 5). A treatment algorithm was constructed in order to guide clinical decision-making for a variety of patient profiles, using recommended treatments as input for each decision node.
Conclusion: These guidelines offer comprehensive and patient-centered treatment profiles for individuals with Knee, Hip, and Polyarticular OA. The treatment algorithm will facilitate individualized treatment decisions regarding the management of OA.

Introduction

Knee and hip osteoarthritis (OA) rank highly among global causes of disability and chronic pain[1]. OA is also responsible for substantial health and societal costs, both directly and as a consequence of impaired work productivity and early retirement[2–6]. Treatment Guidelines derived from expert synthesis of systematic appraisal of existing evidence have an important role in promulgating effective treatment approaches and advocating for access of patients to appropriate remedies.

Here we update and expand prior Osteoarthritis Research Society International (OARSI) Guidelines to address non-surgical management of Knee, Hip and Polyarticular OA[7,8]. In addition, we provide guidance for four subgroups representative of clinically relevant comorbidity heuristics that are common in people with OA and confound its treatment– (1) gastrointestinal (GI) comorbidities, (2) cardiovascular (CV) comorbidities, (3) frailty, and (4) widespread pain and/or depression. To enhance the generalizability and utility of the guidelines, we developed a conceptual treatment pathway that accommodates a range of patient profiles and disease stages.

Methods

We developed these guidelines following the process described by the Grading of Recommendations Assessment, Development, and Evaluation (GRADE) methodology (available at www.gradeworkinggroup.com), which was adapted for the current project as described below [9]. Conflicts of interest and disclosures were determined and managed according to OARSI Ethics Committee policies.

Teams involved (see Appendix for a list of panel and team members)

A Core Expert Panel (six members) led by a chair (TM) consisted of content and methodological experts; they supervised the project and were responsible for defining the project scope, crafting the clinical questions, coordinating with the Literature Review Team, providing feedback on the evidence report, and drafting the manuscript based on voting by a panel (described below). A Literature Review Team led by a chair (RB) consisted of methodological experts in evidence based medicine, meta-analysis, and Guideline Development process including GRADE; they performed the literature review, graded the quality of evidence, developed the summary of findings tables, produced an evidence report and drafted the manuscript. The chair of the Core Expert Panel (TM) and the chair of the Literature Review Team (RB) both participated in and engaged in oversight of the respective activities of both teams in order to ensure ease of information transfer and pragmatic logistic planning. A Voting Panel (13 members) was drawn from the fields of rheumatology, orthopedic surgery, primary care, sports medicine, physical therapy, and pharmacology, embodying the wide international representation of OARSI. This group was selected for its diverse expertise and experience in OA management both in academic medicine and private practice. We recruited a Patient Panel consisting of three patients/advocates from Europe and the United States. During a special session convened at the 2018 OARSI convention, we conveyed our findings to the Patient Panel and received their commentary on the content and solicited suggestions for relevant additions to the final report. The structure of the Final Evidence Report was predicated on the guidance we received from the Patient Panel.

Systematic literature search

The key clinical questions addressed in the guidelines were determined *a priori* using the patient/population/problem, intervention, comparison/control, outcome (PICO) format developed by the Core Expert Panel[10]. The full list of PICO questions is available in Supplementary Table 1. The Literature Review Team, in consultation with the Core Expert Panel, devised and executed a systematic literature search based on the PICO questions. We searched Medline, PubMed, EMBASE, Google Scholar, and the Cochrane Databases from inception through December 2017 (Supplementary Table 2). We manually searched the reference lists of the most recent systematic reviews and meta-analyses and reviewed the supplements of OARSI, American College of Rheumatology (ACR) and European League Against Rheumatism (EULAR) conference proceedings that had been published through December 2017. The systematic search was updated on July 12th, 2018.

Study selection and PICO question matching

We included randomized controlled trials (RCTs), systematic reviews, and meta-analyses involving adults with symptomatic knee and/or hip OA that reported on outcomes of interest. Outcomes of interest and their relative importance were determined by the Core Expert Panel *a priori* in accordance with GRADE methodology (Supplementary Table 3). The same critical and important outcomes were applicable to each PICO question. We utilized a web-based screening platform to conduct abstract

screening and full text screening of the references procured from our literature search (http://rheumatology.tuftsmedicalcenter.org/CTCIA/). During the abstract screening stage, two independent reviewers (EV, MO) scrutinized the title and abstract of each reference to determine potential eligibility. Abstracts that were included after the abstract screening stage were deemed eligible for full text review, during which full manuscripts for each abstract were obtained and examined thoroughly by the same independent reviewers (EV, MO). Upon completion of abstract and full text screening, any discordant responses were resolved by a third reviewer (RB). The final included references were matched to a respective PICO question; this document was disseminated to the Core Expert Panel prior to initiating data extraction. Panel members were tasked with alerting the Literature Review Team of potential omissions or inappropriate inclusions.

Data extraction and analysis

Data were extracted using RevMan software (MO)[11]. We assessed the quality of evidence at the individual study level using the Cochrane Risk of Bias tool[12]. For continuous outcomes standardized mean differences (SMDs) and 95% Confidence Intervals (CI) were calculated for each study. To account for clinical and methodological heterogeneity, we conducted meta-analyses using random effects models[13]. We analyzed dichotomous outcomes using the Mantel-Haenszel method and reported the results as risk ratios (RRs) with 95% CIs[14]. Inconsistency was assessed with the I^2 statistic; between-trial variance was assessed using Tau squared[15,16]. Studies contributing heavily to high levels of inconsistency, and/or between-trial variability, were annotated in footnotes and brought to the attention of the Core Expert Panel and the voting panel. All meta-analyses were conducted using RevMan software[11]. Data extraction, analyses, and study quality ratings were double-checked by a second reviewer for consistency and accuracy (EV).

We planned *a priori* sensitivity analyses limiting by study quality, in which we chose to eliminate "Very Low Quality" RCTs. The definition of "Very Low Quality" was agreed upon by the Literature Review Team and the Core Expert Panel *a priori* and referred to those RCTs that received $\geq$2 High Risk of Bias ratings or one specific High Risk Rating in the "Other" category in addition to $\geq$2 Unclear Risk ratings or $\geq$3 Unclear Risk of Bias ratings in dimensions other than the "Other" category using the Cochrane Risk of Bias tool[12]. Within the final Evidence Report, sensitivity analyses limiting by study quality took precedence over the full analysis sets that included Very Low Quality trials. The Voting Panel was given full access to both sets of results.

Quality assessment and evidence report formulation

The OARSI updated guidelines should be considered, in context, as a systematic literature review supporting a GRADE process of expert evaluation of the evidence base and its quality, and subsequent voting and formulating recommendations. Though we systematically reviewed the literature and performed updated meta-analyses of relevant outcomes for 97% of the included interventions, we could not provide full-scale meta-analytic reports for each of these meta-analyses for this manuscript, because it extends beyond the scope of this manuscript and due to the space and resource constraints. The Core Expert panel reviewed all relevant materials, including RevMan files and GRADE tables, prior to the initiation of voting. Voting Panel members were also presented with all supplementary materials pertaining to the background analyses of the GRADE Evidence Tables throughout the voting process, had the opportunity to review the evidence synthesis, as well as the primary data contributing to each analysis, and form their own judgments about the credibility of results. Voting Panel members were given opportunities to discuss and debate the results of the evidence synthesis and primary data, and to re-vote if necessary.

These guidelines were constructed according to GRADE methodological standards[9]. GRADE methodology centers on the objective assessment of evidence quality and encourages evidence-based voting. Decision-making that occurred in all stages of guideline development was transparent and consensus-based, and to further promote objectivity, formal voting sessions were anonymous. The quality of evidence was assessed at the outcome level by the following criteria: summary of study-level risk of bias assessments, inconsistency between trial results, indirectness of the evidence to that particular PICO, and imprecision of the effect estimate. We constructed GRADE Evidence Profiles for each PICO question and generated Evidence Tables by exporting the results of all analyses from RevMan into GRADEpro web-based software[17]. We compiled GRADE Evidence Profiles both for full analysis sets and for the sensitivity analyses limited by study quality. Two independent reviewers (MO, RB) did GRADE quality assessments; conflicts were resolved by consensus. We attempted to minimize indirectness by enforcing strict study inclusion criteria. For example, studies with mixed knee and hip populations were segregated to "Mixed OA" tables, and the evidence for "Knee only" and "Hip only" OA comprised studies with populations consisting solely of participants with OA of each respective joint location. In recognizing the potential for small study effects among several intervention classes of OA treatment, the Panel incorporated downgrades for potential small study effects in a GRADE quality assessment rubric that was drafted *a priori* (Supplementary Table 4). In our ratings of imprecision, we penalized trials with extremely small sample size ($\leq$30 participants) with two quality downgrades. We also accounted for deficiencies in sample size by incorporating strict guidelines that downgraded the quality of evidence either once or twice for imprecision based on the magnitude of the CI of observed effect estimates using validated benchmarks. The panel members were provided with the additional materials describing trial sponsorship and author affiliations. Further details of our GRADE quality evaluation rubric are available in Supplementary Table 4.

In the event that no adequate evidence was found for a given intervention, evidence quality was designated by default as "Very Low". Completed GRADE Evidence Profiles were compiled in a comprehensive final Evidence Report (available in the Online Data Supplement).

Formulation of recommendations

Recommendations formulated by GRADE methodology possess both directionality ("in favor" or "against") and strength ("strong" or "conditional")[18]. We identified three determinants of the direction and strength of recommendations, adapted from GRADE methodology: magnitude of estimates of effect of the interventions on critical outcomes, confidence in those estimates, and estimates of typical values and preferences. Since we did not present data on individuals' values and preferences, we asked that the Voting Panel members make inferences about values and preferences based on their experiences with the target population.

Voting and consensus building

Voting on recommendations was carried out online using a web-based and anonymous survey application (http://www.surveymonkey.com). We held an initial voting session during which Voting Panel members selected Core Treatments (treatments

deemed appropriate for use by the majority of patients in nearly any scenario and deemed safe in conjunction with first line and second line treatments) from a pre-specified list of candidates; during this session, Voting Panel members were asked simply to indicate agreement or disagreement with the inclusion of a particular treatment in the list of Core Treatments for a given joint location. Three subsequent voting sessions took place during which Voting Panel members were asked to select the directionality and strength of their recommendations for the remainder of the treatments from voting matrices that were stratified by comorbidities. To facilitate processing of the results and to accommodate potential lack of consensus, additional voting sessions and supplementary group discussions were planned in advance.

Interpreting the recommendations

The key to formulating recommendations by GRADE methodology is to assess the balance between benefits and harms of a particular intervention[19]. Strong recommendations typically indicate that Voting Panel members feel confident that the benefits of a particular intervention outweigh the harms, or that the harms outweigh the benefits. Conversely, an intervention may receive a conditional recommendation if it carries risks that could potentially outweigh the benefits. Other factors that influence the direction and strength of recommendations include evidence quality and the uncertainty in values and preferences. Interventions that are supported by high quality evidence are more likely to receive strong recommendations. A higher degree of uncertainty in values and preferences is more likely to result in a conditional recommendation.

Direction and strength of recommendations (Table I)

Core Treatment selections were designated as "strong recommendations in favor" by default. Level designations based on percentage of votes "in favor" and strength of recommendation are shown in Table I. The list of "Recommended Treatments"- i.e., those reaching Level 1A, 1B, or 2 is shown in Tables II–IV. The full percentage gradient of votes "in favor" is displayed alongside the corresponding strata in Supplementary Tables 5, 6, and 7. Interventions that are strongly not recommended for use, and the rationales behind their designations, are presented in Supplementary Table 8.

Good Clinical Practice Statements

This term was used to describe statements that are supplementary to treatment recommendations and were made based on expert experience in the absence of direct, supportive RCT evidence. Good Clinical Practice Statements were developed during the course of extensive discussion which took place among Core Expert Panel members and Voting Panel members after the

Table I
Translating voting data into the treatment algorithm

Level	% in favor	% against	% Conditional/strong
Level 1A	75–100	0–25	>50 strong
Level 1B	75–100	0–25	>50 conditional
Level 2	60–74	26–40	*conditional by default*
Level 3	41–59	41–59	*conditional by default*
Level 4B	26–40	60–74	*conditional by default*
Level 4A	0–25	75–100	>50 conditional
Level 5	0–25	75–100	>50 strong

Table II
Recommended treatments, by level, for knee osteoarthritis

Recommendation level	Strength	Treatment type	No comorbidities	Gastrointestinal	Cardiovascular	Frailty	Widespread pain/depression
CORE	Strong	Arthritis Education; Structured Land-Based Exercise Programs (Type 1- strengthening and/or cardio and/or balance training/neuromuscular exercise OR Type 2- Mind-body Exercise including Tai Chi or Yoga) with or without Dietary Weight Management					
Level 1A	Strong	Pharmacologic	Topical NSAIDs	Topical NSAIDs		Topical NSAIDs	*refer to Level 1B*
High Consensus *≥75% "in favor"*		Non-Pharmacologic	*refer to Level 1B*	*refer to Level 1B*		*refer to Level 1B*	*refer to Level 1B*
Level 1B	Conditional	Pharmacologic	• Non-selective NSAIDs • Non-selective NSAID + PPI • COX-2 Inhibitors IACS	COX-2 Inhibitors IACS, IAHA	IACS, IAHA	IACS, IAHA	• Non-selective NSAIDs • Non-selective NSAID + PPI • COX-2 Inhibitors
High Consensus *≥75% "in favor" & >50% "conditional" Recommendation*		Non-Pharmacologic	Aquatic Exercise, Gait Aids, Self-Management Programs	Aquatic Exercise, Gait Aids, Self-Management Programs		Aquatic Exercise, Gait Aids, Self-Management Programs	Aquatic Exercise, Cognitive Behavioral Therapy (with or without Exercise), Self-Management Programs, Gait Aids
Level 2	Conditional	Pharmacologic	IAHA	Non-selective NSAID + PPI	*see below*	*see below*	Duloxetine, IACS, IAHA, Topical NSAIDs
Low Consensus *60%-74% "in favor"*		Non-Pharmacologic	Cognitive Behavioral Therapy with Exercise	Cognitive Behavioral Therapy with Exercise		Cognitive Behavioral Therapy with Exercise	*none recommended*
Good Clinical Practice Statements	Conditional	Various	*Intra-articular (IA) treatment*	*IA treatment, NSAID risk mitigation*		*IA treatment, NSAID risk mitigation*	*Pain management program, IA treatment*

IA treatment: Intra-articular corticosteroids (IACS) are conditionally recommended for acute (1–2 weeks) and short-term (4–6 weeks) pain relief; Intra-articular Hyaluronic Acid (IAHA) is conditionally recommended for longer term treatment effect, as it was associated with symptom improvement beyond 12 weeks and demonstrated a favorable safety profile.
NSAID risk mitigation: In situations where the patient and physician choose to proceed with an oral NSAID treatment regimen despite a lack of recommendation, we suggest using the lowest possible dose of oral NSAID for shortest treatment duration along with gastric protection with a PPI[23].
Pain management program: Based on clinical assessment, it may be appropriate to refer individuals of this phenotype to a multidisciplinary chronic/widespread pain management program.

Table III
Recommended treatments, by level, for hip osteoarthritis

Recommendation level	Strength	Treatment type	No comorbidities	Gastrointestinal	Cardiovascular	Frailty	Widespread pain/depression
CORE	Strong	Arthritis Education; Structured Land-Based Exercise Programs (Type 1- strengthening and/or cardio and/or balance training/neuromuscular)					
Level 1A	Strong	Pharmacologic	*refer to Level 1B*	*refer to Level 1B*		*refer to Level 1B*	*refer to Level 1B*
≥75% "in favor" & >50% "strong" Recommendation		Non-Pharmacologic	*refer to Level 1B*	*refer to Level 1B*		*refer to Level 1B*	*refer to Level 1B*
Level 1B	Conditional	Pharmacologic	Non-selective NSAIDs	COX-2 Inhibitors	*see below*	*see below*	*see below*
≥75% "in favor" & >50% "conditional" Recommendation		Non-Pharmacologic	Mind-body Exercise, Self-Management Programs, Gait Aids	Mind-body Exercise, Self-Management Programs, Gait Aids		Mind-body Exercise, Self-Management Programs, Gait Aids	Mind-body Exercise, Gait Aids
Level 2	Conditional	Pharmacologic	• Non-selective NSAID + PPI • COX-2 Inhibitors	Non-selective NSAID + PPI	*see below*	*see below*	• Non-selective NSAIDs • Non-selective NSAID + PPI • COX-2 Inhibitors
60%-74% "in favor"		Non-Pharmacologic	*see below*	*see below*		*see below*	Cognitive Behavioral Therapy, Self-Management Programs
Good Clinical Practice Statements	Conditional	Various	*Weight management*	*Weight management, NSAID risk mitigation*	*NSAID risk mitigation*	*NSAID risk mitigation*	*Pain management program, Weight management, NSAID risk mitigation*

Weight Management: Dietary Weight Management with or without an exercise component is unlikely to have a significant beneficial effect on Hip OA symptoms. There was no RCT evidence assessing the effects of Dietary Weight Management, and the voting for Dietary Weight Management in Hip OA patients was based on indirect evidence for Knee OA patients. However, Dietary Weight Management may be recommended for certain patients (e.g., individuals presenting with body mass index ≥30 kg/m^2) as part of a healthy lifestyle regimen.
NSAID risk mitigation: In situations where the patient and physician choose to proceed with an oral NSAID treatment regimen despite a lack of recommendation, we suggest using the lowest possible dose of oral NSAID for shortest treatment duration along with gastric protection with a PPI[23].
Pain management program: Based on clinical assessment, it may be appropriate to refer individuals of this phenotype to a multidisciplinary chronic/widespread pain management program.

completion of all voting. All Core Expert Panel members and Voting Panel members were given the opportunity to review the Good Clinical Practice Statements, and they were adopted with consensus of both panels. Good Clinical Practice Statements are intended to act as qualifiers for existing treatment recommendations, not to act as stand-alone recommendations.

Results

Systematic literature search (Fig. 1)

Our systematic search returned 12,535 potentially relevant abstracts. Of these, 1,190 were eligible for full text review, and 407 RCT reports contained extractable data on outcomes of interest and were included in our Final Evidence Report.

Algorithm of non-surgical treatment pathway for knee, hip, and polyarticular osteoarthritis (Fig. 2)

The algorithm was designed as a patient-centered guide to clinical practice by incorporating typical assessment cycles and treatment selections that accommodate different comorbidity profiles. The initial assessment predicates the structure of the subsequent treatment pathway for an individual patient based on joint localization (item 1) and clinically relevant comorbidities (item 2) and establishes goals and expectations. Items 3 and 4 concern clinical, emotional, and environmental factors that influence the intensity of the treatment and the individual's capacity to adhere to treatment. Factors assessed at the initial visit can be monitored for change at follow-up assessments. During the initial assessment, clinicians select Core Treatment(s) tailored to individual needs and preferences. However, depending on an individual's current clinical status and preferences, Level 1A (strong recommendation) or 1B treatments (conditional recommendation) can be added. Tables II–IV display treatment recommendations for Knee, Hip, and Polyarticular OA, with stratification for comorbidity groups.

In selecting an initial treatment option, clinicians are advised to choose a treatment from the "Level 1A" strata of the treatment selection tables. In circumstances where no treatments have been strongly recommended, clinicians are advised to select an appropriate non-pharmacologic or pharmacologic treatment from the "Level 1B" strata. Good clinical practice statements were intended to provide supportive information on specific intervention types based on expert experience and are applicable throughout the course of the regimen, as appropriate. Re-assessments present an opportunity to assess treatment response and explore barriers to adherence and/or adjust the intervention dosage. Individuals who do not achieve an acceptable state despite using recommended treatments will need additional support and advice, or referral to a specialized multidisciplinary pain clinic or surgical intervention.

Recommendations for knee osteoarthritis (Table II)

Core Treatments (treatments deemed appropriate for use by the majority of patients in nearly any scenario and deemed safe for use in conjunction with first line and second line treatments)

Structured land-based exercise programs, dietary weight management in combination with exercise, and mind-body exercise (such as Tai Chi and Yoga) were considered by the panel to be effective and safe for all patients with Knee OA, regardless of comorbidity. These treatments are recommended for use alone or along with interventions of any recommendation level, as deemed appropriate for the individual. Education about OA is considered a standard of care, despite a lack of RCT data addressing the topic.

Table IV
Recommended treatments, by level, for polyarticular osteoarthritis

Recommendation level	Strength	Treatment type	No comorbidities	Gastrointestinal	Cardiovascular	Frailty	Widespread pain/depression
CORE	Strong	Arthritis Education; Structured Land-Based Exercise Programs (Type 1- strengthening and/or cardio and/or balance training/neuromuscular)					
Level 1A	Strong	Pharmacologic	*refer to Level 1B*	*refer to Level 1B*		*refer to Level 1B*	*refer to Level 1B*
≥75% "in favor" & >50% "strong" Recommendation		Non-Pharmacologic	*refer to Level 1B*	*refer to Level 1B*		*refer to Level 1B*	*refer to Level 1B*
Level 1B	Conditional	Pharmacologic	Non-selective NSAIDs Topical NSAIDs	COX-2 Inhibitors	*see below*	*see below*	*see below*
≥75% "in favor" & >50% "conditional" Recommendation		Non-Pharmacologic	Mind-body Exercise, Dietary Weight Management (with or without Exercise), Self-Management Programs, Gait Aids	Mind-body Exercise, Dietary Weight Management (with or without Exercise), Self-Management Programs, Gait Aids		Mind-body Exercise, Self-Management Programs, Gait Aids	Mind-body Exercise, Cognitive Behavioral Therapy, Dietary Weight Management (with or without Exercise), Self-Management Programs, Gait Aids
Level 2	Conditional	Pharmacologic	• Non-selective NSAID+PPI • COX-2 Inhibitors	Non-selective NSAID+PPI Topical NSAIDs	Topical NSAIDs	Topical NSAIDs	• Non-selective NSAIDs • Non-selective NSAID + PPI • COX-2 Inhibitors
60%-74% "in favor"		Non-Pharmacologic	*None recommended*	*None recommended*		*None recommended*	*None recommended*
Good Clinical Practice Statements	Conditional	Various	*NA*	*NSAID risk mitigation*		*NSAID risk mitigation*	*Pain management program*

NSAID risk mitigation: In situations where the patient and physician choose to proceed with an oral NSAID treatment regimen despite a lack of recommendation, we suggest using the lowest possible dose of oral NSAID for shortest treatment duration along with gastric protection with a PPI[23].
Pain management program: Based on clinical assessment, it may be appropriate to refer individuals of this phenotype to a multidisciplinary chronic/widespread pain management program.

Clinicians are encouraged to continually provide their patients with necessary information about OA disease progression and self-care techniques and to promote hope, optimism, and a positive expectation of benefit from treatment.

Level 1A recommendations (≥75% in favor & >50% strong recommendation)

Topical non-steroidal anti-inflammatory drugs (NSAIDs) were strongly recommended for use in Knee OA patients with no comorbidities. High quality evidence involving a large number of patients showed modest benefits over the course of 12 weeks. The adverse events from topical NSAIDs were minimal and mild. The most common adverse events associated with topical NSAIDs were local skin reactions, which were minor and transient. Topical NSAIDs were also strongly recommended for Knee OA patients with GI or CV comorbidities and for patients with frailty for the same reasons as described above.

No interventions were strongly recommended for use for individuals with Knee OA with concomitant widespread pain disorders (e.g., fibromyalgia) and/or depression.

Level 1B (≥75% in favor & >50% conditional recommendation) and level 2 (60–74% in favor) recommendations

Aquatic exercise, gait aids, cognitive behavioral therapy with an exercise component, and self-management programs were the recommended non-pharmacologic options for individuals with Knee OA and no comorbidities, and for individuals with GI or CV comorbidities or with widespread pain disorders and/or depression. Aquatic exercise, though it is supported by a modest evidence base and demonstrates robust benefits on pain and objective measures of function, received a conditional recommendation because of accessibility issues, financial burden, as well as issues with uptake. Aquatic exercise was not recommended for patients who suffered from frailty due to potential risk of accidental injury.

Use of Oral NSAIDs was conditionally recommended for individuals with Knee OA who do not have comorbid conditions. The Panel recommends the use of non-selective NSAIDs, preferably with the addition of a proton pump inhibitor (PPI), or selective COX-2 inhibitors. For individuals with GI comorbidities, selective COX-2 inhibitors and non-selective NSAIDs in combination with a PPI were conditionally recommended due to their benefits on pain and functional outcomes, but more importantly, because they have a more favorable upper GI safety profile than non-selective NSAIDs. NSAIDs of any class were not recommended for patients with CV comorbidities due to evidence associating NSAID use with heightened CV risk[20–23]. NSAIDs were not recommended in patients with frailty. However, a *Good Clinical Practice Statement* was made specifying that when NSAIDs are chosen for treatment of at-risk patients (including patients with frailty) those with more favorable safety profiles may be used at the lowest possible dose, for the shortest possible treatment duration.

The use of intra-articular corticosteroids (IACS) and hyaluronan (IAHA) were conditionally recommended in individuals with knee OA in all groups. A *Good Clinical Practice Statement* applying to intra-articular (IA) treatments for all comorbidity subgroups was added, noting that intra-articular corticosteroid (IACS) may provide short term pain relief, whereas Intra-articular hyaluronic acid (IAHA) may have beneficial effects on pain at and beyond 12 weeks of treatment and a more favorable long-term safety profile than repeated IACS.

Conditionally recommended treatments for patients with widespread pain and/or depression included oral NSAIDs of any category, duloxetine, IACS, IAHA and topical NSAIDs. Use of duloxetine was supported by moderate quality evidence in a large number of patients and was specifically recommended for this

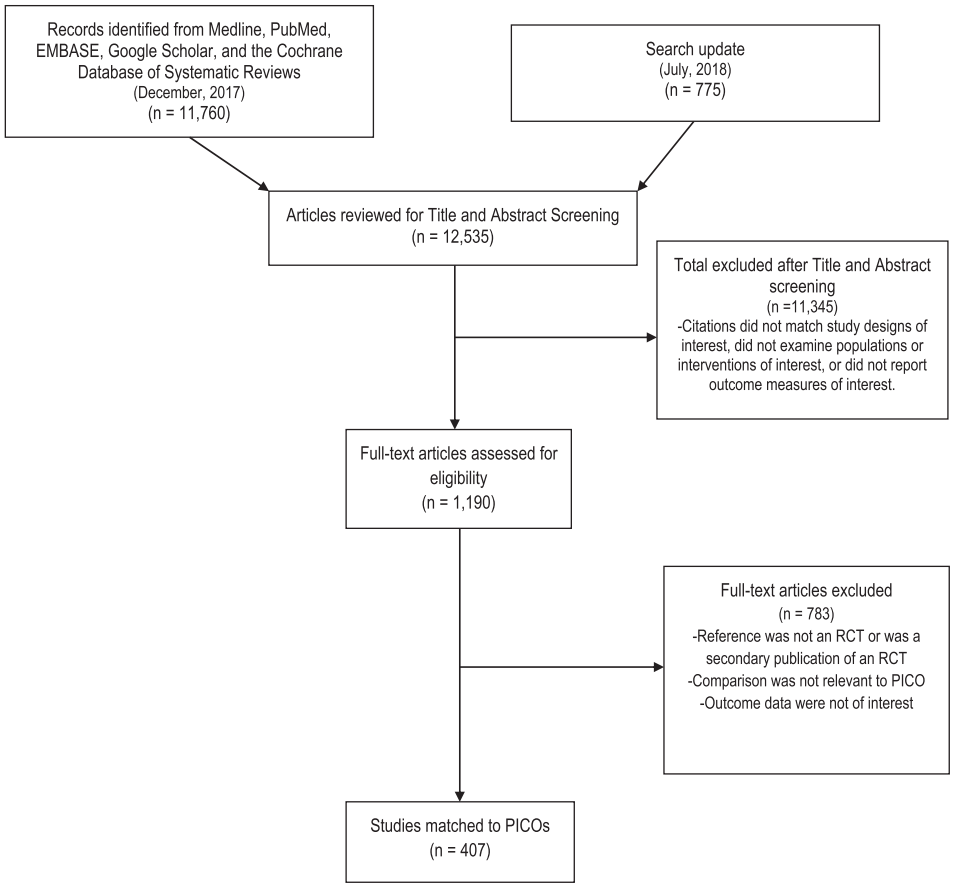

Fig. 1. Flowchart of the trial selection process.

comorbidity class due to its specific effects on depressive symptoms. With regard to the use of topical NSAIDs in patients with widespread pain, the Voting Panel members explicitly noted that the number of joints being treated, as well as the concomitant use of any oral NSAID, should be carefully monitored in this population due to potential risk of exceeding total recommended doses of a NSAID. The following *Good Clinical Practice Statement* was made for patients with Knee OA and widespread pain and/or depression: based on a clinical assessment, referral to a multidisciplinary chronic/widespread pain management program may be appropriate for the best management of their symptoms.

Recommendations for hip osteoarthritis (Table III)

Core Treatments (treatments deemed appropriate for use by the majority of patients in nearly any scenario and deemed safe for use in conjunction with first line and second line treatments)

For patients with Hip OA, only structured land-based exercise programs were considered eligible for Core Treatment designation. Arthritis education was, again, considered a standard of care.

Level 1A recommendations (≥75% in favor & >50% strong recommendation)

No treatment was strongly recommended for use in Hip OA patients of any comorbidity subgroup. This could partially be due to a lack of direct evidence in support of treatments for Hip OA.

Level 1B (≥75% in favor & >50% conditional recommendation) and level 2 (60–74% in favor) recommendations

Despite a lack of direct evidence, mind-body exercise (Tai Chi or Yoga) was conditionally recommended for Hip OA patients in all comorbidity subgroups because its favorable efficacy and safety profile in patients with Knee OA was considered generalizable to Hip OA. Self-management programs were also conditionally recommended for patients in all comorbidity subgroups; use of these programs resulted in a modest benefit on quality of life in one RCT conducted in individuals with Hip OA. Cognitive behavioral therapy was only recommended for patients with widespread pain and/or depression. The use of gait aids was recommended in patients from each comorbidity subgroup, with the exception of patients with widespread pain and/or depression. Dietary weight management was not recommended for Hip OA individuals of any comorbidity subgroup because of lack of direct evidence for its effectiveness specifically for symptoms of Hip OA. A *Good Clinical Practice Statement* was made that dietary weight management may be recommended for certain individuals (e.g., individuals presenting with body mass index ≥30 kg/m^2) of any comorbidity subgroup as a part of a healthy lifestyle regimen.

Use of oral NSAIDs was conditionally recommended for Hip OA patients without comorbidities and for patients with widespread pain and/or depression. In both treatment profiles, non-selective NSAIDs preferably with the addition of a PPI, and selective COX-2 inhibitors were conditionally recommended. For patients with GI comorbidities, the use of oral NSAIDs was restricted to selective

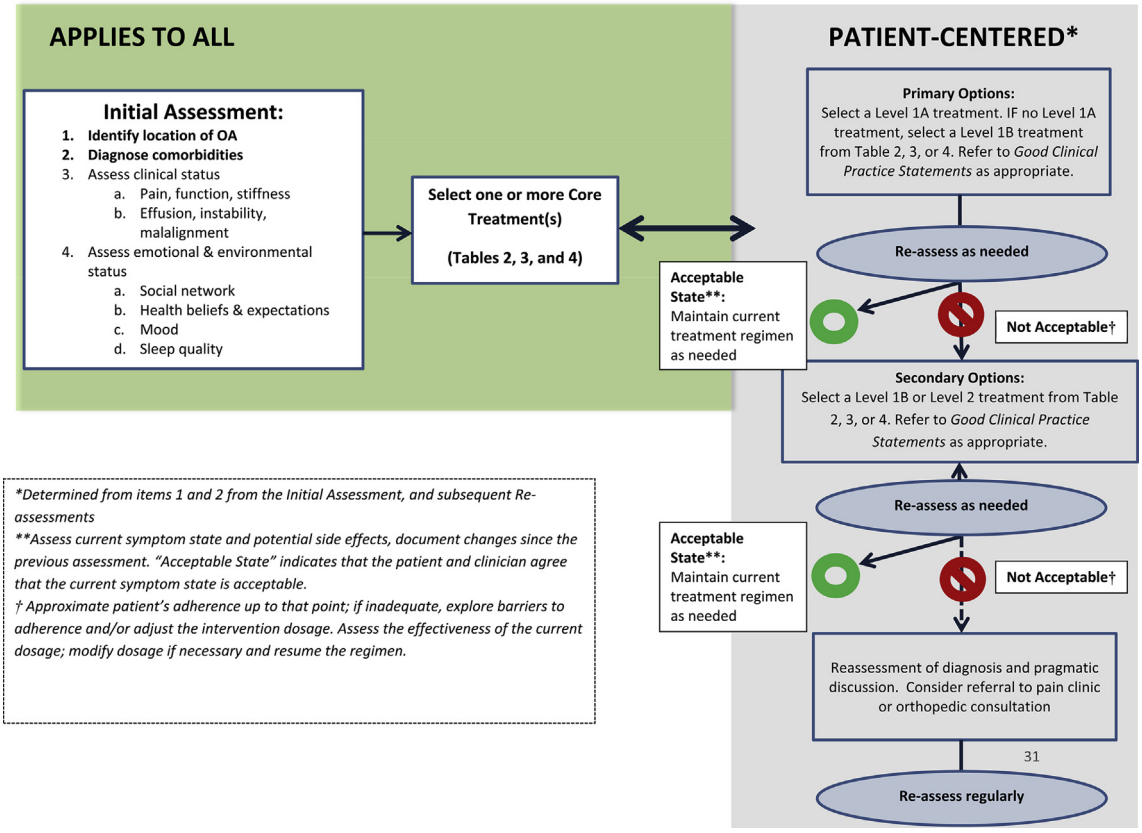

Fig. 2. Treatment algorithm.

COX-2 inhibitors or non-selective NSAIDs in combination with a PPI. Though no pharmacologic treatment option was conditionally recommended for Hip OA patients with comorbid CV conditions or frailty, a *Good Clinical Practice Statement* was made specifying that NSAIDs with more favorable safety profiles may be used in high-risk patients (including patients with frailty) at the lowest possible dose, for the shortest possible treatment duration, for symptomatic relief.

The following *Good Clinical Practice Statement* was made for patients with Hip OA and widespread pain and/or depression: based on a clinical assessment, referral to a multidisciplinary chronic/widespread pain management program may be appropriate for the best management of their symptoms.

Recommendations for polyarticular osteoarthritis (Table IV)

Core Treatments (treatments deemed appropriate for use by the majority of patients in nearly any scenario and deemed safe for use in conjunction with first line and second line treatments)

Structured land-based exercise programs were designated as Core Treatments for patients with Polyarticular OA, with arthritis education as a standard of care.

Level 1A recommendations (≥75% in favor & >50% strong recommendation)

No treatment was strongly recommended for use in patients of any comorbidity subgroup with Polyarticular OA.

Level 1B (≥75% in favor & >50% conditional recommendation) and level 2 (60–74% in favor) recommendations

Gait aids and mind-body exercise were conditionally recommended for patients with Polyarticular OA of any comorbidity subgroup even in the absence of direct evidence, due to their favorable efficacy and safety profiles in individuals with Knee OA. Self-management programs were also conditionally recommended for patients in all comorbidity subgroups. Dietary weight management, with or without an exercise component, was conditionally recommended for individuals with Polyarticular OA with no comorbid conditions, with GI or CV conditions, and with widespread pain and/or depression. Dietary weight management was not recommended for individuals with frailty due to potential risks associated with weight loss in these conditions. Cognitive behavioral therapy was recommended for individuals with widespread pain and/or depression.

Non-selective NSAIDs, preferably with the addition of a PPI, and selective COX-2 inhibitors were conditionally recommended for individuals with Polyarticular OA without comorbidities and for individuals with widespread pain and/or depression. For individuals with GI comorbidities, the use of oral NSAIDs was restricted to selective COX-2 inhibitors or non-selective NSAIDs in combination with a PPI. Though oral NSAIDs overall were not recommended for individuals with Polyarticular OA with cardiovascular conditions or frailty, the following *Good Clinical Practice Statement* was made: NSAIDs with more favorable safety profiles may be used in high-risk patients (including patients with frailty) at the lowest possible dose, for the shortest possible treatment duration, for symptomatic relief.

Though locally administered interventions such as IACS and IAHA are generally not indicated for Polyarticular OA, topical NSAIDs were conditionally recommended for individuals without comorbidities, with GI and CV comorbidities, and with frailty. For individuals with Polyarticular OA, the number of joints being treated, as well as the concomitant use of any oral NSAID, should be carefully monitored by the treating physician to avoid the potential

risk of exceeding total recommended doses of NSAIDs. Topical NSAIDs were not recommended for patients with Polyarticular OA and comorbid widespread pain disorders and/or depression.

The following *Good Clinical Practice Statement* was made for individuals with Polyarticular OA and widespread pain and/or depression: based on a clinical assessment, referral to a multidisciplinary chronic/widespread pain management program may be appropriate for the best management of symptoms.

Non-recommended treatments for knee, hip, and polyarticular OA

We recommend against using any interventions graded as Level 3, Level 4A, or Level 4B (Supplementary Tables 5, 6, and 7). Level 5 interventions were strongly recommended against, indicating that there are no clinical scenarios in which these treatments would be deemed appropriate for individuals with OA. Level 5 interventions and the rationale behind their designation are shown in Supplementary Table 8.

Discussion

These updated OARSI guidelines have taken a more patient-centered approach than earlier versions by allowing recommendations to be predicated on the distribution of osteoarthritis and various comorbidity profiles. The Core Treatments recommended are, in all cases, non-pharmacological. Our focus on specific comorbidities resulted in treatment recommendations that were highly influenced by concerns from the Voting Panel about safety and potential harms. In interpreting the comorbidity-specific recommendations, however, it is important to note that the comorbidity subgroups are conceptual representations of real-world conditions only, and that the exact conditions and characteristics qualifying for membership in each subgroup have not been specifically delineated. The subgroups were intended to remain broadly representative so as to not limit the interpretation of the recommendations by exclusion. Additionally, it is important to note that in real-world clinical practice, many individuals may fall into more than one comorbidity subgroup during the course of their treatment pathway, or may experience more than one type of comorbidity concurrently.

Of the non-Core interventions, topical NSAIDs were recommended more strongly than all oral analgesics due to a favorable balance of consistent efficacy and minor, transient side effects. A typical total NSAID dose from topical application to one joint is substantially less than the recommended oral dose of the same drug[24]. Conversely, APAP (acetaminophen/paracetamol), which has long been regarded as a mainstay of OA treatment, was not recommended by the majority of the Voting Panel for any OA phenotype or comorbidity subgroup. The evidence summarized in our updated meta-analysis suggests that it has little to no efficacy in individuals with OA, with a signal for possible hepatotoxicity. Additionally, the Panel strongly recommended against the use of either oral or transdermal opioids in individuals with OA, largely in response to recent international concerns about the devastating potential for chemical dependency posed by opioid medications[25–30]. Further support for this recommendation against opioids is provided by the strong evidence for limited or no relevant benefit of opioids on OA symptoms[31–33]. The recommendations for topicals, opioids, and APAP are different than those made in the prior Guidelines, although emerging concerns about both opioids and APAP were evident even at that time.

In a development from previous guidelines, the consideration of comorbidity subgroups led to the addition of details related to recommendations for oral NSAIDs. In the current guidelines, we planned additional head-to-head analyses *a priori* to assess the comparative efficacy and safety of non-selective NSAIDs vs COX-2 inhibitors; additionally, recommendations for oral NSAIDs included voting specific to the presence of GI or CV comorbidities, with the goal of gaining a deeper insight on the specific scenarios in which NSAIDs are appropriate. COX-2 inhibitors were strongly not recommended in individuals with CV comorbidities. Some recent evidence has suggested that CV risks of NSAIDs may apply to all NSAID categories; however, definitive conclusions about the CV risks of other NSAIDs cannot be made given the current body of evidence[20,21,23,34]. The use of non-selective NSAIDs was not recommended in individuals with GI comorbidities. The recommendations made by our Voting Panel were in agreement with the conclusions of the most recent RCT and meta-analytic data assessing the safety of NSAIDs[35,36]. Some recent studies have assessed the comparative safety and efficacy of specific NSAID types and doses, but such an undertaking was beyond the scope of this guideline[21,23,35,37].

For the first time, mind-body exercises (Tai Chi and Yoga) are recommended as Core Treatment options for individuals with knee OA, highlighting the importance of the holistic wellbeing of the individuals. Panel members also made the difficult decision to transfer treatments, such as aquatic exercise and gait aids, from being Core Treatments to conditionally positive recommendations, since in their own experiences, they do not strongly align with people's values and preferences.

Other treatments for which the status of recommendations has changed in these guidelines include duloxetine, bracing of the knee, and topical capsaicin. Previously, duloxetine was considered an “appropriate” treatment for individuals with knee OA or multi-joint OA without comorbidities and for individuals with multi-joint OA with comorbidities. In the current guidelines, duloxetine was only recommended as a Level 2 treatment for knee OA patients with depression and/or widespread pain disorders. Its status was equivocal (40–59% in favor) for individuals with knee OA without comorbidities and with frailty; it was conditionally not recommended for patients with GI or CV comorbidities since it demonstrated higher rates of GI adverse events in a large sample of patients. Duloxetine was not recommended for patients with hip or polyarticular OA due to the lack of evidence. Topical capsaicin and bracing of the knee (described as a biomechanical intervention in the previous guidelines) were recommended against in the current guidelines due to inadequate efficacy and safety balance, stemming from very poor quality evidence.

With regard to the treatment of Hip OA overall, there was a general trend against the use of pharmacologic treatments among our Voting Panel, partially due to the fact that very few hip-specific RCTs have been published. The most highly recommended treatments for patients with this phenotype were non-pharmacologic interventions. These may be the preferred choice over the longer-term use of pharmacologic treatments that may have a poor side effect profile and a less robust efficacy profile than that demonstrated in Knee OA.

Our guidelines expanded upon previous reports by including several interventions that were previously not assessed, including massage, mobilization and manipulation, thermotherapy, taping interventions, electromagnetic therapies, laser therapy, nerve block therapy (including radiofrequency ablation), intra-articular (IA) platelet rich plasma (PRP), IA stem cell therapy, dextrose prolotherapy, several investigational Disease Modifying OA Drugs (DMOADs) (including methotrexate), and a wider range of nutraceutical products. IA stem cell therapy and IA PRP, in particular, were strongly recommended against because the evidence in support of these treatments is of extremely low quality, and the formulations themselves have not yet been standardized. Future

investigation is needed to fully evaluate the appropriateness of these treatments in OA.

We also investigated the efficacy of FX006, a newly U.S. Food and Drug Administration-approved long-acting extended-release corticosteroid for IA use, against placebo and against conventional IACS. Separate recommendations were not made regarding the use of FX006 for knee OA, because further RCT evidence evaluating the comparative efficacy and safety of FX006 will be needed to distinguish recommendations for this intervention from those currently in place for traditional IACS.

Though they do not a currently have regulatory approval, we analyzed published data on anti-nerve growth factor (anti-NGF) treatments for OA and included the evidence tables in the formal voting session. Anti-NGFs showed benefits on pain and functional outcomes in patients with knee and hip OA; they were, however, associated with a higher rate of specific adverse events, such as parasthesia. A recent retrospective investigation also highlighted an association of anti-NGFs with a rapid progression of joint destruction, particularly when administered with NSAIDs[38]. Further investigation and review of the body of evidence related to these drugs should be undertaken if they are approved for use in OA.

As these guidelines are intended for an International constituency, we assembled an international panel of experts with a variety of professional backgrounds, including general practice, orthopedic surgery, rheumatology, sports medicine, and physiotherapy. The selection of this diverse multidisciplinary Panel was deliberate with the aim of producing guidelines that would be relevant to a number of clinical scenarios and representative in an international context. However, we are conscious that our panel did not include experts from Africa, South America, or India. A wider geographical representation would be desirable for any future revision.

A more rigorous GRADE methodology was adopted for these guidelines in that they tied evidence quality to the strength of final recommendations. This facilitates a more objective process that accurately reflects the state of the available data. We modified the GRADE approach in some ways to suit the process of these guidelines and to accommodate the body of evidence for OA. First, we drafted a quality assessment rubric a priori to set objective standards for each dimension of quality addressed by GRADE, including detailed percentage cutoffs for “serious” vs “very serious” risk of bias and inconsistency, and specific cut-points for “serious” vs “very serious” imprecision in SMDs using validated SMD intervals[39]. Doing this not only ensured consistency across the report, but also increased ease of interpretation. We categorized the resultant recommendations by levels that expressed a gradient of votes “in favor” and “against” a given treatment. In doing this, we have preserved the initial judgments of the Voting Panel of the evidence base and, in certain circumstances, have portrayed the ambiguity that practicing clinicians may encounter in selecting a particular treatment. Recommendations formulated by the GRADE approach possess both directionality and strength, allowing for a more nuanced interpretation when necessary. In the previous guidelines, treatments were designated as either “Appropriate”, “Uncertain”, or “Inappropriate”. In the current guidelines, treatments have received “strong” or “conditional” recommendations in favor or against. In addition, we have reported the full “gradient” of percentages in favor and against within the data supplement. The intended result of this heightened detail is to encourage the practice of evidence-based medicine in OA care.

In contrast to previous OARSI guidelines, we have conducted meta-analyses and quality assessments for each treatment and have provided evidence from all eligible studies along with the sensitivity analyses limiting by study quality. Additionally, the list of therapeutics eligible for consideration in the evidence report was not constrained as in the previous effort. We also went into further detail on certain treatments for which the evidence base in the previous report was limited, such as balneotherapy, biomechanical interventions, and bisphosphonates.

An additional aspect of these guidelines is the creation of a treatment algorithm, which offers more structured guidance to clinicians by allowing them to personalize the treatment pathways based on an individual patient profile on a long-term and ongoing basis. Ultimately, the treatment pathway has the potential to serve as the blueprint for a personalized, web-based or mobile application that would increase the visibility and accessibility of these guidelines to those who stand to benefit the most from its recommendations.

The main limitation of these guidelines was that the voting for a majority of the recommendations was based on indirect evidence combined with expert opinion. The reason for this is because there are few direct RCT data assessing the efficacy of OA interventions in patients with GI or CV comorbidities, frailty, or widespread pain and/or depression. Additionally, there is a lack of RCT evidence directly assessing the interventions of interest in patients with Polyarticular OA. It is also important to note that these guidelines do not provide specific guidance on hand, shoulder, or spine OA. The Panel recommends generating a larger body of RCT evidence in these areas to allow for more robust guideline development specific to these individuals.

Though the use of GRADE methodology was a strength of these guidelines, it also introduced some limitations in the interpretation of the evidence. Since evidence quality is downgraded not only based on risk of bias, but also the preciseness of the estimates, and homogeneity of the samples, many interventions were judged to have a low quality body of evidence for reasons that were related to small sample size or other methodological factors. Conversely, we were limited in our ability to address some of the biases common in the evidence body for OA, particularly publication bias and small study effects. Even after developing *a priori* and applying a comprehensive set of objective measures to deal with multiple biases and deficiencies that are prevalent in the OA evidence base, we may not have accounted for all of these biases to the fullest extent. With the growing evidence base and addition of larger studies of higher quality, we hope quality measures can be redefined in a more stringent manner to reduce all these biases in the future guidelines. Finally, for logistical reasons, we were limited in the number of Voting Panel members we could select and the number of formal voting sessions we could hold. These recommendations are not intended to support payment or insurance decisions and should not be used for denial of treatments to patients.

In conclusion, the 2019 OARSI guidelines for Knee, Hip and Polyarticular OA are comprehensive and more patient-centered, and provide a useful tool for individuals and physicians to facilitate individualized treatment decisions regarding the management of OA. We ensured that our guidelines development process was transparent and systematic by using GRADE methodology and well-defined group-consensus technique.

Author contributions

Bannuru, Bennell, Bierma-Zeinstra, Kraus, Lohmander, McAlindon, and Osani were responsible for the conception and design of the study. Bannuru and Osani acquired the data and performed data analysis and quality assessment. All authors made substantial contributions in the interpretation of the results.

Bannuru and Osani drafted the article and all authors revised it critically for important intellectual content.

All authors approved the final version to be submitted.

Conflict of interest

Full disclosure statements from all Panel members were solicited and reviewed by the OARSI Ethics Committee upon initiating the preliminary planning stages of the guideline development process. Disclosures were updated throughout the guideline development process, and final disclosure statements were submitted by every author upon submission of the manuscript. No member of the committee disclosed conflict(s) of interest that would preclude them from participating in the guideline development process. Members of the committee who disclosed potential conflict of interest pertinent to any specific intervention category were prohibited from participating in discussion, evidence synthesis, and/or review of those particular sections. No Panel members are employees of any pharmaceutical or medical device company. Dr. Bannuru is supported by the National Center for Complementary and Integrative Health, US (K23AT009374). The contents of this manuscript are solely the responsibility of the authors and do not necessarily represent the official views of the National Center for Complementary and Integrative Health.

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Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.joca.2019.06.011.

Appendix

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Voting Panel: Abbott, Arden, Bhandari, Blanco, Espinosa, Haugen, Lin, Mandl, Moilanen, Nakamura, Snyder-Mackler, Trojian, Underwood.

Patient Panel: Angie Botton van Bemden, Ingrid Lether, Sarah Rudkin, Maartin de Wit.

References

1. Cross M, Smith E, Hoy D, Nolte S, Ackerman I, Fransen M, *et al.* The global burden of hip and knee osteoarthritis: estimates from the global burden of disease 2010 study. Ann Rheum Dis 2014;73(7):1323–30.
2. Hermans J, Koopmanschap MA, Bierma-Zeinstra SM, van Linge JH, Verhaar JA, Reijman M, *et al.* Productivity costs and medical costs among working patients with knee osteoarthritis. Arthritis Care Res (Hoboken). 2012;64(6):853–61.
3. Hunter DJ, Schofield D, Callander E. The individual and socioeconomic impact of osteoarthritis. In: Nat Rev Rheumatol 2014;vol. 10:437–41. United States.
4. Le Pen C, Reygrobellet C, Gerentes I. Financial cost of osteoarthritis in France. The "COART" France study. Jt Bone Spine 2005;72(6):567–70.
5. Kingsbury SR, Gross HJ, Isherwood G, Conaghan PG. Osteoarthritis in Europe: impact on health status, work productivity and use of pharmacotherapies in five European countries. Rheumatology (Oxford) 2014;53(5):937–47.
6. Sharif B, Garner R, Hennessy D, Sanmartin C, Flanagan WM, Marshall DA. Productivity costs of work loss associated with osteoarthritis in Canada from 2010 to 2031. Osteoarthritis Cartilage 2017;25(2):249–58.
7. McAlindon TE, Bannuru RR, Sullivan MC, Arden NK, Berenbaum F, Bierma-Zeinstra SM, *et al.* OARSI guidelines for the non-surgical management of knee osteoarthritis. Osteoarthr Cartil/OARS 2014;22(3):363–88.
8. Zhang W, Moskowitz RW, Nuki G, Abramson S, Altman RD, Arden NK, *et al.* OARSI recommendations for the management of hip and knee osteoarthritis, Part II: OARSI evidence-based, expert consensus guidelines. Osteoarthritis Cartilage 2008;16(2):137–62.
9. Guyatt GH, Oxman AD, Vist GE, Kunz R, Falck-Ytter Y, Alonso-Coello P, *et al.* GRADE: an emerging consensus on rating quality of evidence and strength of recommendations. Bmj 2008;336(7650):924–6.
10. Guyatt GH, Oxman AD, Kunz R, Atkins D, Brozek J, Vist G, *et al.* GRADE guidelines: 2. Framing the question and deciding on important outcomes. J Clin Epidemiol 2011;64(4):395–400.
11. The Cochrane Collaboration. RevMan 5.3. http://tech.cochrane.org/revman.
12. The Cochrane Collaboration. The Cochrane risk of bias tool. http://handbook.cochrane.org.
13. DerSimonian R, Laird N. Meta-analysis in clinical trials. Contr Clin Trials 1986;7(3):177–88.
14. Mantel N, Haenszel W. Statistical aspects of the analysis of data from retrospective studies of disease. J Natl Cancer Inst 1959;22(4):719–48.
15. Higgins JP, Thompson SG. Quantifying heterogeneity in a meta-analysis. Stat Med 2002;21(11):1539–58.
16. Rucker G, Schwarzer G, Carpenter JR, Schumacher M. Undue reliance on I(2) in assessing heterogeneity may mislead. BMC Med Res Methodol 2008;8:79.
17. Evidence Prime. GRADEpro GDT: GRADEpro Guideline Development Tool [Software]. McMaster University, 2015, https://gradepro.org.
18. Andrews J, Guyatt G, Oxman AD, Alderson P, Dahm P, Falck-Ytter Y, *et al.* GRADE guidelines: 14. Going from evidence to recommendations: the significance and presentation of recommendations. J Clin Epidemiol 2013;66(7):719–25.
19. Andrews JC, Schünemann HJ, Oxman AD, Pottie K, Meerpohl JJ, Coello PA, *et al.* GRADE guidelines: 15. Going from evidence to recommendation-determinants of a recommendation's direction and strength. J Clin Epidemiol 2013;66(7):726–35.
20. Nissen SE, Yeomans ND, Solomon DH, Lüscher TF, Libby P, Husni ME, *et al.* Cardiovascular safety of celecoxib, naproxen, or ibuprofen for arthritis. N Engl J Med 2016;375(26):2519–29.
21. Trelle S, Reichenbach S, Wandel S, Hildebrand P, Tschannen B, Villiger PM, *et al.* Cardiovascular safety of non-steroidal anti-

inflammatory drugs: network meta-analysis. BMJ 2011;342:c7086.
22. Mukherjee D, Nissen SE, Topol EJ. Risk of cardiovascular events associated with selective COX-2 inhibitors. Jama 2001;286(8):954–9.
23. Bally M, Dendukuri N, Rich B, Nadeau L, Helin-Salmivaara A, Garbe E, *et al*. Risk of acute myocardial infarction with NSAIDs in real world use: bayesian meta-analysis of individual patient data. Bmj 2017;357:j1909.
24. Underwood M, Ashby D, Carnes D, Castelnuovo E, Cross P, Harding G, *et al*. Topical or oral ibuprofen for chronic knee pain in older people. The TOIB study. Health Technol Assess 2008;12(22). iii-iv, ix-155.
25. Deveza LA, Hunter DJ, Van Spil WE. Too much opioid, too much harm. Osteoarthritis Cartilage 2018;26(3):293–5.
26. Jeffery MM, Hooten WM, Henk HJ, Bellolio MF, Hess EP, Meara E, *et al*. Trends in opioid use in commercially insured and Medicare Advantage populations in 2007-16: retrospective cohort study. Bmj 2018;362:k2833.
27. Inacio MCS, Cashman K, Pratt NL, Gillam MH, Caughey G, Graves SE, *et al*. Prevalence and changes in analgesic medication utilisation 1 year prior to total joint replacement in an older cohort of patients. Osteoarthritis Cartilage 2018;26(3):356–62.
28. Birke H, Kurita GP, Sjøgren P, Højsted J, Simonsen MK, Juel K, *et al*. Chronic non-cancer pain and the epidemic prescription of opioids in the Danish population: trends from 2000 to 2013. Acta Anaesthesiol Scand 2016;60(5):623–33.
29. Volkow ND, McLellan AT. Opioid abuse in chronic pain–misconceptions and mitigation strategies. N Engl J Med 2016;374(13):1253–63.
30. Vowles KE, McEntee ML, Julnes PS, Frohe T, Ney JP, van der Goes DN. Rates of opioid misuse, abuse, and addiction in chronic pain: a systematic review and data synthesis. Pain 2015;156(4):569–76.
31. da Costa BR, Nüesch E, Kasteler R, Husni E, Welch V, Rutjes AW, *et al*. Oral or transdermal opioids for osteoarthritis of the knee or hip. Cochrane Database Syst Rev 2014;(9). Cd003115.
32. Krebs EE, Gravely A, Nugent S, Jensen AC, DeRonne B, Goldsmith ES, *et al*. Effect of opioid vs nonopioid medications on pain-related function in patients with chronic back pain or hip or knee osteoarthritis pain: the SPACE randomized clinical trial. Jama 2018;319(9):872–82.
33. Smith SR, Deshpande BR, Collins JE, Katz JN, Losina E. Comparative pain reduction of oral non-steroidal anti-inflammatory drugs and opioids for knee osteoarthritis: systematic analytic review. Osteoarthritis Cartilage 2016;24(6):962–72.
34. Barcella CA, Lamberts M, McGettigan P, Fosbøl EL, Lindhardsen J, Torp-Pedersen C, *et al*. Differences in cardiovascular safety with non-steroidal anti-inflammatory drug therapy—a nationwide study in patients with osteoarthritis. Basic Clin Pharmacol Toxicol 2019;124(5):629–41.
35. Bhala N, Emberson J, Merhi A, Abramson S, Arber N, Baron JA, *et al*. Vascular and upper gastrointestinal effects of non-steroidal anti-inflammatory drugs: meta-analyses of individual participant data from randomised trials. Lancet 2013;382(9894):769–79.
36. Solomon DH, Husni ME, Wolski KE, Wisniewski LM, Borer JS, Graham DY, *et al*. Differences in safety of nonsteroidal anti-inflammatory drugs in patients with osteoarthritis and patients with rheumatoid arthritis: a randomized clinical trial. Arthritis Rheum 2018;70(4):537–46.
37. da Costa BR, Reichenbach S, Keller N, Nartey L, Wandel S, Jüni P, *et al*. Effectiveness of non-steroidal anti-inflammatory drugs for the treatment of pain in knee and hip osteoarthritis: a network meta-analysis. Lancet 2017;390(10090):e21–33.
38. Hochberg MC. Serious joint-related adverse events in randomized controlled trials of anti-nerve growth factor monoclonal antibodies. Osteoarthritis Cartilage 2015;23(Suppl 1):S18–21.
39. Cohen J. Statistical power analysis for the behavioral sciences. In: Erlbaum Associates. 2nd edn. 1988. Hillsdale.