EULAR recommendations for the non-pharmacological core management of hip and knee osteoarthritis

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ABSTRACT

The objective was to develop evidence -based recommendations and a research and educational agenda for the non-pharmacological management of hip and knee osteoarthritis (OA). The multidisciplinary task force comprised 21 experts: nurses, occupational therapists, physiotherapists, rheumatologists, orthopaedic surgeons, general practitioner, psychologist, dietician, clinical epidemiologist and patient representatives. After a preliminary literature review, a first task force meeting and five Delphi rounds, provisional recommendations were formulated in order to perform a systematic review. A literature search of Medline and eight other databases was performed up to February 2012. Evidence was graded in categories I–IV and agreement with the recommendations was determined through scores from 0 (total disagreement) to 10 (total agreement). Eleven evidence-based recommendations for the non-pharmacological core management of hip and knee OA were developed, concerning the following nine topics: assessment, general approach, patient information and education, lifestyle changes, exercise, weight loss, assistive technology and adaptations, footwear and work. The average level of agreement ranged between 8.0 and 9.1. The proposed research agenda included an overall need for more research into non-pharmacological interventions for hip OA, moderators to optimise individualised treatment, healthy lifestyle with economic evaluation and long-term follow-up, and the prevention and reduction of work disability. Proposed educational activities included the required skills to teach, initiate and establish lifestyle changes. The 11 recommendations provide guidance on the delivery of non-pharmacological interventions to people with hip or knee OA. More research and educational activities are needed, particularly in the area of lifestyle changes.

INTRODUCTION

Osteoarthritis (OA) is one of the most common chronic diseases, with an estimated overall prevalence in the general adult population of 11% and 24% for hip and knee OA, respectively.[1] OA is age related, with manifestations often not occurring until middle age. In elderly people, OA is the most common cause of disability, including pain and limitations of activities and participation.[2–4] As life expectancy is increasing the number of people living for prolonged periods with severe OA is expected to grow.

The need for high-quality care for a condition with major personal and societal impact is generally recognised and several guidelines for such care are available.[5–9] International recommendations for management of OA are often divided into three main categories: non-pharmacological, pharmacological and surgical.[6] During the past decade, much emphasis has been put on non-pharmacological management. However, recommendations are not sufficiently specific about the content, timing, intensity, frequency, duration and mode of delivery of each non-pharmacological option. This lack of detailed guidance may be one of the reasons why the quality of care for people with hip or knee OA is found to be suboptimal in several studies.[10 11]

In order to deal with this problem, the European League Against Rheumatism (EULAR) convened a group of experts to produce evidence-based recommendations for the non-pharmacological management of people with hip or knee OA, in accordance with the EULAR standard operating procedures,[12] and to develop a research and educational agenda for future activities. These recommendations would provide more detail and would therefore be an addition to existing management guidelines and would be easier to implement. The target groups for these recommendations are all healthcare providers involved in the delivery of non-pharmacological interventions, researchers in the field of OA, officials in healthcare governance, reimbursement agencies and policy makers. In addition, people with hip or knee OA can use the recommendations for information on non-pharmacological management strategies.

METHODS

The task force aimed to aggregate available information on non-pharmacological management of hip and knee OA into practical recommendations, using EULAR standardised operational procedures.[12] These involved the assembly of an expert committee to develop consensus, based both on research evidence provided by a systematic literature review and expert opinion.

The task force comprised 21 people with particular knowledge of OA from 10 European

countries, specifically: two nurses (SO, JdlT); one psychologist (RG); one dietician (PC); two occupational therapists (AH, IK); three physiotherapists (KBH, HL, TN); five rheumatologists (JWJB, PGC, MD, KP, JAdS); two orthopaedic surgeons (LSL, GZ); one general practitioner (CDM); two persons representing people with hip and/or knee OA (OA, IP); a clinical epidemiologist (TPMVV); and a research fellow (LF).

The process was based on both research evidence and consensus (see online supplementary appendix tables S1–S2 and figures S1–S12), and included, between June 2011 and May 2012, two task force meetings, systematic literature reviews (SLR) and extensive discussions. If a recommendation was shown to be inaccurate, based on data from the SLR, it could be rejected. Research evidence was graded in categories I–IV (table 1).[12] During the second task force meeting, votes for level of agreement (LOA) were cast anonymously, by giving a score on a numeric rating scale from 0 (total disagreement) to 10 (total agreement) for each recommendation; mean and 95% CI of scores were calculated. Topics for the research and educational agenda were formulated based on discussions of the lack of evidence to substantiate the recommendations and weaknesses in current healthcare delivery.

RESULTS

Development of the recommendations

After the first meeting, a total of 168 propositions were suggested by the experts. Propositions that were identical were merged and propositions containing one word only were excluded. The second Delphi round comprised 140 propositions, with topics being very broad and including far more non-pharmacological interventions than currently included in these recommendations. After five Delphi rounds, consensus on 11 recommendations was achieved, which are presented with complete formulation in table 2 with the accompanying level of evidence (LOE) and LOA. The 11 recommendations are ordered in a logical sequence or procedural and chronological hierarchy rather than by any considered importance.

The terms 'non-pharmacological' and 'non-surgical' management were discussed by the expert group. The terms were considered to be negative owing to their prefix 'non' and were therefore not considered optimal; finding a new terminology was included in the research agenda (table 3). In addition, research evidence specifically for hip OA was sparse and, in general, recommendations for the management of people with hip OA were derived largely from trials including people with both hip and knee OA or with knee OA only.

Initial assessment

Research data on how a comprehensive assessment of people with hip or knee OA should best be carried out are scarce. Since initial assessment will always be a part of the management in any person with hip or knee OA, controlled trials evaluating assessment will have difficulties in selecting the most appropriate comparator. One randomised, controlled trial (RCT) comparing a comprehensive assessment and management approach with usual care showed no difference in pain or physical function.[13] However, in that study, both approaches included initial assessments, but with different content and were executed by different professionals.[13]

The group considered a comprehensive initial assessment to be a prerequisite for the individualised management strategy described in recommendation 2. The recommendation on the initial assessment included the following elements: the person's physical status, activities of daily living, participation, mood and health education needs, health beliefs and motivation to self-manage. In the absence of evidence from studies on the effectiveness of various forms of assessment, the group based the recommended content of the initial assessment on the main areas of disease consequences, including potentially interacting personal and environmental factors described in the literature.[14–22] Evaluation of cardiovascular disease, people's expectations and self-efficacy were also discussed as important aspects in a biopsychosocial approach.[14 17] Moreover, the group found that a comprehensive assessment, which is applicable to the initial consultation, should also be repeated during regular follow-up of the person.

Individualised treatment

The task force agreed unanimously that the overarching principle for treatment of a person with hip or knee OA should be individualised, which is in line with previous guidelines.[7–9 23] Individualised treatment does not imply that every treatment should be individually provided, it means rather that treatment is personalised, or tailored. RCTs on individualised non-pharmacological management are scant. The available studies showed reduced pain (mean difference, 95% CI (0–20 point scale): −1.19, −2.1 to −0.3 and −1.10, −1.84 to −0.19; and (0–100 scale): −17.0, −23.6 to −10.4) and improved physical function (mean difference, 95% CI (0–68 point scale): 3.65, 1.0 to 6.3 and 3.33, 0.78 to 5.88) compared with usual care,[24–26] but not compared with group-based rehabilitation[25 27 28] or information on healthy lifestyle.[29 30] Follow-ups at 9, 18 or 30 months showed no effect on pain.[31 32]

As the data underpinning this recommendation are limited the factors to be considered for the tailoring of management were mainly based on prognostic factors shown in the literature. An important and modifiable risk factor for knee OA is weight,[20 33 34] implying individualised targeting at weight reduction in people who are overweight or obese.

Moreover, individualised treatment being the standard of care in OA and chronic disease in general[7 35 36] was considered to imply informed, shared decision-making, taking into account the person's wishes and preferences. The group noted that with the conduct of an RCT to study the impact of individualisation, the patient's view cannot be wholly taken into account and that some element of individualisation will always be incorporated in any treatment. To better understand individualised treatment, the group found that future research should focus on factors that affect outcome—that is, moderators, not individualisation as such.

Comprehensive package of care

This recommendation deals with the provision of an integrated package of care rather than single treatments alone or in succession. The group recommended five core interventions to be

Table 1 Categories of levels of evidence

Category	Level of evidence
Ia	Meta-analysis of randomised controlled trials
Ib	At least one randomised controlled trial
IIa	At least one controlled trial without randomisation
IIb	At least one type of quasi-experimental study
III	Descriptive studies, such as comparative studies, correlation studies or case–control studies
IV	Expert committee reports or opinions and/or clinical experience of respected authorities

Table 2 EULAR recommendations for the non-pharmacological core management of hip and knee OA, with levels of evidence (LOE) and level of agreement (LOA). The propositions are ordered by topic

No.	Recommendation	LOE I–IV	LOA (95% CI)
1	In people with hip or knee OA, initial assessments should use a biopsychosocial approach including: a physical status (including pain; fatigue; sleep quality; lower limb joint status (foot, knee, hip); mobility; strength; joint alignment; proprioception and posture; comorbidities; weight) b activities of daily living c participation (work/education, leisure, social roles) d mood e health education needs, health beliefs and motivation to self-manage	Ib, mixed	8.6 (7.9 to 9.2)
2	Treatment of hip and/or knee OA should be individualised according to the wishes and expectations of the individual, localisation of OA, risk factors (such as age, sex, comorbidity, obesity and adverse mechanical factors), presence of inflammation, severity of structural change, level of pain and restriction of daily activities, societal participation and quality of life	Ib, mixed Ib, knee	8.7 (8.2 to 9.2)
3	All people with knee/hip OA should receive an individualised management plan (a package of care) that includes the core non-pharmacological approaches, specifically: a information and education regarding OA b addressing maintenance and pacing of activity c addressing a regular individualised exercise regimen d addressing weight loss if overweight or obese e* reduction of adverse mechanical factors (eg, appropriate footwear) f* consideration of walking aids and assistive technology	Ib, hip Ib, knee	8.7 (8.2 to 9.3)
4	When lifestyle changes are recommended, people with hip or knee OA should receive an individually tailored programme, including long-term and short-term goals, intervention or action plans, and regular evaluation and follow-up with possibilities for adjustment of the programme	Ib, mixed Ib, knee	8.0 (7.1 to 9.0)
5	To be effective, information and education for the person with hip or knee OA should: a* be individualised according to the person's illness perceptions and educational capability b* be included in every aspect of management c† specifically address the nature of OA (a repair process triggered by a range of insults), its causes (especially those pertaining to the individual), its consequences and prognosis d† be reinforced and developed at subsequent clinical encounters; e† be supported by written and/or other types of information (eg, DVD, website, group meeting) selected by the individual f† include partners or carers of the individual, if appropriate	Ia, mixed	8.4 (7.7 to 9.1)
6	The mode of delivery of exercise education (eg, individual 1 : 1 sessions, group classes, etc) and use of pools or other facilities should be selected according both to the preference of the person with hip or knee OA and local availability. Important principles of all exercise include: a† 'small amounts often' (pacing, as with other activities) b† linking exercise regimens to other daily activities (eg, just before morning shower or meals) so they become part of lifestyle rather than additional events c* starting with levels of exercise that are within the individual's capability, but building up the 'dose' sensibly over several months	Ia, knee, delivery mode Ia, mixed, water-based exercise	8.9 (8.5 to 9.3)
7	People with hip and/or knee OA should be taught a regular individualised (daily) exercise regimen that includes: a strengthening (sustained isometric) exercise for both legs, including the quadriceps and proximal hip girdle muscles (irrespective of site or number of large joints affected) b aerobic activity and exercise c adjunctive range of movement/stretching exercises * Although initial instruction is required, the aim is for people with hip or knee OA to learn to undertake these regularly on their own in their own environment	Ia, hip, overall exercise Ia, knee, overall exercise Ia, knee, strength Ia, knee, aerobic Ia, mixed, mixed programmes	8.5 (7.7 to 9.3)
8	Education on weight loss should incorporate individualised strategies that are recognised to effect successful weight loss and maintenance*—for example: a† regular self-monitoring, recording monthly weight b† regular support meetings to review/discuss progress c† increase physical activity d† follow a structured meal plan that starts with breakfast e† reduce fat (especially saturated) intake; reduce sugar; limit salt; increase intake of fruit and vegetables (at least '5 portions' a day) f† limit portion size; g† addressing eating behaviours and triggers to eating (eg, stress) h† nutrition education i† relapse prediction and management (eg, with alternative coping strategies)	III, hip Ia, knee	9.1 (8.6 to 9.5)
9	a‡ The use of appropriate and comfortable shoes is recommended. b Recommendation rejected: a lateral-wedged insole could reduce symptoms in medial knee pain.	Ib, knee. Ib, knee	8.7 (8.2 to 9.2) 8.0 (7.0 to 9.1)
10	Walking aids, assistive technology and adaptations at home and/or at work should be considered, to reduce pain and increase participation—for example: a† a walking stick used on the contralateral side, walking frames and wheeled 'walkers' b* increasing the height of chairs, beds and toilet seats c* hand-rails for stairs d* replacement of a bath with a walk-in shower e* change to car with high seat level, easy access and automatic gear change	III, hip III, knee	8.9 (8.5 to 9.3)

Continued

Table 2 Continued

No.	Recommendation	LOE I–IV	LOA (95% CI)
11	People with hip or knee OA at risk of work disability or who want to start/return to work should have rapid access to vocational rehabilitation, including counselling about modifiable work-related factors such as altering work behaviour, changing work tasks or altering work hours, use of assistive technology, workplace modification, commuting to/from work and support from management, colleagues and family towards employment	III, hip III, knee Ib, mixed, sick leave	8.9 (8.3 to 9.5)

Recommendations with different LOE within the recommendation are listed below. In the absence of grading of evidence for hip OA populations, the LOE equals IV. LOA was computed as a 0–10 scale, based on 17 votes of agreement with the recommendation.
*The specific element was not included in composite interventions and LOE for the inclusion of this specific element could not be graded.
†The specific element was included in composite interventions and LOE for the inclusion of this specific element was graded as Ib (ie, no. 5c–f, mixed populations; no. 6a and b, mixed or knee populations; no. 8, knee populations; no. 10a, knee populations).
‡Comparisons between different pairs of comfortable shoes.
LOA, level of agreement; LOE, level of evidence; OA, osteoarthritis.
Mixed, the evidence is extracted from studies including a mixed population—that is, people with hip and/or knee OA.

considered comprehensively in every patient with hip or knee OA. The recommendation specifically implies that a person with hip or knee OA should receive education about her/his condition (3a), and be managed accordingly (3b–e).

With the exception of walking aids and assistive technology and dealing with adverse mechanical factors, the literature supports the delivery of combined interventions including information and education, exercise and/or weight reduction.

In people with hip and/or knee OA the combination of patient education or self-management intervention plus exercise was found to have a significant effect on pain, but a less marked effect on function.[26 31 37–40] In people with hip OA the effect of such combinations was mainly seen on function (0–100 point scale) at 3 and 6 months after intervention (mean difference, 95% CI −7.5, −13.9 to −1.0; and −8.4, −15.1 to −1.7).[41 42] In people with knee OA effects on pain and/or function were seen in eight studies,[24 25 43–48] whereas no effect was seen in four studies.[32 49–51] The addition of advice from a dietician for overweight or obese patients to the combination of patient education or self-management intervention plus exercise was found to improve both pain and function in patients with hip or knee OA.[52–55]

Principles of lifestyle changes

Recommendation 4 deals with key elements of the delivery of interventions aimed to initiate and maintain lifestyle changes. It is known that behavioural changes are difficult to achieve and maintain, and the effect of advice and counselling by healthcare providers is disappointing.[56] The literature search for this recommendation was limited to lifestyle changes considered most relevant for hip and knee OA—that is, exercise and weight loss.

The common feature in the trials supporting this recommendation was to teach and encourage behavioural change strategies through goal setting of physical activity and weight changes, action plans to maintain changes and regular follow-up over at least 1 year to re-evaluate and discuss goals and action plans.[28 39 40 53 57–62]

Reports examining the effectiveness of specific elements to be included in interventions aiming to change behaviour are scarce. The literature suggests that the following factors improve adherence to exercise or physical activity: individual exercise, graded activity, individualisation according to the person's exercise goals, feedback on progress made towards the goals, iterative problem solving with emphasis on skills that will improve adherence, reinforcements of maintaining exercise such as additional motivational programmes, exercise plans and log books, written information and audiotape or videotape, and booster sessions.[28 39 40 61–63] In addition, some studies found an effect on pain[39 40] or function[59] from lifestyle interventions that integrate such elements. A systematic review including a mixed population of people with OA and/or rheumatoid

Table 3 Research and educational agenda for non-pharmacological management of hip and knee OA

Research theme	Research questions
Terminology	Defining non-pharmacological management Finding an appropriate terminology for non-pharmacological management
General	Evaluating effectiveness and safety of non-pharmacological management strategies, specifically in hip OA
Individualised treatment	Assessing moderators of the outcome of hip and knee OA to optimise individualised treatment
Delivery of care	Defining to whom, and at what stage, the package of care needs to be delivered Assessing by which professionals the package of care can best be delivered
Lifestyle changes	Assessing the long-term outcomes (≥ 2 years) of exercise, physical activity and weight reduction with outcomes including adherence and cardiovascular morbidity
Footwear	Assessing the effectiveness and costs of various forms of footwear
Assistive technology	Assessing the use of, and satisfaction with, assistive technology
Work ability	Assessing the effectiveness and costs of interventions aiming to prevent or reduce work disability and/or increase return, or entering, the workforce
Research methodology	Developing and including measures of societal participation Developing and including measures of adherence Including economic analyses in studies on non-pharmacological management Conducting studies with appropriate sample sizes
Education	**Research questions**
	Need for training courses on the required skills to initiate and establish lifestyle changes; this education should be aimed at professionals, people with arthritis and the public

arthritis found effect sizes of 0.21 (95% CI 0.08 to 0.34) for pain and 0.69 (95% CI 0.49 to 0.88) for increased physical activity from lifestyle interventions aiming at increasing physical activity.[64] Over 40% of the included lifestyle interventions prompted problem solving, self-monitoring, goal setting and regular feedback.[64]

For people with knee OA or knee pain, improvements were seen in pain, function and weight loss from diet interventions that included individual weight-loss goals, problem solving on how to reach these goals and follow-up visits to re-evaluate and discuss goals in combination with exercise.[53 60] In obese patients, weight-loss programmes with explicit weight-loss goals showed a higher mean change in weight than programmes without explicit goals.[65] This indicates that the elements in recommendation 4 are important for the change and long-term maintenance of behaviour. The group discussed the importance of regular follow-up that includes feedback on the progress towards explicit goals and extends over a long time to achieve long-term effects of a healthy lifestyle.

Principles of information and education

Recommendation 5 is concerned with the content and method of delivery of various forms of educational programmes to best benefit the person with hip or knee OA. It is grounded in the general recognition that appropriate information and education are indispensable in prompting adequate self-management in chronic diseases. The recommendation is underpinned by the majority of studies on education interventions provided to patients with hip and/or knee OA. In general, small, but statistically significant effect sizes on pain (0.06, 95% CI 0.02 to 0.10) and physical function (0.06, 95% CI 0.02 to 0.10) have been reported from attending education or self-management programmes.[6 66] Lower costs of community-based care and medication up to 12 months has been achieved from attending a combined self-management and exercise programme, and a reduced number of medical consultations from attending self-management programmes in patients with hip and/or knee OA have been reported.[32 67 68]

The literature review included trials that compared education or self-management programmes with usual care, attention controls or no intervention. These trials described one or several elements from 5c to f (table 2) in their interventions.[69–85] The literature did not support the additional value of spouse-assisted coping skills training,[79] and no trials were found for individualisation according to illness perception and educational capability, or for inclusion of education in every aspect of management. The group, however, considered the inclusion of spouses in the intervention to be a question of individualisation and appropriate in some cases. One systematic review found that, in people with OA, effective self-management interventions followed a protocol, included elements of cognitive behavioural theory or social cognitive theory and were led by trained health professionals.[86] These elements are not specifically dealt with in the recommendation, yet they were supported by the group.

Principles of exercise education

Recommendation 6 deals with the principles of the delivery of education about exercise and physical activity. There is convincing evidence for the overall effectiveness of exercise on pain (ES, 95% CI: 0.40, 0.30 to 0.50) and function (ES, 95% CI: 0.37, 0.25 to 0.49) in people with knee OA,[87] and to a lesser extent in people with hip OA (ES, 95% CI, pain 0.38, 0.08 to 0.68).[88]

Few studies have directly compared different exercise 'dosage' (frequency, intensity and duration) and progression approaches in people with OA.[87 89 90] One RCT reported reduced pain from attending a progressive functional strengthening programme compared with a non-progressive programme in people with knee OA,[90] but two trials could not show any differences from attending various intensity levels of aerobic or resistance-exercise programmes.[89 91] Hence, the optimal exercise 'dosage' and rate of progression remain uncertain.

In patients with knee OA different delivery modes (individual, group-based or home programmes) have all been shown to effectively reduce pain (individual, ES, 95% CI 0.55, 0.29 to 0.81; group-based, ES, 95% CI 0.37, 0.24 to 0.51; and, home, ES, 95% CI 0.28, 0.16 to 0.39) and improve function (individual, ES, 95% CI 0.52, 0.19 to 0.86; group-based, ES, 95% CI 0.35, 0.19 to 0.50; and, home, ES, 95% CI 0.28, 0.17 to 0.38) compared with education, telephone calls, waiting list, relaxation, ultrasound, hot-packs or no treatment.[87] In patients with hip and/or knee OA, water-based exercise was found to significantly reduce pain (ES, 95% CI 0.19, 0.04 to 0.35) and improve function (ES, 95% CI 0.26, 0.11 to 0.42) compared with education, telephone calls or no intervention.[92] Home-based exercise was found to be as effective as water-based exercise in one small RCT in people with hip OA.[93] Water-based exercise can include swimming and/or different types of exercise programmes. Since the different modes of delivery are equally effective, the person's preference, findings of the initial assessment and local availability should determine the choice of mode of delivery in clinical practice.

The literature suggests that pacing of activity and/or integrating physical activity into daily living as part of a comprehensive exercise regimen is more effective in people with hip or knee OA or with knee pain than usual care or written information, but not compared with standardised exercise or a pharmacy review.[24–26 29 31 38 46 57 58 77–79 94]

This recommendation suggests the need for an increase in the intensity and/or duration of exercise over time. This is based on the literature, where most strength training exercise programmes evaluated in people with knee OA included dynamic exercises with progression over time.[95] Moreover, in one study comparing progressive and non-progressive approaches in people with knee OA, the former was found to reduce pain more effectively.[90] General recommendations for dosage and progression of exercise in older people and people with chronic disease are aerobic moderate-intensity training for at least 30 min/day or up to 60 min for greater benefit, and progressive strength training involving the major muscle groups at least 2 days/week at a level of moderate to vigorous intensity (60–80% of one repetition maximum) for 8–12 repetitions.[96 97] These recommendations emphasise that in people with chronic disease who do not reach the recommended level, they should be as physically active as their abilities and condition allow.[97]

Exercise regimen

Before considering the evidence for specific exercises in hip and knee OA, it should be noted that although exercise has been shown to reduce pain in patients with hip OA,[88] overall there is a lack of information to support treatment effects of exercise in hip OA.[8 88 98–103] The LOE for the recommendation of different types of exercise in people with hip OA therefore could not be graded. For knee OA, however, high-quality research evidence has reported that exercise reduces pain and improves

physical function.[6 87 104] Results for the effect of exercise on quality of life are inconsistent.[90 92 95 99 102 104 105]

Research about strengthening exercises in knee OA shows that both specific quadriceps strengthening exercises or strength training for the lower limb reduce pain effectively (ES, 95% CI 0.29, 0.06 to 0.51 and 0.53, 0.27 to 0.79, respectively) and improve physical function (ES, 95% CI 0.24, 0.06 to 0.42 and 0.58, 0.27 to 0.88, respectively).[87] The literature on strength training in people with knee OA in most cases describes dynamic exercises, whereas research on isometric exercises is sparse.[95] Hip strengthening exercises have been poorly evaluated in people with hip OA.[103] However, in people with medial tibiofemoral knee OA, hip strengthening exercises reduced knee pain and improved physical function.[106]

Aerobic training (walking) is effective in reducing pain (ES, 95% CI 0.48, 0.13 to 0.43) and improving physical function (ES, 95% CI 0.35, 0.11 to 0.58) in patients with knee OA.[87]

The evidence for mixed exercise programmes, including strengthening, aerobic and flexibility components, in patients with knee OA is conflicting.[107 108] One type of exercise has not been shown to be better than another (strength, aerobic or mixed exercises).[87 107 108]

The group reached consensus that mixed programmes should be recommended. However, it was noted that with mixed programmes the minimal requirements to improve or maintain muscle strength, aerobic capacity and/or joint range of motion need to be met,[97] as some reports suggest that mixed programmes may be less effective than focused programmes.[108]

This recommendation states that initial instruction is required, but that in the longer term the person should integrate exercise into daily life. This part of the recommendation is substantiated by studies showing that the number of supervised sessions influences outcome in people with knee OA.[87] Twelve or more directly supervised sessions have been shown to be more effective than a smaller number on pain (ES 0.46, 95% CI 0.32 to 0.60 vs ES 0.28, 95% CI 0.16 to 0.40, p=0.03) and physical function (ES 0.45, 95% CI 0.29 to 0.62 vs ES 0.23, 95% CI 0.09 to 0.37, p=0.02).[87]

In addition, it was noted that research evidence is growing for tai chi and yoga. Though not included in the literature review, tai chi has been found to be effective for the reduction of pain in patients with hip or knee OA, with ES ranging from 0.28 to 1.67.[108]

Education on weight loss

In recommendation 8, the principles of education about weight management are included. The recommendation is mainly supported by the literature in knee OA, as no evidence to support the effect of weight loss in patients with hip OA is available. However, being overweight or obese has been shown to be associated with hip OA (OR=1.11, 95% CI 1.07 to 1.16).[33]

In patients with knee OA, the effectiveness of weight-loss programmes on body weight, pain and/or physical function was demonstrated in programmes delivered as weekly supervised sessions for a range of 8 weeks to 2 years.[54 60 109–113] The effects on pain, function and weight loss from attending weight-loss programmes were small but significant (ES, 95% CI, pain 0.20, 0.00 to 0.39; physical function 0.23, 0.04 to 0.42; mean weight loss, 95% CI, 6.1 kg, 4.7 to 7.6).[109] The interventions included strategies on how to reduce calorie intake by meal plans, reduce fat and sugar, reduce portion size, meal replacements, and comprised behavioural modifications, self-monitoring, weight-loss goals and maintaining body weight in participants who had reached their goals and/or exercises for some of them.[54 60 109–112] Overall, the evidence from RCTs for the maintenance of achieved weight loss after the interventions have ended is absent in people with hip and knee OA.

In general, in overweight or obese populations, healthy eating, limiting fat and salt intake, eating at least five portions of fruit and vegetables a day, being physically active for at least 30 min/day and elements such as self-monitoring, explicit weight-loss goals, and motivational interviewing have all been suggested to promote weight loss and that regular follow-up over 4 years helps in maintenance of the weight loss.[65 114–118] Weight-loss programmes in older obese people that included explicit weight-loss goals showed mean changes in weight of −4.0 kg (95% CI −7.3 to −0.7), which was significantly more than programmes without explicit weight-loss goals (mean change, 95% CI, −1.3 kg, −2.9 to 0.3).[65] To achieve a structured meal plan with a balanced combinations of low calorie and sufficient vitamin and mineral intake, meal replacement bars or powders can be an addition to healthy eating.[54 60 109 110] Though not included in the literature review, it has been suggested that bariatric surgery should be part of comprehensive weight management in people with hip or knee OA who are morbidly obese, and could help reduce weight and joint pain.[119 120]

Footwear

Although research evidence is scant, the group was unanimous in its view that the use of appropriate footwear should be recommended in patients with hip or knee OA. Shoes may help through different mechanisms, such as acting as shock absorbers or controlling foot pronation.[121 122] Appropriate shoes implies no raised heel, thick, shock-absorbing soles, support for the arches of the foot and a shoe size big enough to give a comfortable space for the toes.[121–123]

In patients with hip OA there is no evidence to support the effect of specific shoes or insoles on pain or function. In patients with knee OA, the use of shoes with shock-absorbing insoles for 1 month reduced pain and improved physical function in a pre–post test design.[124] No differences in knee pain from the use of specialised shoes (unstable Masai technology shoe or variable-stiffness shoe) compared with conventional athletic shoes have been seen, but reduced pain was seen in both groups over time.[125 126] In addition, decreased knee joint loads were found when specialised mobility shoes were used.[121]

The literature on the effectiveness of the use of lateral wedged insoles in patients with medial knee OA found no significant effect on pain or function.[121 127 128] There is no support for whether one type of insole would be better than another,[129] and adverse effects including foot-sole pain, low-back pain and popliteal pain have been reported.[121 128 129] In light of evidence for no clinical effects of the use of lateral wedged insoles and the report of adverse effects, the group rejected the recommendation (table 2, 9b).

Assistive technology and adaptations at home and/or at work

The frequent use of assistive technology and the high satisfaction rates with its use indicate that walking aids, assistive technology and adaptations are important and useful for people with hip or knee OA.[130–133] There are, however, no clinical trials to substantiate elements in this proposition, except for the use of a cane in patients with knee OA.[134] However, the group was unanimous in its view that in all patients with hip or knee OA walking aids, assistive technology and adaptations at home and/or at work should be considered systematically and recurrently. The group noted that the value of some of these interventions is so obvious and has an immediate effect

in individual cases that further research into the effectiveness of specific devices or adaptations can hardly be expected. Cross-sectional studies show that walking aids, assistive technology and adaptations at home and/or work are important and often used by people with hip or knee OA. Most people with severe hip (63%) or knee pain (90%) reported the use of walking aids.[130 131] In people with arthritis, a mean of 9.9–10.8 devices has been reported to be in use and the satisfaction rate for all categories of device was more than 87%.[132] Moreover, unmet needs for new assistive technology to help perform activities that individuals could not do were identified.[132] Having access to a walking aid or other assistive technologies can be a help and provide security for individuals with constant or fluctuating symptoms. The group found that future observational studies on the use, satisfaction from and suggestions for new technology or improvements of existing technology are needed.

Management of work ability

Recommendation 11 deals with the effectiveness of work-related interventions. The proportion of employed people who have work disability due to OA is substantial. Although there are known occupational risk factors for knee OA and its progression—for example, heavy work, knee squatting or bending, lifting and specific sports,[18] there are no studies to support the effect of vocational rehabilitation on pain, physical function or quality of life specifically in patients with hip or knee OA. One study in patients with peripheral OA found that a specialist-run, protocol-based early intervention significantly reduced the number of days of sick leave compared with standard primary care.[135] The intervention was administered by a rheumatologist and comprised three main elements: education, protocol-based clinical management and administrative duties. The educational part included information about the condition, reassurance that serious disease was not present, self-management, exercises, ergonomic care, booklets, optimal level of physical activity and early return to work. Descriptive studies have found that environmental factors, such as having access to public transport or a car for mobility outside home are facilitators and that the absence of these is associated with limitations to daily activity.[136 137] Some elements in this recommendation may have to be adapted to the country in which they are executed, since availability and accessibility of services in the healthcare and social security system may vary greatly. The group concluded that there is a clear paucity of research evidence for work-related interventions in people with hip and knee OA.

DISCUSSION

Eleven recommendations for the core non-pharmacological management of people with hip and knee OA were developed based on research evidence and expert consensus. While the 11 evidence-based recommendations are not exhaustive and do not include all existing non-pharmacological treatments, they cover the main principles of non-pharmacological management. The selected recommendations support a patient-centred, multidisciplinary approach rather than a discipline-specific approach.

There was a considerable body of evidence underlying the recommendations, with systematic reviews and/or RCTs available for most. It is worth noting, however, that overall the research evidence for hip OA was poorer than for knee OA, limiting conclusions about the effectiveness of non-pharmacological interventions in this patient group. Moreover, most trials found in the literature review used pain or physical function as the primary outcome and surprisingly few included quality-of-life outcome measures. Mental health, physical independence, autonomy and social participation have been reported as important domains by people with OA and older adults.[138 139] Given these observations, the task force recommends that future research should include well-powered studies to evaluate the effect of core non-pharmacological treatments specifically in people with hip OA, moderators of effect and the inclusion of quality-of-life measurements that reflect physical, mental and social health in their evaluation.

Several RCTs found in the systematic literature review compared two non-pharmacological interventions and found no significant differences in pain or physical function between them. This does not mean that the interventions were ineffective, but that neither was better than the other. For example, a well-powered RCT compared a behavioural graded activity intervention with education and exercise following the Dutch physiotherapy guideline for patients with hip and/or knee OA and found no differences between groups.[57] Nevertheless, both groups showed improvements in pain and physical function over time. Moreover, it was found that non-pharmacological interventions often consisted of combinations of different treatments, with the combinations varying largely between studies. This hampered comparisons between studies and also the ability to define the effect of the individual components, so that the underpinning of every specific element in some of the recommendations proved to be difficult. Hence, the aim of developing detailed recommendations could not always be fulfilled. However, compared with previous recommendations[5–9] the current recommendations are more specific. They provide substantiated and more detailed recommendations about content (for patient education, exercise, weight reduction and combined treatment), frequency (at least 12 sessions, activity pacing and follow-ups) and mode of delivery (1 : 1, group-based or home exercise) than previously published recommendations. In addition, principles for optimising long-term adherence and effect are described. The optimal exercise volume ('dose') could not be substantiated. Exercise volume is difficult to investigate as it includes exercises performed at a gym or at the physiotherapy clinic and the total amount of exercise performed in daily life. Exercise volume therefore varies widely between individuals. The matter of timing lacks research evidence and the topic was included in the research agenda. Furthermore, the effect sizes for several non-pharmacological interventions reported in the literature were generally relatively low. It should be noted, however, that the costs of these interventions are generally limited, and the occurrence of adverse effects is low. The results of the LOA in addition to the traditional determination of the LOE are therefore important, as this reflects the experts' interpretation of all the above-mentioned aspects.

Limitations to the methodological quality of the systematic literature review were that only one person (LF) extracted data from the literature. According to the assessment of multiple systematic reviews,[140] at least two independent data extractors are recommended. However, the research fellow (LF) presented and discussed all results with the conveners (JWJB, KBH, TPMVV) and the extracted data were, thereafter, reviewed by experts in the committee. Another limitation was that, owing to limited time and resources, no scoring of the methodological quality of the systematic reviews or individual trials included in the literature review was done. Also, owing to limited resources, some potential healthcare providers playing a role in the management of hip and knee OA, such as the podiatrist or rehabilitation specialist, were not represented in the task force.

To obtain a broad consensus and practical applicability of the recommendations, the task force had an inclusive and multidisciplinary approach. Nine different professional disciplines and people with OA were included in the committee. The task force followed a procedure similar to that used for other management recommendations, such as for the general management of OA, rheumatoid arthritis and ankylosing spondylitis,[8 9 141 142] but is the first with such an inclusive approach. It has been strongly recommended that a minimum of two patient research partners with the relevant disease are included in development of recommendations.[143] The participation of the people with OA in this task force was successful, with their experiential knowledge ensuring that clinical relevance was integrated throughout the process.

Finally, the task force reached consensus on a research and educational agenda, with general topics including the definition and nomenclature for non-pharmacological and non-surgical management and the need for more knowledge on their effectiveness in hip OA. Specific needs for additional research and/or education included the optimisation of tailoring of treatment and the mode of delivery, the long-term effects of lifestyle interventions, vocational rehabilitation and footwear, the measurement of adherence and participation and the conduct of studies with a sufficient sample size. An important subject regarding education pertained to lifestyle interventions, highlighting the need for educational activities not only for healthcare providers, but also for people with OA and the public.

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Appendix

Expert consensus on propositions

Before the first task force meeting, a general literature search of practice guidelines, overviews of systematic reviews and evidence-based recommendations was undertaken to obtain an overview of current recommendations and addressed treatment modalities in people with hip or knee OA. For this purpose, the databases Medline, Embase, Pedro, CINAHL, OTseekers, PsychInfo, AMED, G-I-N and The Cochrane Database of systematic reviews were searched up to March 2011. After removing duplicates, 984 hits were retrieved and after excluding recommendations on pharmacological or surgical treatment or other diagnoses than OA, 31 studies remained. The 31 studies addressed 30 different non-pharmacological treatment modalities. The results were presented at the first task force meeting. All addressed treatment modalities and potential topics for propositions were discussed. After the first meeting, the experts were asked to contribute independently with 10 propositions about non-pharmacological management and its content. Experts' consensus was achieved using the Delphi technique. In total, five Delphi rounds, facilitated by the convenor, were performed by e-mail. All members of the task force, except for the convenor and the research fellow, responded during each round. The preliminary literature review as well as the first Delphi rounds included propositions covering different aspects of non-pharmacological treatment, for example thermal modalities, Transcutaneous Electric Nerve Stimulation, acupuncture, manual therapy and traction. Consensus on 11 propositions was reached in the 5th Delphi round concerning the topics; initial assessment, individualised treatment, comprehensive care, principles of life style changes, patient education, exercise, and weight loss, footwear, assistive technology, and vocational rehabilitation.

Systematic literature search

A systematic literature search was undertaken by the research fellow (LF) supported by her mentors (JWJB, KBH and TPMVV), using Medline (In-Process & Other Non-Indexed Citations 1948-), Embase (1980-), AMED (1985-), PsychINFO (1806-), CINAHL (1981-), Cochrane Database of Systematic Reviews (2005-), Database of Abstracts of Reviews of Effects (1994-), Cochrane Central Register of Controlled Trials (1898-), and PEDro (1929-). The search comprised a general and proposition-specific searches and were all performed up to

February 2012. The general search combined a search query for hip or knee OA with a search query for study design. Study designs of interest were; systematic review/meta-analysis, randomised controlled trial (RCT)/ controlled trial (CT), or observational studies. Systematic reviews were included if they had undertaken a literature search of at least two databases, were of a time frame of more than one year and presented at least one meta-analysis of RCTs. Effect-sizes presented in the results derived from the latest systematic review containing the largest number of studies. Propositions that were not substantiated by at least one meta-analysis of RCT's were followed by a proposition-specific search for RCT/CT's. If the propositions still was not substantiated, a proposition-specific search for observational studies was performed. RCTs were included if they described a random allocation procedure and presented between group comparisons. The general search queries and proposition-specific search queries for Medline are included in Table S1-2; these were adapted for the other databases. Part I, II and III (Table S1-2) were combined with "and" as appropriate. The extraction procedures are presented in Figures S1-12. Studies were included if they: a. evaluated the effect of non-pharmacological treatment related to the propositions; b. used clinical outcomes (pain, physical function, quality of life) or other outcomes relevant to the proposition (adherence, activity level, weight, sick-leave); c. concerned persons diagnosed with hip or knee OA or with persisting knee pain, if 45 years or older. In case of a mixed sample, studies were included if they provided a separate analysis for people with hip and/or knee OA or if the majority of included persons were diagnosed with hip or knee OA. Reviews, dissertations, case-reports, editorials, commentaries, meeting abstracts, and protocols were excluded.

For every recommendation, all results obtained by the research fellow were discussed with the convenor and co-applicants. If needed, the extracted data were then reviewed by a committee member and any additional data known by the member could be included.

Table S1 General search queries for Medline. These were adapted for other databases.

General search query		**General search query**	
Part I, Osteoarthritis		**Part II, Study design**	
OA	1. Osteoarthritis/	SR/ MA	1. exp Meta-Analysis as Topic/
	2. osteoarthrit$.tw.		2. Meta-Analysis.pt.
	3. osteoarthros$.tw.		3. quantitative review$.tw.
	4. degenerative arthrit$.tw.		4. quantitative overview$.tw.
	5. arthrosis.tw.		5.statistical pool$.tw.
	6. arthroses.tw.		6. data pool$.tw.
	7. or/1-6		7. (meta analy$ or metaanaly$ or meta?analy$).tw.
	8. Hip/		8. exp "Review Literature as Topic"/
	9. Hip Joint/		9. Review.pt.
	10. hip$.tw.		10. Systematic review$.tw.
	11. or/8-10		11. or/1-10
	12. Knee/		
	13. knee$.tw.	RCT/ CT	1. randomized controlled trial.pt.
	14. exp Knee joint/		2. controlled clinical trial.pt.
	15. or/12-14		3. randomized.ab.
	16. 11 or 15		4. placebo.ab.
	17. 7 and 16		5. drug therapy.fs.
	18. Osteoarthritis, hip/		6. randomly.ab.
	19. Osteoarthritis, Knee/		7. trial.ab.
	20. coxitis.tw.		8. groups.ab.
	21. gonarthritis.tw.		9. or/1-8
	22. or/17-21		10. (animals not (humans and animals)).sh.
			11. 9 not 10
		Obs.	1. exp Cohort Studies/
			2. cohort stud$.tw.
			3. exp Prospective Studies/
			4. prospective stud$.tw.
			5. exp Risk/
			6. risk.tw.
			7. relative risk$.tw.
			8. exp Incidence/
			9. incidence.tw.
			10. exp Longitudinal Studies/
			11. longitudinal studies.tw.
			12. or/1-11
			13. exp Case-Control Studies/
			14. case-control stud$.tw.
			15. exp Retrospective Studies/
			16. retrospective stud$.tw.
			17. exp Odds Ratio/
			18. odds ratio$.tw.
			19. or/13-18
			20. exp Cross-Sectional Studies/
			21. cross-sectional stud$.tw.
			22. exp Prevalence/
			23. prevalence.tw.
			24. disease frequenc$.tw.
			25. or/20-24
			26. 12 or 19 or 25

OA, osteoarthritis; SR, systematic review; MA, meta-analysis; RCT/CT, randomised controlled trial/controlled trial; Obs., observational studies.

Table S2 Proposition-specific search queries for Medline (proposition 1-11). These were adapted for other databases.

1	1. Medical History Taking/ 2. medical history.tw. 3. exp Physical examination/ 4. examination.tw. 5. assessment$.tw. 6. measurement$.tw. 7. or/1-6 8. biopsychosocial.tw. 9. psychosocial.tw. 10. exp Holistic Health/ 11. exp Holistic Nursing/ 12. holistic.tw. 13. (comprehensive or thorough or full or complete).tw. 14. or/8-13 15. exp "Activities of Daily Living"/ 16. activit$ of daily living.tw. 17. exp Disability Evaluation/ 18. disabilit$.tw. 19. ((limitation$ or reduc$ or restrict$) and activit$).tw. 20. ((limitation$ or reduc$ or restrict$) and physical function).mp. 21. or/15-20 22. social behavior/ or exp social adjustment/ or exp social isolation/ or exp social environment/ 23. (social function$ or social behavior or social adjustment or social isolation or social environment).tw. 24. participation.tw. 25. exp Work/ 26. work.tw. 27. exp Education/ 28. education.tw. 29. societal participation.tw. 30. exp Leisure Activities/ 31. (leisure or recreation).tw. 32. or/22-31 33. pain.tw. 34. exp Pain Measurement/ 35. exp Fatigue/ 36. fatigue.tw. 37. exp Sleep Disorders/ 38. sleep.tw. 39. exp Foot Joints/ 40. (foot or feet).tw. 41. exp "Range of Motion, Articular"/ 42. range of motion.tw. 43. Muscle Strength/ 44. (muscle strength or muscular strength).tw. 45. Joint Instability/ 6. (joint$ adj2 instability).tw. 47. alignement.tw. 48. exp Proprioception/ 49. proprioception.tw. 50. joint position sense.tw. 51. Posture/ 52. posture.tw. 53. Comorbidity/ 54. comorbidity.tw. 55. exp Body Weight/ 56. body weight.tw. 57. body mass index/
4	1. exp Life Style/ or exp Health Behavior/ or exp Adaptation, psychological 2. lifestyle$.tw. 3. exp goals/ 4. (goal or action plan).tw. 5. (re adj2 (evaluation or examination)).tw. 6. (reinforcement or booster or adjustment or adherence).tw. 7. (individual$ adj4 (treatment$ or therap$ or prorgram$ ro management$)).tw. 8. (tailor$ adj4 (treatment$ or therap$ or prorgram$ ro management$)).tw. 9. (target$ adj4 (treatment$ or therap$ or prorgram$ ro management$)).tw. 10. or/1-9
5	1. exp Health Education/ 2. exp Patient Education as Topic/ 3. exp Self Care/ 4. (health education or patient education or self care).tw. 5. (self adj2 manage$).tw. 6. (information or advice or counsel$).tw. 7. or/1-6
6	1. exp Exercise Tolerance/ or exp Exercise/ or exp Exercise Therapy/ 2. exercise.tw. 3. physical activity.tw. 4. or/1-3 5. (pacing or dose or progression or link$ or integrate or adhere$).tw. 6. 4 and 5
7	Covered by the general search for SR / MA
8	1. exp Weight Loss/ 2. weight loss$.tw. 3. (los$ adj2 weight).tw. 4. weight reduction$.tw. 5. (reduc$ adj2 weight).tw. 6. weight decreas$.tw. 7. (decreas$ adj2 weight).tw. 8. weight control$.tw. 9. (control$ adj2 weight).tw. 10. or/1-9 11. exp Maintenance/ 12. (maint$).tw. 13. (retention$ or preserv$ or sustain$ or continu$ or keep).tw. 14. or/11-13 15. 10 and 14 16. exp Diet/ 17. diet.tw. 18. exp Health Promotion/ 19. (nutrition adj2 education).tw. 20. ((meal or activity or individual or patient) adj2 (plan or goal)).tw. 21. (eating adj2 (behavio$ or trigger$)).tw. 22. ((self adj3 (monitor$ or record$ or assess$))

58. body mass index.tw.
59. or/33-58
60. exp Emotions/
61. exp Depressive Disorder/
62. (emotion$ or depression or mood or fear or anxiety or affect or frustration or anger or loneliness or sadness).tw.
63. or/60-62
64. exp Motivation/
65. motivation$.tw.
66. exp Attitude to Health/
67. exp Health Behavior/
68. (health belief$ or health behavior or attitude to health).tw.
69. or/64-68
70. 21 or 32 or 63 or 69
71. 14 or 70

2
1. Individualized medicine/
2. individual$.tw.
3. (individual$ adj4 (treatment$ or therap$ or prorgram$ or management$)).tw.
4. (tailor$ adj4 (treatment$ or therap$ or prorgram$ or management$)).tw.
5. (target$ adj4 (treatment$ or therap$ or prorgram$ or management$)).tw.
6. exp Classification/
7. classif$.tw.
8. stratif$.tw.
9. categor$.tw.
10. or/1-9

3
1. exp health services/ or exp patient care/ or exp preventive health services/ or exp rehabilitation/
2. exp Patient Care Management/
3. (multidisciplinary or rehabilitation or complex intervention or package of care).tw.
4. ((multifaceted or multimodal or integrated or complex or combined) adj2 management).tw.
5. (education or information or advise).tw.
6. or/1-5

and weight).tw.
23. (portion size or (reduc$ adj2 (fat or sugar or salt)) or vegetables).tw.
24. (((relapse adj2 prediciton) or booster session$ or support) and adj2 weight).tw.
25. or/16-24
26. 10 or 15 or 25

9
1.exp Shoes/
2.insole$.tw.
3.lateral wedge$.tw.
4.shoe$.tw.
or/1-4

10
1. Walkers/
2. walker$.tw.
3. (walking adj3 aids).tw.
4. (walking adj3 stick$).tw.
5. (walking adj3 frame$).tw.
6. self-help devices/ or wheelchairs/
7. assistive device$.tw.
8. crutch$.tw.
9. (environmental adj3 modification$).tw.
10. (height adj3 (bed$ or chair$ or seat$)).tw.
11. (adaptation$ adj3 home).tw.
12. (adaptation$ adj3 work).tw.
13. (cane or canes).tw.
14. (rail$ adj4 stair$).tw.
15. (handrail$ or (hand adj rail$)).tw.
16. (walk adj3 shower).tw.
17. (automatic adj gear).tw.
18. (car or cars or driving).tw.
19. occupational therapy/
20. or/1-20

11
1. exp Rehabilitation, Vocational/
2. vocation$.tw.
3. (occupational adj3 rehabilitation).tw.
4. exp Work/
5. work$.tw.
6. job$.tw.
7. career.tw.
8. exp Employment/
9. employment.tw.
10. exp Disability Evaluation/
11. or/1-10

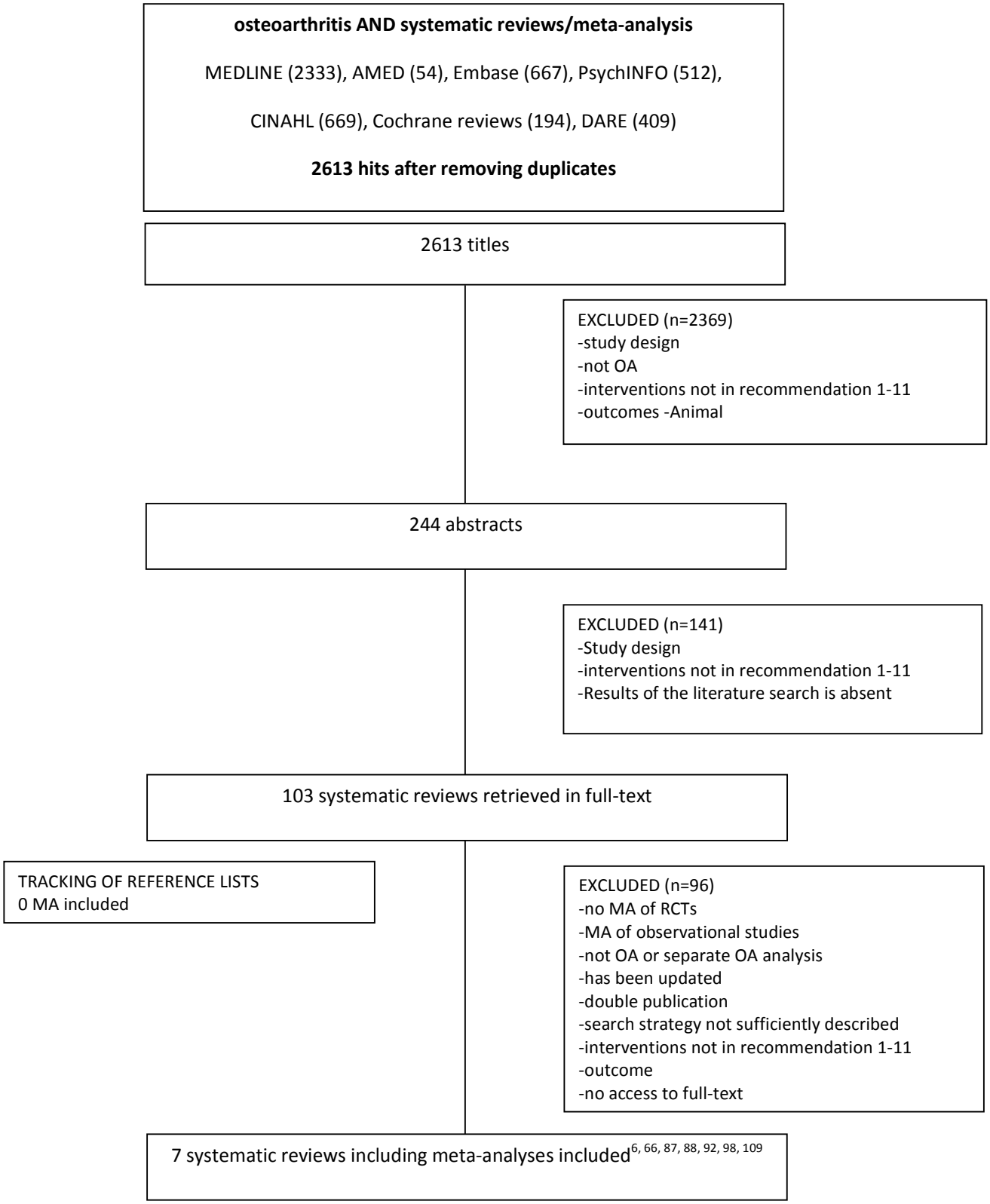

Figure S1 General literature search combining the search query for osteoarthritis and meta-analysis.

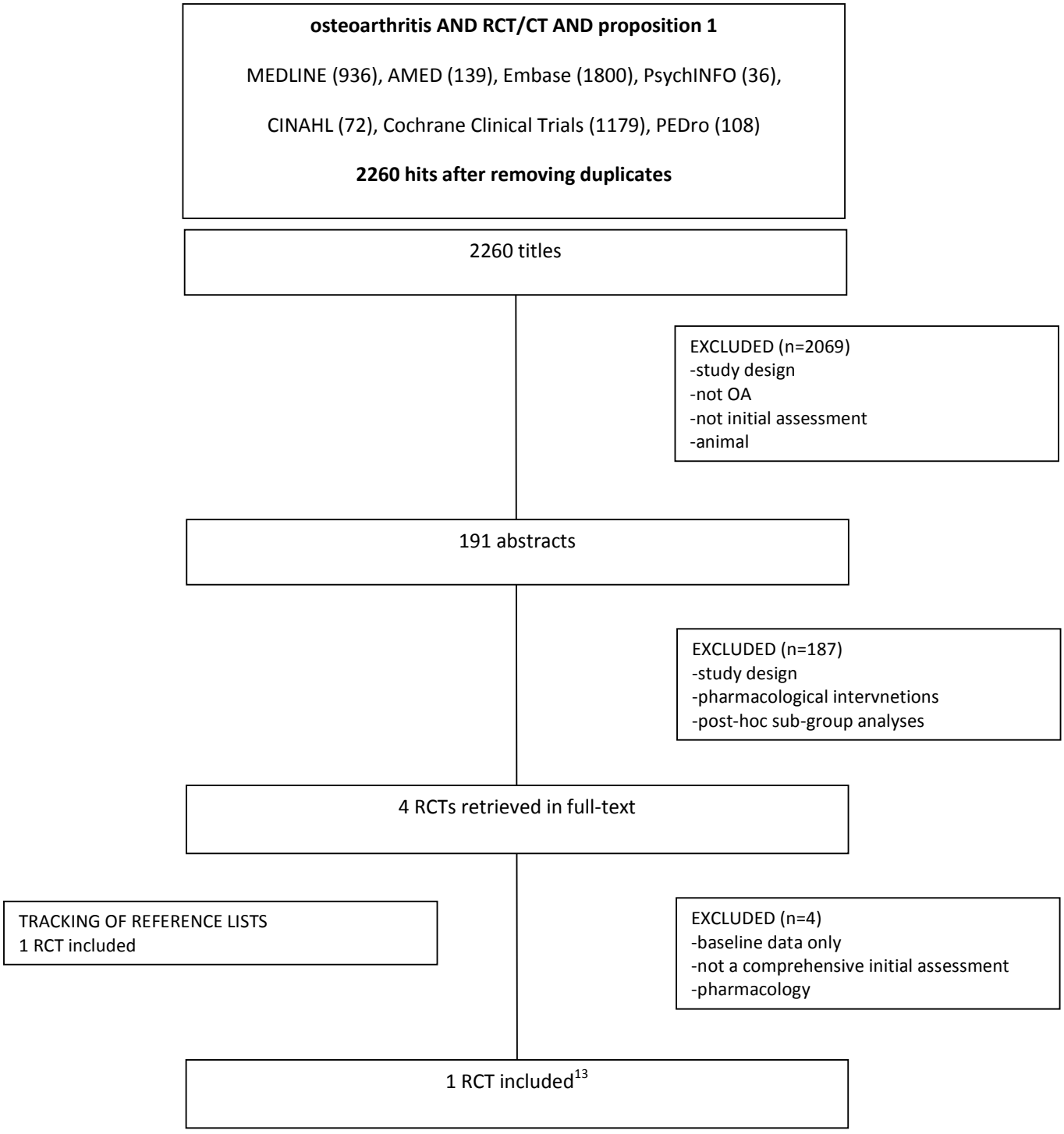

Figure S2 Proposition-specific search literature search for proposition 1.

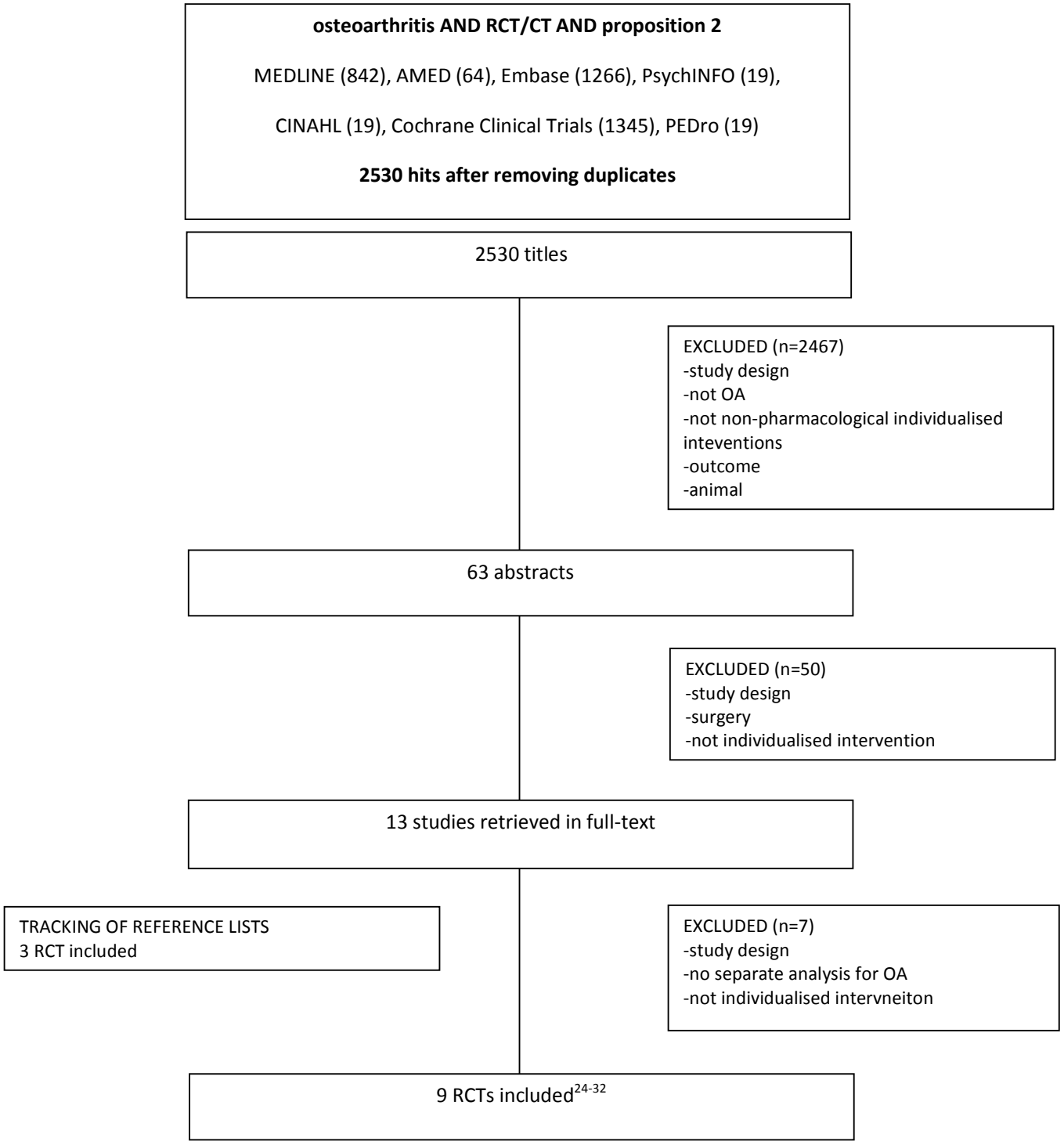

Figure S3 Proposition-specific literature search for proposition 2

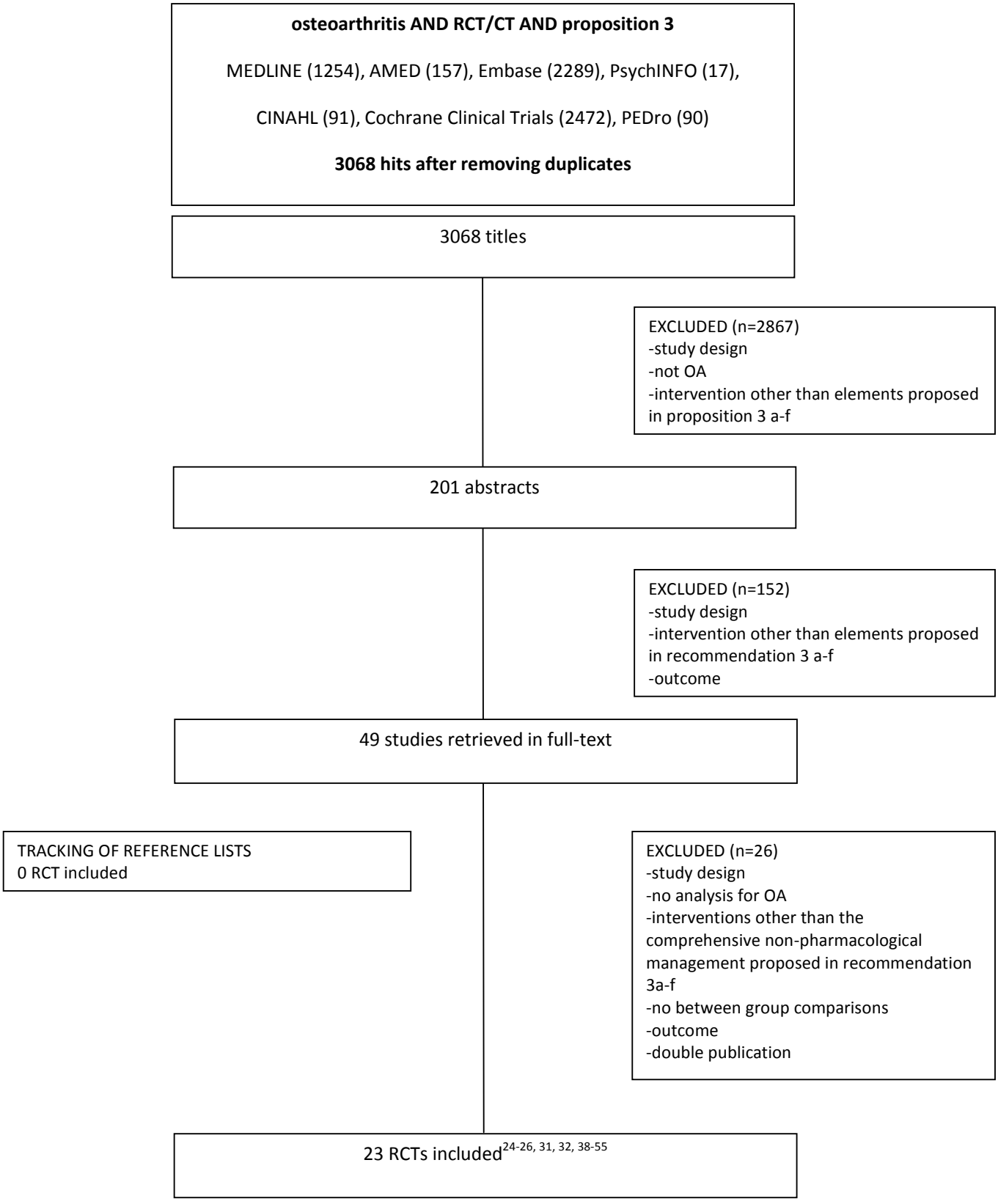

Figure S4 Proposition-specific literature search for proposition 3.

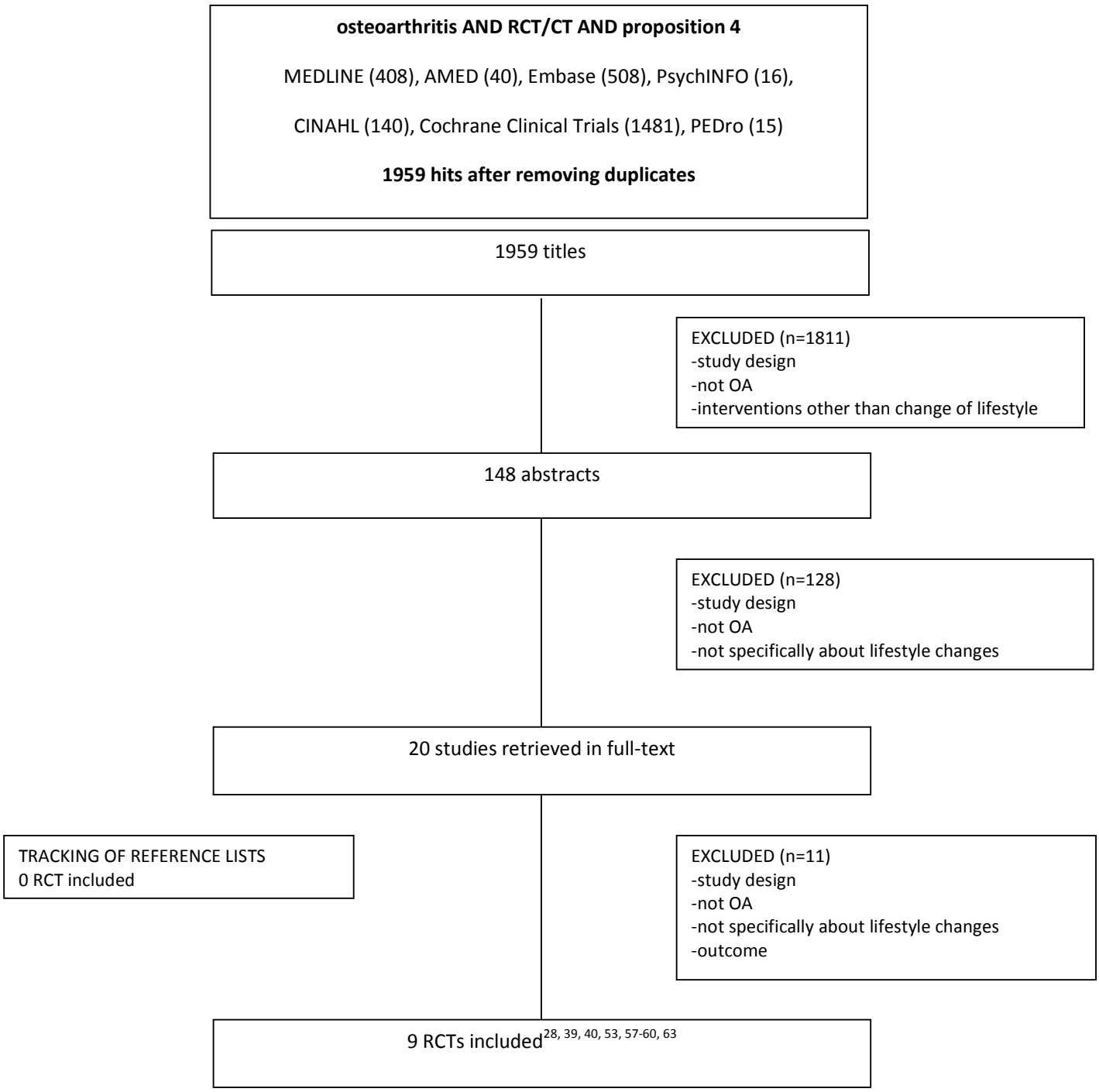

Figure S5 Proposition-specific literature search for proposition 4.

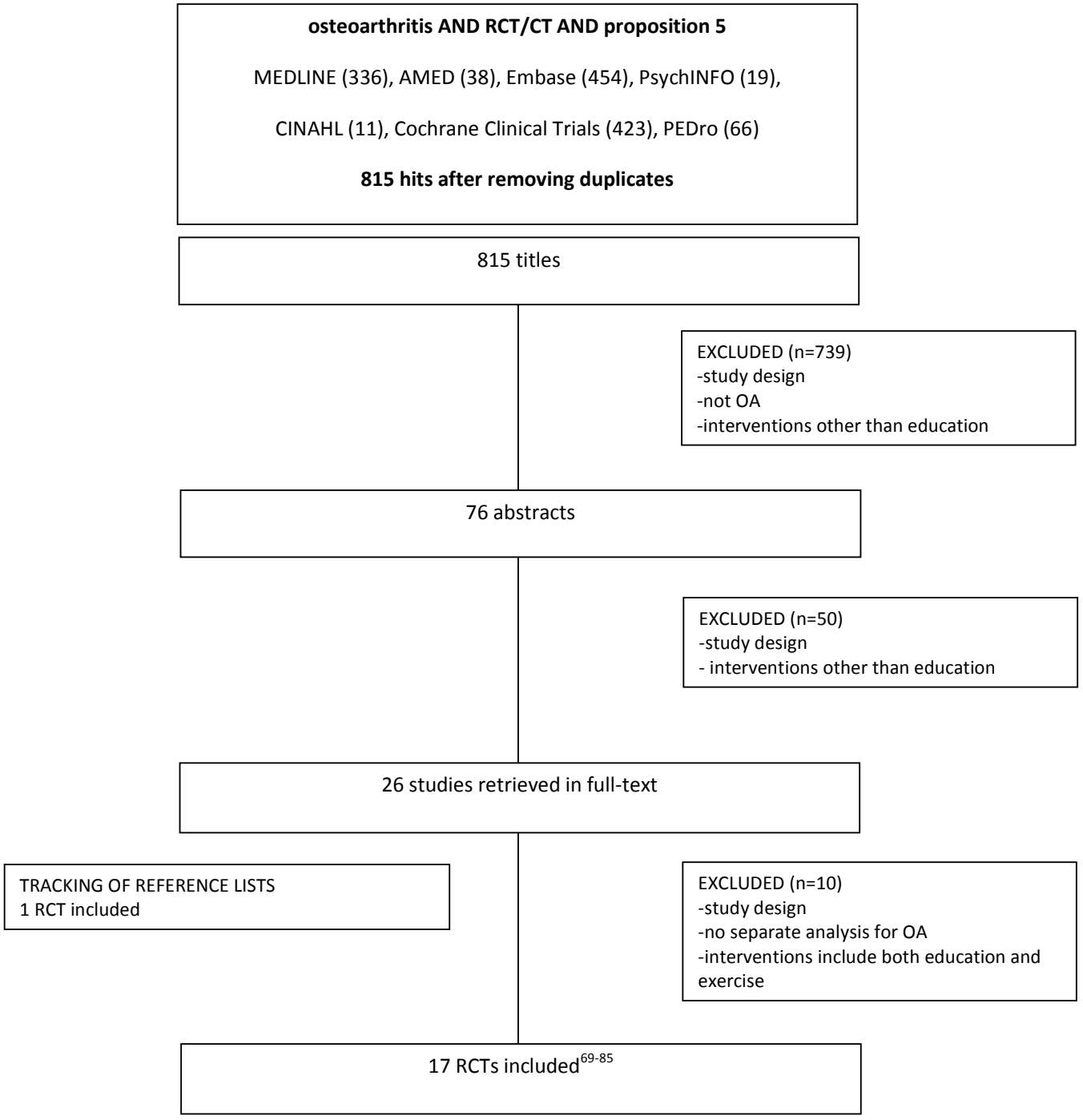

Figure S6 Proposition-specific literature search for proposition 5.

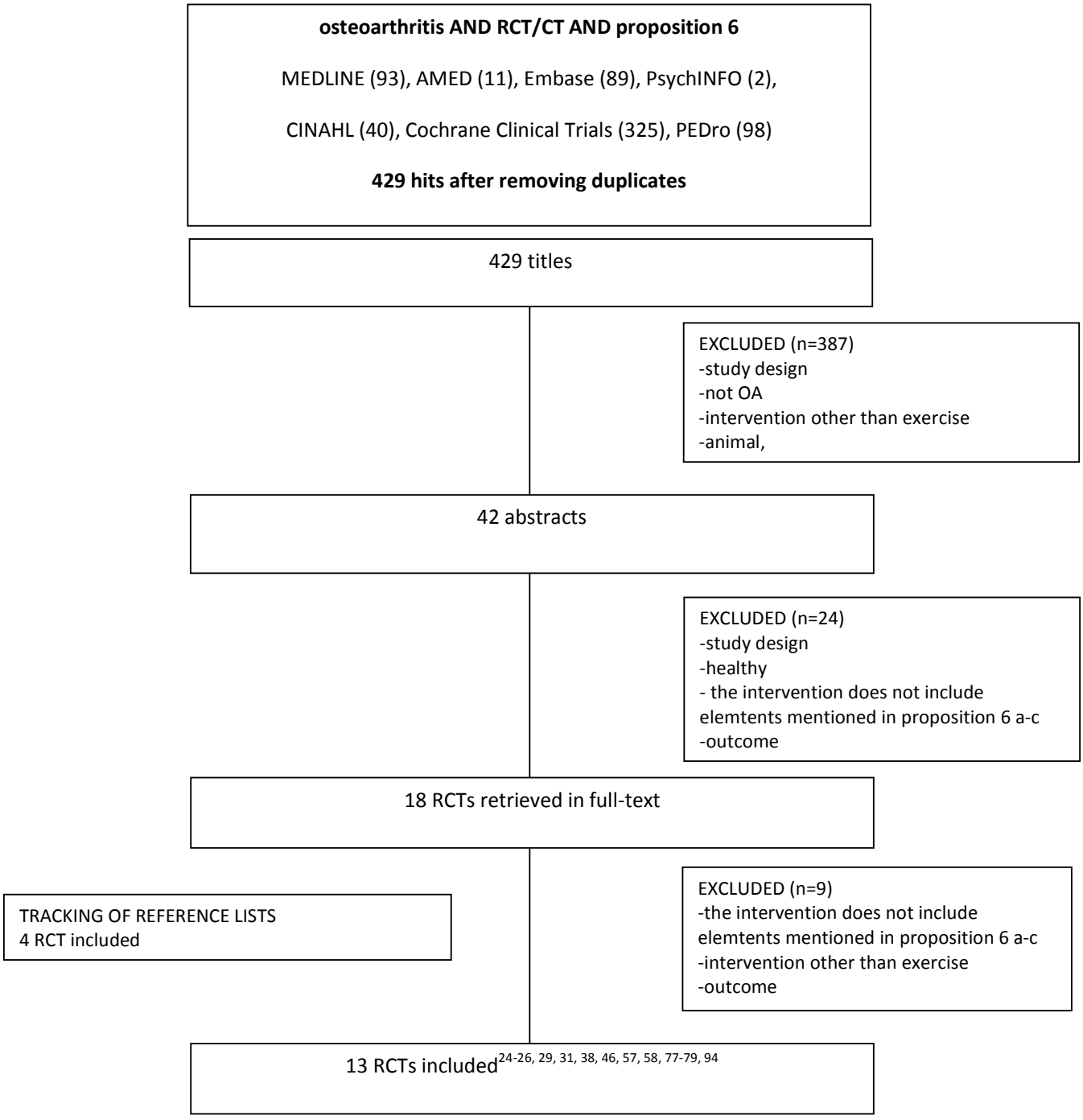

Figure S7 Proposition-specific literature search for proposition 6.

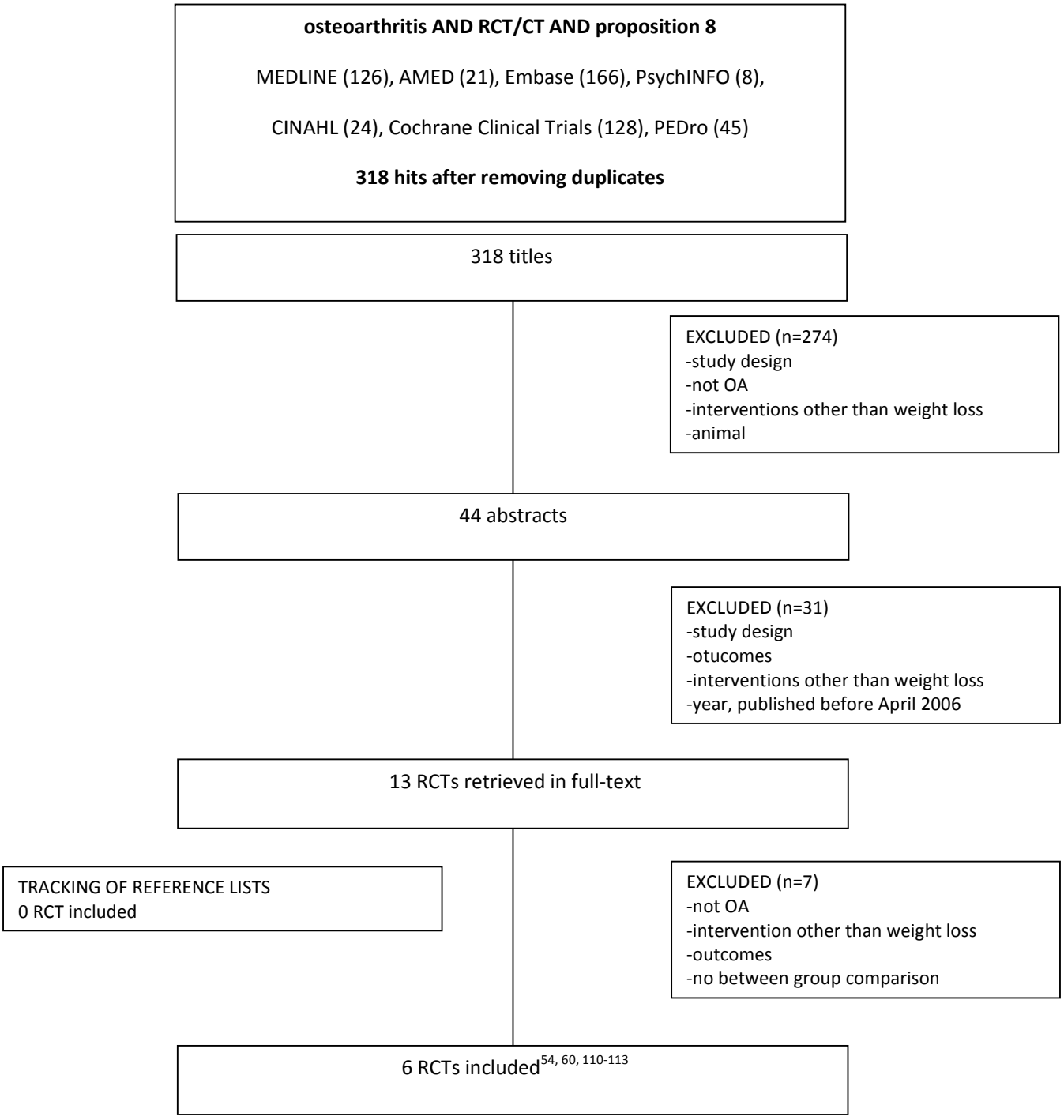

Figure S8 Proposition-specific literature search for proposition 8. Time limit April 2006 to February 2012.

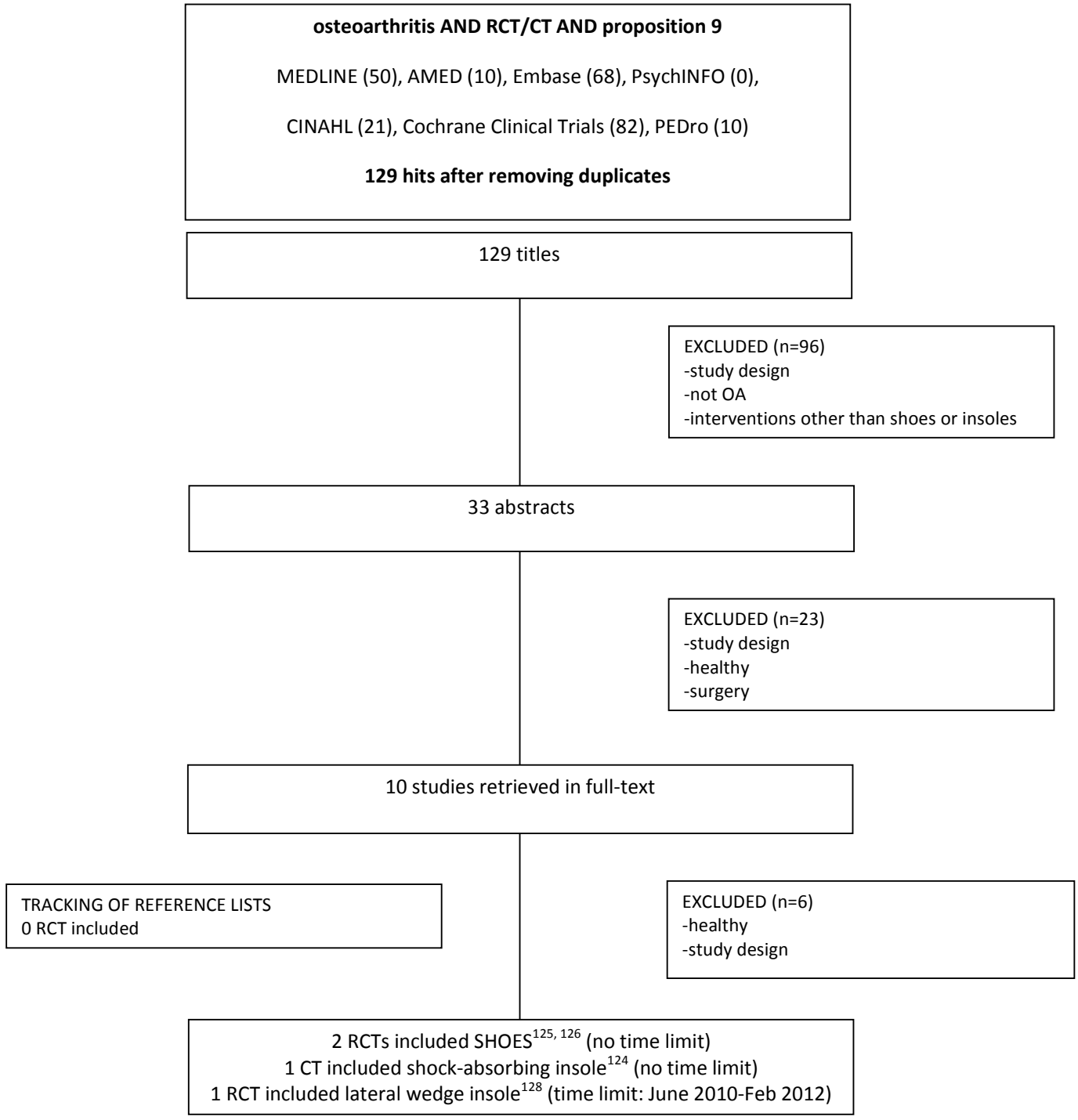

Figure S9 Proposition-specific search for proposition 9.

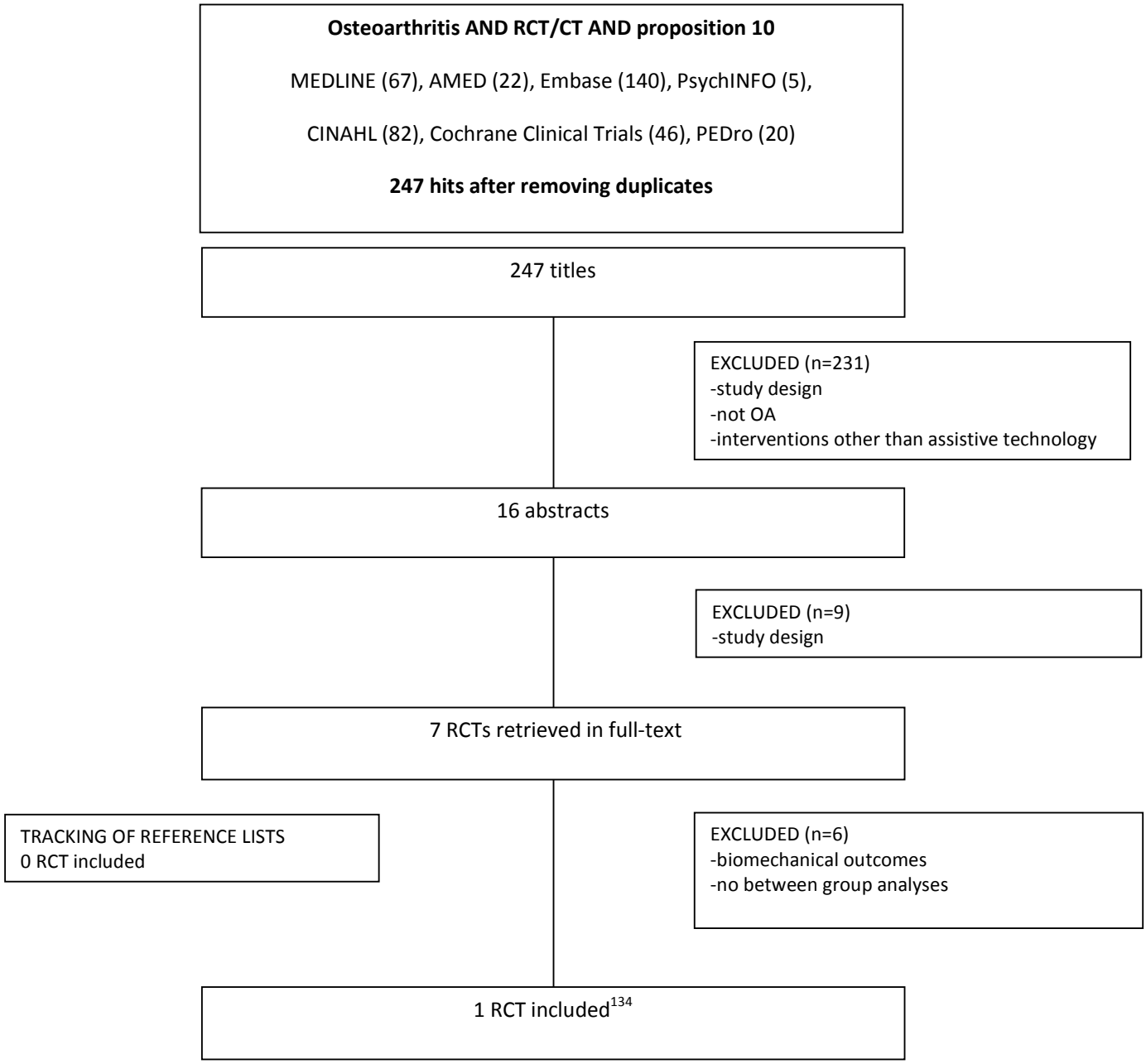

Figure S10. Proposition-specific literature search for proposition 10.

Figure S11 Proposition-specific literature search for proposition 10.

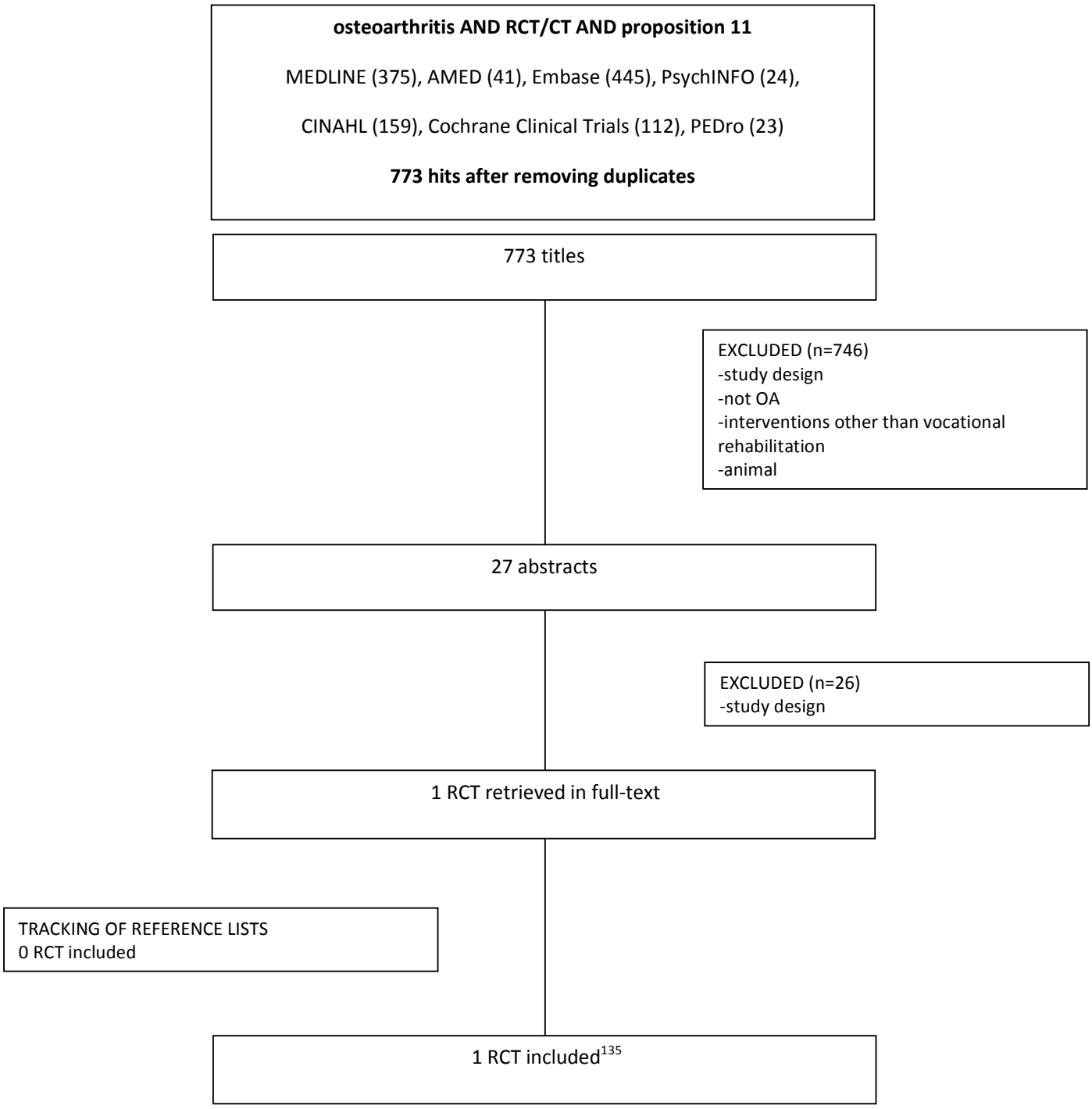

Figure S12. Proposition-specific search for proposition 11.

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Empowering Rheumatology Professionals

2019 American College of Rheumatology/Arthritis Foundation Guideline for the Management of Osteoarthritis of the Hand, Hip, and Knee

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Objective. To develop an evidence-based guideline for the comprehensive management of osteoarthritis (OA) as a collaboration between the American College of Rheumatology (ACR) and the Arthritis Foundation, updating the 2012 ACR recommendations for the management of hand, hip, and knee OA.

Methods. We identified clinically relevant population, intervention, comparator, outcomes questions and critical outcomes in OA. A Literature Review Team performed a systematic literature review to summarize evidence supporting the benefits and harms of available educational, behavioral, psychosocial, physical, mind-body, and pharmacologic therapies for OA. Grading of Recommendations Assessment, Development and Evaluation methodology was used to rate the quality of the evidence. A Voting Panel, including rheumatologists, an internist, physical and occupational therapists, and patients, achieved consensus on the recommendations.

Results. Based on the available evidence, either strong or conditional recommendations were made for or against the approaches evaluated. Strong recommendations were made for exercise, weight loss in patients with knee and/or hip OA who are overweight or obese, self-efficacy and self-management programs, tai chi, cane use, hand orthoses for first carpometacarpal (CMC) joint OA, tibiofemoral bracing for tibiofemoral knee OA, topical nonsteroidal antiinflammatory drugs (NSAIDs) for knee OA, oral NSAIDs, and intraarticular glucocorticoid injections for knee OA. Conditional recommendations were made for balance exercises, yoga, cognitive behavioral therapy, kinesiotaping for first CMC OA, orthoses for hand joints other than the first CMC joint, patellofemoral bracing for patellofemoral knee OA, acupuncture, thermal modalities, radiofrequency ablation for knee OA, topical NSAIDs, intraarticular steroid injections and chondroitin sulfate for hand OA, topical capsaicin for knee OA, acetaminophen, duloxetine, and tramadol.

Conclusion. This guideline provides direction for clinicians and patients making treatment decisions for the management of OA. Clinicians and patients should engage in shared decision-making that accounts for patients' values, preferences, and comorbidities. These recommendations should not be used to limit or deny access to therapies.

INTRODUCTION

Osteoarthritis (OA) is the most common form of arthritis, affecting an estimated 302 million people worldwide (1–5), and is a leading cause of disability among older adults. The knees, hips, and hands are the most commonly affected appendicular joints. OA is characterized by pathology involving the whole joint, including cartilage degradation, bone remodeling, osteophyte formation, and synovial inflammation, leading to pain, stiffness, swelling, and loss of normal joint function.

As OA spans decades of a patient's life, patients with OA are likely to be treated with a number of different pharmaceutical and nonpharmaceutical interventions, often in combination. This report provides recommendations to guide patients and clinicians in choosing among the available treatments. Certain principles of management apply to all patients with OA (see Comprehensive Management of OA below and Figure 1). Some recommendations are specific to a particular joint (e.g., hip, knee, patellofemoral joint, first carpometacarpal joint [CMC]) or particular patient populations (e.g., those with erosive OA).

METHODS

This guideline, from the American College of Rheumatology (ACR) and the Arthritis Foundation (AF), follows the ACR guideline development process (https://www.rheumatology.org/Practice-Quality/Clinical-Support/Clinical-Practice-Guidelines), using the Grading of Recommendations Assessment, Development and Evaluation (GRADE) methodology to rate the quality of the available evidence and to develop the recommendations (6). ACR policy guided management of conflicts of interest and disclosures (https://www.rheumatology.org/Practice-Quality/Clinical-Support/Clinical-Practice-Guidelines/Osteoarthritis). A full description of the methods is presented in Supplementary Appendix 1 (on the *Arthritis Care & Research* web site at http://onlinelibrary.wiley.com/doi/10.1002/acr.24131/abstract).

Briefly, this work involved 5 teams: 1) a Core Leadership Team that supervised and coordinated the project and drafted the clinical/population, intervention, comparator, outcomes (PICO) questions that served as the basis for the evidence report and manuscript; 2) a Literature Review Team that completed the literature screening and data abstraction and produced the Evidence Report (Supplementary Appendix 2, http://onlinelibrary.wiley.com/doi/10.1002/acr.24131/abstract); 3) an Expert Panel that had input into scoping and clinical/PICO question development; 4) a Patient Panel; and 5) an interprofessional Voting Panel that included rheumatologists, an internist, physical and occupational therapists, and patients (Supplementary Appendix 3, http://onlinelibrary.wiley.com/doi/10.1002/acr.24131/abstract).

This guideline included an initial literature review limited to English-language publications from inception of the databases to October 15, 2017, with updated searches conducted on August 1, 2018 and relevant papers included. Studies published after August 1, 2018 were not evaluated for this guideline. Supplementary Appendix 4 (http://onlinelibrary.wiley.com/doi/10.1002/acr.24131/abstract) shows search terms used and databases reviewed, and Supplementary Appendix 5 (http://onlinelibrary.wiley.com/doi/10.1002/acr.24131/abstract) highlights the study selection process. The guideline evidence base results from our own systematic review of randomized

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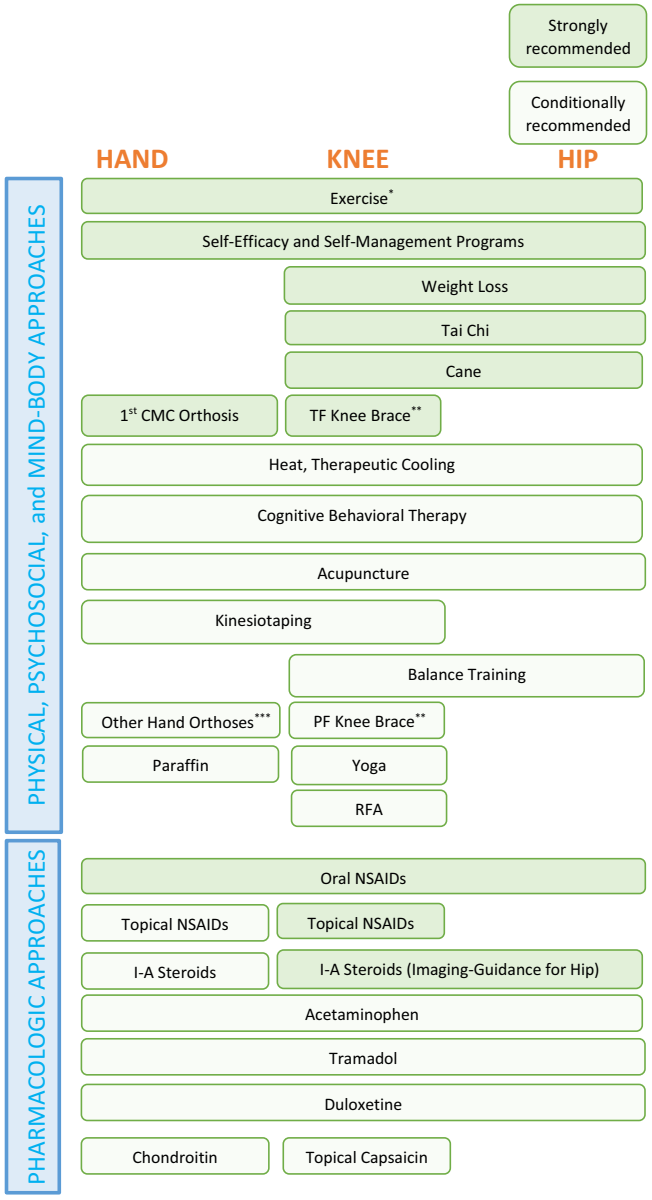

Figure 1. Recommended therapies for the management of osteoarthritis (OA). Strongly and conditionally recommended approaches to management of hand, knee, and/or hip OA are shown. No hierarchy within categories is implied in the figure, with the recognition that the various options may be used (and reused) at various times during the course of a particular patient's disease. * = Exercise for knee and hip OA could include walking, strengthening, neuromuscular training, and aquatic exercise, with no hierarchy of one over another. Exercise is associated with better outcomes when supervised. ** = Knee brace recommendations: tibiofemoral (TF) brace for TF OA (strongly recommended), patellofemoral (PF) brace for PF OA (conditionally recommended). *** = Hand orthosis recommendations: first carpometacarpal (CMC) joint neoprene or rigid orthoses for first CMC joint OA (strongly recommended), orthoses for joints of the hand other than the first CMC joint (conditionally recommended). RFA = radiofrequency ablation; NSAIDs = nonsteroidal antiinflammatory drugs; IA = intraarticular.

controlled trials (RCTs), rather than focusing on systematic reviews and meta-analyses published by others, as was done for the 2012 ACR recommendations for the use of nonpharmacologic and pharmacologic therapies in hand, hip, and knee OA (7). Systematic reviews of observational studies published by others were included if, in the opinion of the Voting Panel, they added critical information for the formulation of a recommendation: for example, related to adverse effects that may not be seen in shorter-duration RCTs. Subsequent updates of this guideline will consider studies included here and new RCTs published since completion of the literature review for the current publication.

Although RCTs are considered the gold standard for evaluation, a number of limitations of RCTs proved particularly important in the formulation of the final recommendations: possible publication bias (favoring publication of positive results), inadequate blinding, and inadequate provision of active comparators and appropriate sham alternatives. Further, short-duration RCTs cannot provide adequate prognostic information when applied to a complex disease such as OA, in which pathophysiologic processes are slowly progressive over decades.

We focused on management options that are available in the US and, for pharmacologic therapies, we additionally focused on agents that are available in pharmaceutical-grade formulations, thus eliminating most nutraceuticals. We limited our review to the English-language literature. We reviewed www.clinicaltrials.gov to identify phase 2 and 3 trials that may be far enough along to be US Food and Drug Administration (FDA)–approved and available by the time this guideline was published.

A hierarchy of outcome measures assessing pain and function in OA was developed based on the published literature (8,9). This hierarchy is detailed in Supplementary Appendix 1 (http://onlinelibrary.wiley.com/doi/10.1002/acr.24131/abstract).

Using GRADE, a recommendation can be either in favor of or against the proposed intervention and either strong or conditional (10,11). The strength of the recommendation is based on a 70% consensus among the Voting Panel members. Much of the evidence proved indirect (did not specifically address the PICO question as written) and of low-to-moderate quality (12,13). The Voting Panel made *strong recommendations* when it inferred compelling evidence of efficacy and that benefits clearly outweighed harms and burdens. Thus, a strong recommendation means that the Voting Panel was confident that the desirable effects of following the recommendation outweigh potential undesirable effects (or vice versa), so the course of action would apply to all or almost all patients, and only a small proportion of patients would not want to follow the recommendation.

The Voting Panel made *conditional recommendations* when the quality of the evidence proved low or very low and/

or the balance of benefits versus harms and burdens was sufficiently close that shared decision-making between the patient and the clinician would be particularly important. Conditional recommendations are those for which the majority of informed patients would choose to follow the recommended course of action, but some would not (14,15). Thus, conditional recommendations are particularly value- and preference-sensitive and always warrant a full shared decision-making approach involving a complete and clear explication of benefits, harms, and burdens in language and in a context that patients understand (16). Where recommendations are made regarding a particular approach, details and references regarding that approach can be found in the Evidence Report (Supplementary Appendix 2, http://onlinelibrary.wiley.com/doi/10.1002/acr.24131/abstract).

RESULTS/RECOMMENDATIONS

Comprehensive management of OA

A comprehensive plan for the management of OA in an individual patient may include educational, behavioral, psychosocial, and physical interventions, as well as topical, oral, and intraarticular medications. Recommendations assume appropriate application of physical, psychological, and/or pharmacologic therapies by an appropriate provider. Goals of management and principles for implementing those goals have broad applicability across patients. However, for some patients at some time points, a single physical, psychosocial, mind-body, or pharmacologic intervention may be adequate to control symptoms; for others, multiple interventions may be used in sequence or in combination. Which interventions and the order in which interventions are used will vary among patients. An overview of a general approach to management of OA is outlined in Figure 1 for recommended options, but no specific hierarchy of one option over another is implied other than on the basis of strength of the recommendation. Figure 2 summarizes the approaches that were not recommended.

Treatment decisions should take the personal beliefs and preferences of the patient, as well as the patient's medical status, into consideration. This guideline applies to patients with OA with no specific contraindications to the recommended therapies. However, each patient should be assessed for the presence of medical conditions, such as hypertension, cardiovascular disease, heart failure, gastrointestinal bleeding risk, chronic kidney disease, or other comorbidities, that might have an impact on their risk of side effects from certain pharmacologic agents, as well as injuries, disease severity, surgical history, and access to and availability of services (transportation, distance, ability to take time off work, cost, insurance coverage) that might have an impact on the choice of physical, psychological, and mind-body approaches. It is assumed that such an assessment

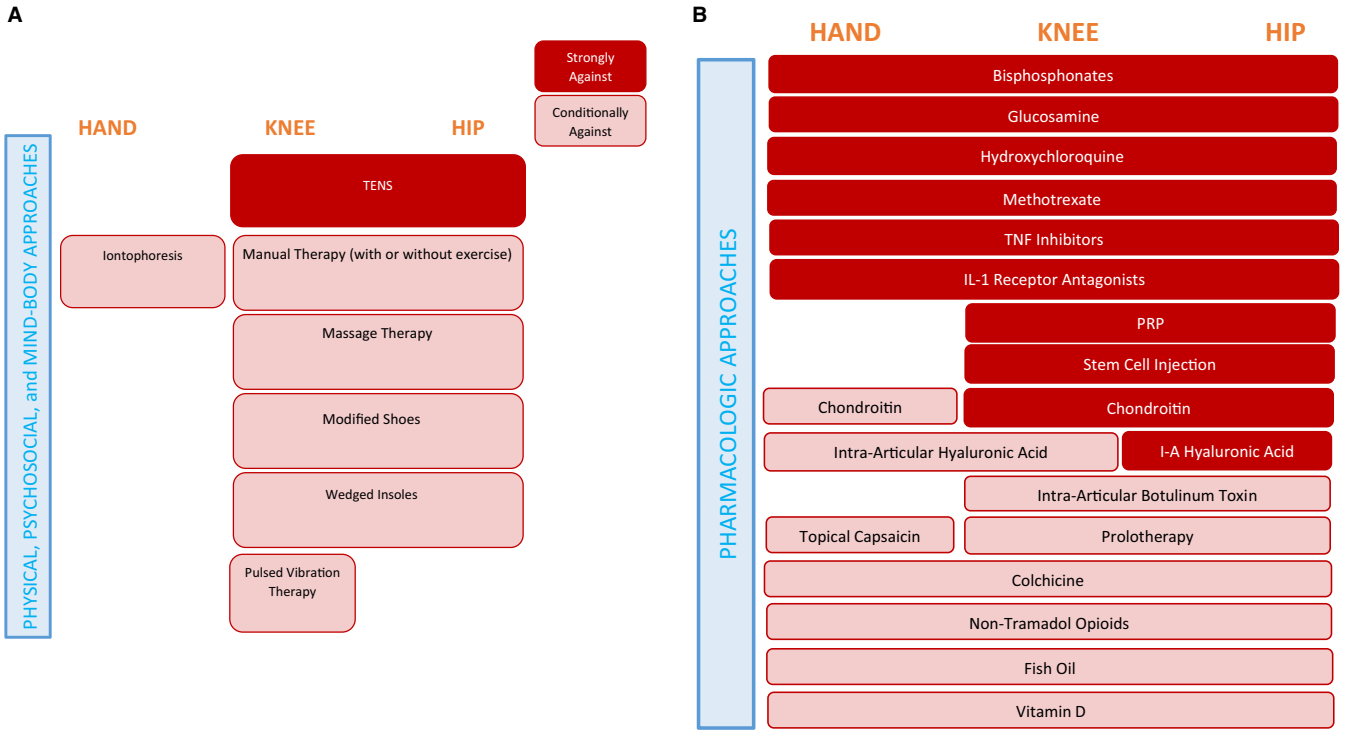

Figure 2. Therapies recommended *against* (physical, psychosocial, and mind-body approaches [**A**] and pharmacologic approaches [**B**]) in the management of hand, knee, and/or hip osteoarthritis. No hierarchy within categories is implied in the figure. TENS = transcutaneous electrical nerve stimulation; TNF = tumor necrosis factor; IL-1 = interleukin-1; PRP = platelet-rich plasma; IA = intraarticular.

will be performed prior to finalization of an individual treatment plan. When choosing among pharmacologic therapies, management should begin with treatments with the least systemic exposure or toxicity.

Patients may experience a variety of additional symptoms as a result of the pain and functional limitations arising from OA and/or comorbidities. These include mood disorders, such as depression and anxiety, altered sleep, chronic widespread pain, and impaired coping skills. The Patient Panel noted that the broader impact of OA on these comorbidities is of particular importance when choosing among treatment options and best addressed by a multimodal treatment plan, rather than one that is limited to the prescription of a single medication. Measures aimed at improving mood, reducing stress, addressing insomnia, managing weight, and enhancing fitness may improve the patient's overall well-being and OA treatment success. Indeed, interventions that have proven beneficial in the management of chronic pain may prove useful in OA (17) even when data specific to patients with OA are limited.

Unless otherwise specified, recommendations regarding physical, psychosocial, and mind-body approaches assume that the patient will be adding the intervention to usual care. For the purposes of this guideline, usual care includes the use of maximally recommended or safely tolerated doses of over-the counter oral nonsteroidal antiinflammatory drugs (NSAIDs) and/or acetaminophen, as has generally been explicitly permitted in clinical trials of nonpharmacologic interventions.

Physical, psychosocial, and mind-body approaches (Table 1)

During the GRADE analysis, clinical trials involving physical modalities and mind-body approaches were often designated as yielding low-quality evidence because blinding with regard to the active treatment was not always possible. This contributed to a preponderance of conditional recommendations for physical modalities and mind-body approaches. The delivery of instruction by physical and occupational therapists is helpful, and often essential, for the appropriate initiation and maintenance of exercise as a part of OA management. In addition to exercise, physical and occupational therapists often incorporate self-efficacy and self-management training, thermal therapies, and instruction in use of and fitting of splints and braces in their practices. Most patients with OA are likely to experience benefit from referral to physical therapy and/or occupational therapy at various times during the course of their disease.

Exercise is strongly recommended for patients with knee, hip, and/or hand OA.

Though exercise is strongly recommended for all OA patients, there is considerably more evidence for the use of exercise in the treatment of knee and hip OA than for hand OA, and the variety of exercise options studied is far greater. While patients and providers seek recommendations on the "best" exercise and the ideal dosage (duration, intensity, and frequency), current evidence

Table 1. Recommendations for physical, psychosocial, and mind-body approaches for the management of osteoarthritis of the hand, knee, and hip

Intervention	Joint		
	Hand	Knee	Hip
Exercise			
Balance training			
Weight loss			
Self-efficacy and self-management programs			
Tai chi			
Yoga			
Cognitive behavioral therapy			
Cane			
Tibiofemoral knee braces		(Tibiofemoral)	
Patellofemoral braces		(Patellofemoral)	
Kinesiotaping	(First carpometacarpal)		
Hand orthosis	(First carpometacarpal)		
Hand orthosis	(Other joints)		
Modified shoes			
Lateral and medial wedged insoles			
Acupuncture			
Thermal interventions			
Paraffin			
Radiofrequency ablation			
Massage therapy			
Manual therapy with/without exercise			
Iontophoresis	(First carpometacarpal)		
Pulsed vibration therapy			
Transcutaneous electrical nerve stimulation			

Strongly recommended
Conditionally recommended
Strongly recommended against
Conditionally recommended against
No recommendation

is insufficient to recommend specific exercise prescriptions. Broad recommendations suggesting one form of exercise over another are based largely on expert opinion. A substantial body of literature (see Evidence Report, Supplementary Appendix 2 [http://onlinelibrary.wiley.com/doi/10.1002/acr.24131/abstract]) supports a wide range of appropriate exercise options and suggests that the vast majority of OA patients can participate in, and benefit from with regard to pain and function, some form of exercise. Exercise recommendations to patients should focus on the patient's preferences and access, both of which may be important barriers to participation. If a patient does not find a certain form of exercise acceptable or cannot afford to participate or arrange transportation to participate, he or she is not likely to get any benefit from the suggestion to pursue that exercise.

In the majority of studies that assessed the role of aerobic exercise in the management of OA, walking was the most common form of exercise evaluated, either on a treadmill or as supervised, community-based, indoor fitness walking. Other studies used supervised group cycling on stationary bicycles. Strengthening exercises have included the use of isokinetic weight machines, resistance exercise training with and without props such as elastic bands, and isometric exercise. Neuromuscular training has been developed to address muscle weakness, reduced sensorimotor control, and functional instability specifically seen with knee OA, with a series of dynamic maneuvers of increased complexity. Aquatic exercise often encompasses aspects of aerobic fitness exercises and exercises for enhancing joint range of motion, in a low-impact environment.

A specific hierarchy of these various forms of exercise could not be discerned from the literature. Patient participants on the Patient and Voting Panels raised the concern that patients who are in pain might be hesitant to participate in exercise. There is no uniformly accepted level of pain at which a patient should or should not exercise, and a common-sense approach of shared decision-making between the treating clinician and the patient regarding when to initiate an exercise program is advisable. However, clinical trials of exercise for OA include patients with pain and functional limitations due to OA, and improvements in OA-specific outcomes have been demonstrated; thus, results are likely to be generalizable to most patients with pain due to OA.

Although there is currently insufficient evidence to recommend one form of exercise over another, patients will likely benefit from advice that is as specific as possible, rather than simple encouragement to exercise. Given the wide range of evidence-based exercise interventions shown to effectively improve pain and function in OA, all patients should be encouraged to consider some form of exercise as a central part of their treatment plan. Individual preferences, access, and affordability are likely to play a role in what works best for an individual patient. Overall, exercise programs are more effective if supervised, often by physical therapists and sometimes in a class setting, rather than when performed by the individual at home. They also tend to be more effective when combined with self-efficacy and self-management interventions or weight loss programs.

Few studies have employed monitoring devices or pre- and postintervention assessment of cardiovascular or musculoskeletal fitness, so targets using these devices or assessments are not available. Future research is essential to establish specific exercise guidelines that will direct the patient and provider toward more individualized exercise prescriptions.

Balance exercises are conditionally recommended for patients with knee and/or hip OA.

Balance exercises include those that improve the ability to control and stabilize body position (American Physical Therapy Association: http://www.apta.org/BalanceFalls/). Although one might expect balance exercises to help reduce the risk of falls in patients with OA, RCTs to date have not addressed this outcome in this population, and the low quality of evidence addressing the use of balance exercises necessitates only a conditional recommendation for balance exercises.

Weight loss is strongly recommended for patients with knee and/or hip OA who are overweight or obese.

A dose-response has been noted with regard to the amount of weight loss that will result in symptom or functional improvement in patients with OA (18). A loss of ≥5% of body weight can be associated with changes in clinical and mechanistic outcomes. Furthermore, clinically important benefits continue to increase with weight loss of 5–10%, 10–20%, and >20% of body weight. The efficacy of weight loss for OA symptom management is enhanced by use of a concomitant exercise program.

Self-efficacy and self-management programs are strongly recommended for patients with knee, hip, and/or hand OA.

Although effect sizes are generally small, the benefits of participation in self-efficacy and self-management programs are consistent across studies, and risks are minimal. These programs use a multidisciplinary group–based format combining sessions on skill-building (goal-setting, problem-solving, positive thinking), education about the disease and about medication effects and side effects, joint protection measures, and fitness and exercise goals and approaches. Health educators, National Commission for Certification Services–certified fitness instructors, nurses, physical therapists, occupational therapists, physicians, and patient peers may lead the sessions, which can be held in person or online. In the studies reviewed, sessions generally occurred 3 times weekly, but varied from 2 to 6 times weekly.

Tai chi is strongly recommended for patients with knee and/or hip OA.

Tai chi is a traditional Chinese mind-body practice that combines meditation with slow, gentle, graceful movements, deep diaphragmatic breathing, and relaxation. The efficacy of tai chi may

reflect the holistic impact of this mind-body practice on strength, balance, and fall prevention, as well as on depression and self-efficacy.

Yoga is conditionally recommended for patients with knee OA.

Yoga is a mind-body practice with origins in ancient Indian philosophy and typically combines physical postures, breathing techniques, and meditation or relaxation (National Center for Complementary and Integrative Health [NCCIH]: https://nccih.nih.gov/health/yoga). Though far less well studied than tai chi, yoga may be helpful in OA through a similar blend of physical and psychosocial factors. Due to lack of data, no recommendation can be made regarding use of yoga to help manage symptoms of hip OA. Other mind-body practices could not be assessed due to insufficient evidence, as well as a lack of standard definitions of certain interventions (hypnosis, qi gong).

Cognitive behavioral therapy (CBT) is conditionally recommended for patients with knee, hip, and/or hand OA.

There is a well-established body of literature (19,20) supporting the use of CBT in chronic pain conditions, and CBT may have relevance for the management of OA. Trials have demonstrated improvement in pain, health-related quality of life, negative mood, fatigue, functional capacity, and disability in conditions other than OA. In OA, limited evidence suggests that CBT may reduce pain (21). Further research is needed to establish whether or not benefits in OA are related to alteration in mood, sleep, coping, or other factors that may co-occur with, result from, or be a part of the experience of OA (22).

Cane use is strongly recommended for patients with knee and/or hip OA in whom disease in 1 or more joints is causing a sufficiently large impact on ambulation, joint stability, or pain to warrant use of an assistive device.

Tibiofemoral knee braces are strongly recommended for patients with knee OA in whom disease in 1 or both knees is causing a sufficiently large impact on ambulation, joint stability, or pain to warrant use of an assistive device, and who are able to tolerate the associated inconvenience and burden associated with bracing.

Patellofemoral braces are conditionally recommended for patients with patellofemoral knee OA in whom disease in 1 or both knees is causing a sufficiently large impact on ambulation, joint stability, or pain to warrant use of an assistive device.

The recommendation is conditional due to the variability in results across published trials and the difficulty some patients will have in tolerating the inconvenience and burden of these braces. Optimal management with knee bracing is likely to require that clinicians are familiar with the various types of braces and where they are available and have expertise in fitting the braces. Patient Voting Panel members strongly emphasized the importance of coordination of care between primary care providers, specialists, and providers of braces.

Kinesiotaping is conditionally recommended for patients with knee and/or first CMC joint OA.

Kinesiotaping permits range of motion of the joint to which it is applied, in contrast to a brace, which maintains the joint in a fixed position. Published studies have examined various products and methods of application, and blinding with regard to use is not possible, thereby limiting the quality of the evidence.

Hand orthoses are strongly recommended for patients with first CMC joint OA.

Hand orthoses are conditionally recommended for patients with OA in other joints of the hand.

A variety of mechanical supports are available, including digital orthoses, ring splints, and rigid or neoprene orthoses, some of which are intended for specifically affected joints (e.g., first CMC joint, individual digits, wrist) and some of which support the entire hand. In addition, gloves may offer benefit by providing warmth and compression to the joints of the hand. Data are insufficient to recommend one type of orthosis over another for use in the hand. Patients considering these interventions will likely benefit from evaluation by an occupational therapist.

Modified shoes are conditionally recommended *against* in patients with knee and/or hip OA.

Modifications to shoes can be intended to alter the biomechanics of the lower extremities and the gait. While optimal footwear is likely to be of considerable importance for those with knee and/or hip OA, the available studies do not define the best type of footwear to improve specific outcomes for knee or hip OA.

Lateral and medial wedged insoles are conditionally recommended *against* in patients with knee and/or hip OA.

The currently available literature does not demonstrate clear efficacy of lateral or medial wedged insoles.

Acupuncture is conditionally recommended for patients with knee, hip, and/or hand OA.

Although a large number of trials have addressed the use of acupuncture for OA, its efficacy remains a subject of controversy. Issues related to the use of appropriate blinding, the validity of sham controls, sample size, effect size, and prior expectations have arisen with regard to this literature. Variability in the results of RCTs and meta-analyses is likely driven, in part, by differences in the type of controls and the intensity of the control

interventions used. In addition, the benefits of acupuncture result from the large contextual effect plus small differences in outcomes between "true" and "sham" acupuncture. The latter is of the same magnitude as the effect of full-dose acetaminophen versus placebo. The greatest number of positive trials with the largest effect sizes have been carried out in knee OA. Positive trials and meta-analyses have also been published in a variety of other painful conditions and have indicated that acupuncture is effective for analgesia. While the "true" magnitude of effect is difficult to discern, the risk of harm is minor, resulting in the Voting Panel providing a conditional recommendation.

Thermal interventions (locally applied heat or cold) are conditionally recommended for patients with knee, hip, and/or hand OA.

The method of delivery of thermal interventions varies considerably in published reports, including moist heat, diathermy (electrically delivered heat), ultrasound, and hot and cold packs. Studies using diathermy or ultrasound were more likely to be sham controlled than those using other heat delivery modalities. The heterogeneity of modalities and short duration of benefit for these interventions led to the conditional recommendation.

Paraffin, an additional method of heat therapy for the hands, is conditionally recommended for patients with hand OA.

Radiofrequency ablation is conditionally recommended for patients with knee OA.

A number of studies have demonstrated potential analgesic benefits with various ablation techniques but, because of the heterogeneity of techniques and controls used and lack of long-term safety data, this recommendation is conditional.

Massage therapy is conditionally recommended *against* in patients with knee and/or hip OA.

Massage therapy encompasses a number of techniques aimed at affecting muscle and other soft tissue (NCCIH: https://nccih.nih.gov/health/massage/massageintroduction.htm#hed2). Studies addressing massage have suffered from high risk of bias, have included small numbers of patients, and have not demonstrated benefit for OA-specific outcomes. Patient participants on the Patient and Voting Panels noted that some studies have shown positive outcomes and minimal risk and felt strongly that massage therapy was beneficial for symptom management (23). However, based on the available evidence regarding OA specifically, a conditional recommendation against the use of massage for reduction of OA symptoms is made, though the Voting Panel acknowledged that massage may have other benefits.

Manual therapy with exercise is conditionally recommended *against* over exercise alone in patients with knee and/or hip OA.

Manual therapy techniques may include manual lymphatic drainage, manual traction, massage, mobilization/manipulation, and passive range of motion and are always used in conjunction with exercise (http://guidetoptpractice.apta.org/content/1/SEC38.extract). A limited number of studies have addressed manual therapy added to exercise versus exercise alone in hip and knee OA. Although manual therapy can be of benefit for certain conditions, such as chronic low back pain, limited data in OA show little additional benefit over exercise alone for managing OA symptoms.

Iontophoresis is conditionally recommended *against* in patients with first CMC joint OA.

There are no published RCTs evaluating iontophoresis for OA in any anatomic location.

Pulsed vibration therapy is conditionally recommended *against* in patients with knee OA.

Few trials have addressed pulsed vibration therapy, and in the absence of adequate data, we conditionally recommend against its use.

Transcutaneous electrical stimulation (TENS) is strongly recommended *against* in patients with knee and/or hip OA.

Studies examining the use of TENS have been of low quality with small size and variable controls, making comparisons across trials difficult. Studies have demonstrated a lack of benefit for knee OA.

Pharmacologic management (Table 2)

RCTs of pharmacologic agents may be subject to a variety of limitations, including generalizability of their findings across patients. Publication bias may reduce the likelihood that negative trials will become part of the published literature. Statistically significant findings may represent benefits so small that they are not clinically important to patients. We have highlighted these considerations where relevant.

Topical NSAIDs are strongly recommended for patients with knee OA and conditionally recommended for patients with hand OA.

In keeping with the principle that medications with the least systemic exposure (i.e., local therapy) are preferable, topical NSAIDs should be considered prior to use of oral NSAIDs (24). Practical considerations (e.g., frequent hand washing) and the lack of direct evidence of efficacy in the hand lead to a conditional recommendation for use of topical NSAIDs in hand OA. In hip OA, the depth of the joint beneath the skin surface suggests that topical NSAIDs are unlikely to

Table 2. Recommendations for the pharmacologic management of osteoarthritis of the hand, knee, and hip

Intervention	Joint		
	Hand	Knee	Hip
Topical nonsteroidal antiinflammatory drugs			
Topical capsaicin			
Oral nonsteroidal antiinflammatory drugs			
Intraarticular glucocorticoid injection			
Ultrasound-guided intraarticular glucocorticoid injection			
Intraarticular glucocorticoid injection compared to other injections			
Acetaminophen			
Duloxetine			
Tramadol			
Non-tramadol opioids			
Colchicine			
Fish oil			
Vitamin D			
Bisphosphonates			
Glucosamine			
Chondroitin sulfate			
Hydroxychloroquine			
Methotrexate			
Intraarticular hyaluronic acid injection	(First carpometacarpal)		
Intraarticular botulinum toxin			
Prolotherapy			
Platelet-rich plasma			
Stem cell injection			
Biologics (tumor necrosis factor inhibitors, interleukin-1 receptor antagonists)			

Strongly recommended
Conditionally recommended
Strongly recommended against
Conditionally recommended against
No recommendation

confer benefit, and thus, the Voting Panel did not examine use in hip OA.

Topical capsaicin is conditionally recommended for patients with knee OA and conditionally recommended *against* in patients with hand OA.

Topical capsaicin is conditionally recommended for treatment of knee OA due to small effect sizes and wide confidence intervals in the available literature. We conditionally recommend against the use of topical capsaicin in hand OA because of a lack of direct evidence to support use, as well as a potentially increased risk of contamination of the eye with use of topical capsaicin to treat hand OA. In hip OA, the depth of the joint beneath the skin surface suggests that topical capsaicin is unlikely to have a meaningful effect, and thus, the Voting Panel did not examine use of topical capsaicin in hip OA. Insufficient data exists to make recommendations about the use of topical lidocaine preparations in OA.

Oral NSAIDs are strongly recommended for patients with knee, hip, and/or hand OA.

Oral NSAIDs remain the mainstay of the pharmacologic management of OA, and their use is strongly recommended. A large number of trials have established their short-term efficacy. Oral NSAIDs are the initial oral medication of choice in the treatment of OA, regardless of anatomic location, and are recommended over all other available oral medications.

While this guideline did not address the relative merits of different NSAIDs, there is evidence suggesting that certain agents may have more favorable side effect profiles than others (25–27). Clinical considerations aimed at risk mitigation for the safe use of NSAIDs, such as appropriate patient selection, regular monitoring for the development of potential adverse gastrointestinal, cardiovascular, and renal side effects and potential drug interactions, were not specifically included in the GRADE process for the formulation of recommendations. Doses should be as low as possible, and NSAID treatment should be continued for as short a time as possible.

Intraarticular glucocorticoid injections are strongly recommended for patients with knee and/or hip OA and conditionally recommended for patients with hand OA.

Trials of intraarticular glucocorticoid injections have demonstrated short-term efficacy in knee OA. Intraarticular glucocorticoid injection is conditionally, rather than strongly, recommended for hand OA given the lack of evidence specific to this anatomic location. There are insufficient data to judge the choice of short-acting over long-acting preparations or the use of low rather than high doses. A recent report (28) raised the possibility that specific steroid preparations or a certain frequency of steroid injections may contribute to cartilage loss, but the Voting Panel was uncertain of the clinical significance of this finding, particularly since

change in cartilage thickness was not associated with a worsening in pain, functioning, or other radiographic features.

Ultrasound guidance for intraarticular glucocorticoid injection is strongly recommended for injection into hip joints.

When available, ultrasound guidance for steroid injection may help ensure accurate drug delivery into the joint, but is not required for knee and hand joints. However, imaging guidance for injection into hip joints is strongly recommended.

Intraarticular glucocorticoid injections versus other injections are conditionally recommended for patients with knee, hip, and/or hand OA.

In OA generally, intraarticular glucocorticoid injection is conditionally recommended over other forms of intraarticular injection, including hyaluronic acid preparations. Head-to-head comparisons are few, but the evidence for efficacy of glucocorticoid injections is of considerably higher quality than that for other agents.

Acetaminophen is conditionally recommended for patients with knee, hip, and/or hand OA.

In clinical trials, the effect sizes for acetaminophen are very small, suggesting that few of those treated experience important benefit, and meta-analysis has suggested that use of acetaminophen as monotherapy may be ineffective (29). Longer-term treatment is no better than treatment with placebo for most individuals. Members of the Patient Panel noted that, for most individuals, acetaminophen is ineffective. For those with limited pharmacologic options due to intolerance of or contraindications to the use of NSAIDs, acetaminophen may be appropriate for short-term and episodic use. Regular monitoring for hepatotoxicity is required for patients who receive acetaminophen on a regular basis, particularly at the recommended maximum dosage of 3 gm daily in divided doses.

Duloxetine is conditionally recommended for patients with knee, hip, and/or hand OA.

While studied primarily in the knee, the effects of duloxetine may plausibly be expected to be similar for OA of the hip or hand. While a variety of centrally acting agents (e.g., pregabalin, gabapentin, selective serotonin reuptake inhibitors, serotonin norepinephrine reuptake inhibitors, and tricyclic antidepressants) have been used in the management of chronic pain, only duloxetine has adequate evidence on which to base recommendations for use in OA. However, in considering all the ways in which OA may be affecting an individual patient, shared decision-making between the physician and patient may include consideration of any of these agents. Considering the utility of these agents in pain management generally, their use may be an appropriate target of future investigations specific to OA. Evidence suggests that duloxetine has efficacy in the treatment of OA when used alone or in combination with NSAIDs; however, there are issues regarding tolerability and side effects. No recommendations were made for the other centrally acting agents due to lack of direct studies of relevance in OA.

Tramadol is conditionally recommended for patients with knee, hip, and/or OA.

Recent work has highlighted the very modest level of beneficial effects in the long-term (3 months to 1 year) management of non-cancer pain with opioids (30). Nonetheless, there are circumstances in which tramadol or other opioids may be appropriate in the treatment of OA, including when patients may have contraindications to NSAIDs, find other therapies ineffective, or have no available surgical options. Patient Panel input demonstrated a high level of understanding concerning addiction potential, but also included an appreciation for the role of these agents when other pharmacologic and physical options have been ineffective. However, RCT evidence addressing the use of tramadol and other opioids for periods longer than 1 year is not available. Clinical trials have demonstrated some symptomatic efficacy, though concerns regarding potential adverse effects remain. If an opioid is being considered, tramadol is conditionally recommended over non-tramadol opioids.

Non-tramadol opioids are conditionally recommended *against* in patients with knee, hand, and/or hip OA with the recognition that they may be used under certain circumstances, particularly when alternatives have been exhausted.

As noted above, evidence suggests very modest benefits of long-term opioid therapy and a high risk of toxicity and dependence. Use of the lowest possible doses for the shortest possible length of time is prudent, particularly since a recent systematic review and meta-analysis suggests that less pain relief occurs during longer trials in the treatment of non-cancer chronic pain (30).

Colchicine is conditionally recommended *against* in patients with knee, hip, and/or hand OA.

Two very small studies have suggested analgesic benefit of colchicine in OA, but the quality of the data was low. In addition, potential adverse effects, as well as drug interactions, may occur with use of colchicine.

Fish oil is conditionally recommended *against* in patients with knee, hip, and/or hand OA.

Fish oil is the most commonly used dietary supplement in the US (31). Despite its popularity, only 1 published trial has addressed its potential role in OA. This study failed to show efficacy of a higher dose of fish oil over a lower dose.

Vitamin D is conditionally recommended *against* in patients with knee, hip, and/or hand OA.

A number of trials in OA demonstrated small effect sizes with vitamin D treatment, while others have shown no benefit and pooling data across studies yielded null results. In addition, limited

and questionable health benefits from vitamin D supplementation have been suggested in other contexts (32,33).

Bisphosphonates are strongly recommended *against* in patients with knee, hip, and/or hand OA.

Though a single small study of an oral bisphosphonate suggested a potential analgesic benefit in OA, the preponderance of data shows no improvement in pain or functional outcomes.

Glucosamine is strongly recommended *against* in patients with knee, hip, and/or hand OA.

Pharmaceutical-grade preparations of glucosamine are available and have been studied in multiple trials. However, discrepancies in efficacy reported in studies that were industry sponsored as opposed to publicly funded have raised serious concerns about publication bias (34,35). In addition, there is a lack of a clear biologic understanding of how efficacy would vary with the type of salt studied. The data that were deemed to have the lowest risk of bias fail to show any important benefits over placebo. These recommendations represent a change from the prior conditional recommendation against the use of glucosamine. The weight of the evidence indicates a lack of efficacy and large placebo effects. Nonetheless, glucosamine remains among the most commonly used dietary supplements in the US (31), and clinicians should be aware that many patients perceive that glucosamine is efficacious. Patients also often perceive that different glucosamine formulas are associated with different degrees of efficacy and seek advice on brands and manufacturers. The potential toxicity of glucosamine is low, though some patients exposed to glucosamine may show elevations in serum glucose levels (36).

Chondroitin sulfate is strongly recommended *against* in patients with knee and/or hip OA as are combination products that include glucosamine and chondroitin sulfate, but is conditionally recommended for patients with hand OA.

A single trial suggested analgesic efficacy of chondroitin sulfate, without evidence of harm, in hand OA.

Hydroxychloroquine is strongly recommended *against* in patients with knee, hip, and/or hand OA.

Well-designed RCTs of hydroxychloroquine, conducted in the subset of patients with erosive hand OA, have demonstrated no efficacy.

Methotrexate is strongly recommended *against* in patients with knee, hip, and/or hand OA.

Well-designed RCTs of methotrexate, conducted in the subset of patients with erosive hand OA, have demonstrated no efficacy.

Intraarticular hyaluronic acid injections are conditionally recommended *against* in patients with knee and/or first CMC joint OA and strongly recommended *against* in patients with hip OA.

In prior systematic reviews, apparent benefits of hyaluronic acid injections in OA have been reported. These reviews have not, however, taken into account the risk of bias of the individual primary studies. Our review showed that benefit was restricted to the studies with higher risk of bias: when limited to trials with low risk of bias, meta-analysis has shown that the effect size of hyaluronic acid injections compared to saline injections approaches zero (37). The finding that best evidence fails to establish a benefit, and that harm may be associated with these injections, motivated the recommendation against use of this treatment.

Many providers want the option of using hyaluronic acid injections when glucocorticoid injections or other interventions fail to adequately control local joint symptoms. In clinical practice, the choice to use hyaluronic acid injections in the knee OA patient who has had an inadequate response to nonpharmacologic therapies, topical and oral NSAIDs, and intraarticular steroids may be viewed more favorably than offering no intervention, particularly given the impact of the contextual effects of intraarticular hyaluronic acid injections (38). The conditional recommendation against is consistent with the use of hyaluronic acid injections, in the context of shared decision-making that recognizes the limited evidence of benefit of this treatment, when other alternatives have been exhausted or failed to provide satisfactory benefit. The conditional recommendation against is not intended to influence insurance coverage decisions.

In contrast, the evidence of lack of benefit is of higher quality with respect to hyaluronic acid injection in the hip. We therefore strongly recommend against hyaluronic acid injections in hip OA.

Intraarticular botulinum toxin injections are conditionally recommended *against* in patients with knee and/or hip OA.

The small number of trials of intraarticular botulinum toxin treatment in knee or hip OA suggest a lack of efficacy. This treatment has not been evaluated in hand OA and, therefore, no recommendation is made with regard to OA of the hand.

Prolotherapy is conditionally recommended *against* in patients with knee and/or hip OA.

A limited number of trials involving a small number of participants have shown small effect sizes of prolotherapy in knee or hip OA. However, injection schedules, injection sites, and comparators have varied substantially between trials. This treatment has not been evaluated in hand OA and, therefore, no recommendation is made with regard to OA of the hand.

Platelet-rich plasma treatment is strongly recommended *against* in patients with knee and/or hip OA.

In contrast to intraarticular therapies discussed above, there is concern regarding the heterogeneity and lack of standardization in available preparations of platelet-rich plasma, as well as techniques used, making it difficult to identify exactly what is being injected. This treatment has not been evaluated in hand OA and, therefore, no recommendation is made with regard to OA of the hand.

Stem cell injections are strongly recommended *against* in patients with knee and/or hip OA.

There is concern regarding the heterogeneity and lack of standardization in available preparations of stem cell injections, as well as techniques used. This treatment has not been evaluated in hand OA and, therefore, no recommendation is made with regard to OA of the hand.

Tumor necrosis factor inhibitors and interleukin-1 receptor antagonists are strongly recommended *against* in patients with knee, hip, and/or hand OA.

Tumor necrosis factor inhibitors and interleukin-1 receptor antagonists have been studied in trials using both subcutaneous and intraarticular routes of administration. Efficacy has not been demonstrated, including in erosive hand OA. Therefore, given their known risks of toxicity, we strongly recommended against their use for any form of OA.

Initial observations addressing the use of anti–nerve growth factor (anti-NGF) agents suggest that significant analgesic benefits may occur but that incompletely explained important safety issues may arise. A small subset of patients treated with these agents had rapid joint destruction leading to early joint replacement. The FDA temporarily halted clinical trials of anti-NGF as a result, but trials have since resumed, with ongoing collection of longer-term efficacy and safety data. As none of these agents were approved for use by the FDA and the longer-term data were not available at the time of the literature review and Voting Panel meeting, we are unable to make recommendations regarding the use of anti-NGF therapy.

DISCUSSION

These 2019 ACR/AF recommendations for the management of OA are based on the best available evidence of benefit, safety, and tolerability of physical, educational, behavioral, psychosocial, mind-body, and pharmacologic interventions, as well as the consensus judgment of clinical experts. The GRADE approach used provided a comprehensive, explicit, and transparent methodology for developing recommendations for OA management. The choice of any single or group of interventions may vary over the course of the disease or with patient and provider preferences, and is optimally arrived at through shared decision-making.

The Voting Panel made strong recommendations for patients to participate in a regular, ongoing exercise program. The literature provides support for choice from a broad menu of exercises for patients with OA. The effectiveness of an exercise program is enhanced when patient preferences and access to exercise programs are considered, as well as when they are supervised or coupled with self-efficacy, self-management, and weight loss programs. Strong recommendations were also made for weight loss in patients with knee and/or hip OA who are overweight or obese, self-efficacy and self-management programs, tai chi, cane use, first CMC joint orthoses, tibiofemoral bracing, topical NSAIDs for knee OA and oral NSAIDs for hand, knee, and/or hip OA, and intraarticular glucocorticoid injections for knee and/or hip OA. The Voting Panel made conditional recommendations for balance exercises, yoga, CBT, kinesiotaping, orthoses for hand joints other than the first CMC, patellofemoral bracing, acupuncture, thermal modalities, radiofrequency ablation, topical NSAIDs, intraarticular steroid injections and chondroitin sulfate for hand OA, topical capsaicin for knee OA, acetaminophen, duloxetine, and tramadol. The recommendations provide an array of options for a comprehensive approach for optimal management of OA encompassing the use of educational, physical, behavioral, psychosocial, mind-body, and pharmacologic interventions. The availability, accessibility, and affordability of some of these interventions vary, but in many communities the AF, as well as local hospitals and other health-related agencies, offer free self-efficacy and self-management programs.

For some patients with more limited disease in whom medication is required, topical NSAIDs represent an appropriate first choice. For others, particularly with hip OA or polyarticular involvement, oral NSAIDs are more appropriate. The appropriate use of other oral agents, particularly acetaminophen and opioids, will continue to evolve (39–41).

Despite the many options available, some patients may continue to experience inadequate symptom control; others will experience adverse effects from the available interventions. Clinicians treating patients in these circumstances should choose interventions with a low risk of harm, but both clinicians and patients may be dissatisfied with the options and unsure of how to choose among them. There are controversies in interpretation of the evidence, particularly with regard to the use of glucosamine and chondroitin, acupuncture, and intraarticular hyaluronic acid injections. Nonetheless, the process of updating treatment guidelines permits scrutiny of the state of the literature and identification of critical gaps in our knowledge about best practices. Further, it highlights the need for ongoing, appropriately funded, high-quality clinical research, as well as development of new treatment modalities, to address the human and economic impact of the most common form of arthritis.

No effective disease-modifying agents for OA have yet been identified though phase 2 and 3 trials are underway, and, for the time being, preventive strategies focus on weight management and injury prevention. Development of more effective therapies that

permit a sophisticated and individualized approach to the patient with OA await the outcome of future investigation. Important directions for research include gaining a more comprehensive understanding of the optimal types of exercises and the modifications that should be used based on disease location and severity, study of the intensity of exercise that would be optimal for a given individual (https://health.gov/paguidelines/second-edition/report.aspx), defining optimal footwear for patients with knee and hip OA and understanding the interaction between footwear and exercise, conducting rigorous RCTs for physical modality options in hand OA, assessing a broader array of outcomes, including fall prevention, assessing optimal use of oral, topical, and injectable agents alone and in combination, obtaining a better understanding of the role of integrative medicine, including massage, herbal products, medical marijuana, and additional mind-body interventions, and exploring agents with novel mechanisms of action for prevention and treatment.

In conclusion, optimal management requires a comprehensive, multimodal approach to treating patients with hand, hip, and/or knee OA offered in the context of shared decision-making with patients, to choose the safest and most effective treatment possible. A large research agenda remains to be addressed, with a need for more options with greater efficacy for the millions of people worldwide with osteoarthritis.

Addendum. Therapies that were approved after the original systematic literature review are not included in these recommendations.

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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

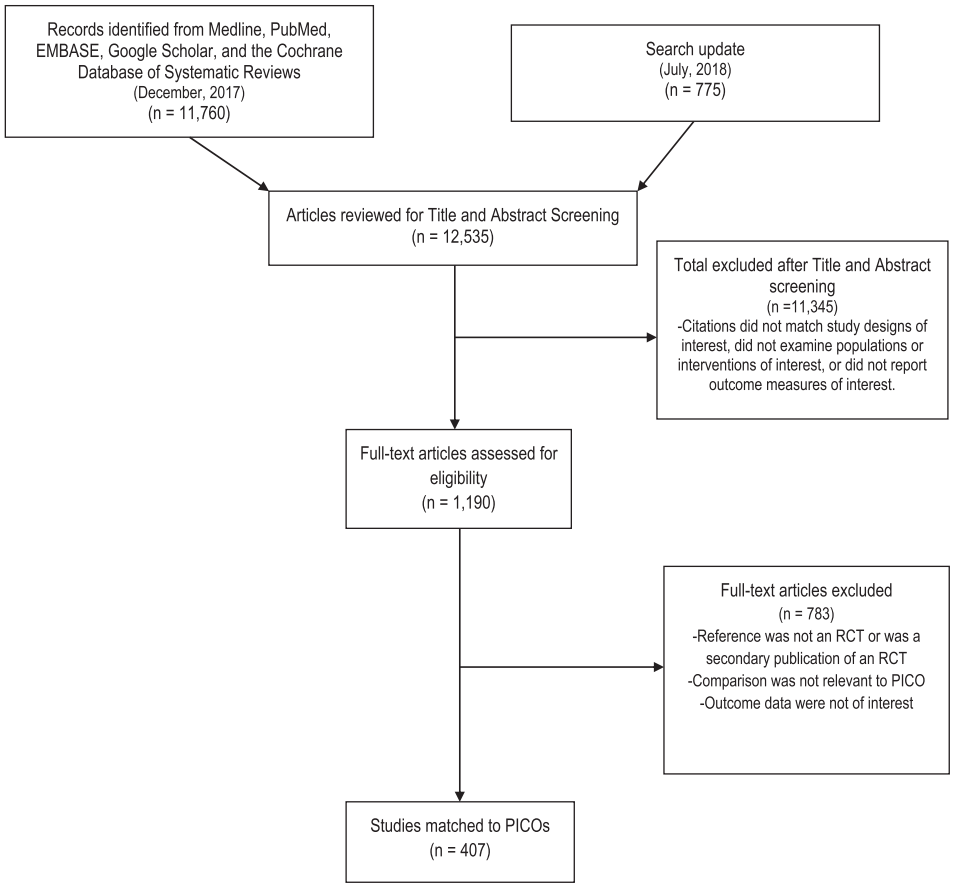

Fig. 1. Flowchart of the trial selection process.

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

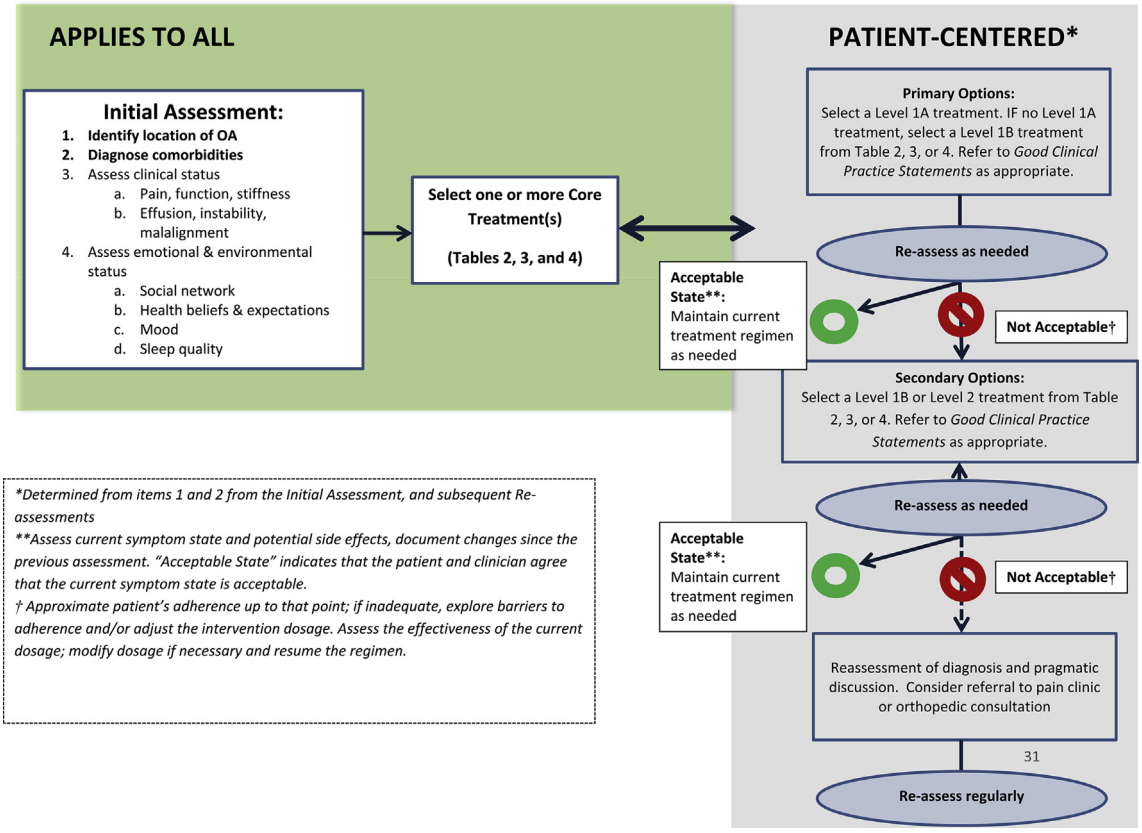

Fig. 2. Treatment algorithm.

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.

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