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Assessment of clinical practice guideline methodology for the treatment of knee osteoarthritis with intra-articular hyaluronic acid☆

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ABSTRACT

Introduction: Clinical practice guidelines are of increasing importance in the decision making for the treatment of knee osteoarthritis. Inconsistent recommendations regarding the use of intra-articular hyaluronic acid for the treatment of knee osteoarthritis have led to confusion among treating physicians.
Methods: Literature search to identify clinical practice guidelines that provide recommendations regarding the use of intra-articular hyaluronic acid treatment for knee osteoarthritis was conducted. Included guidelines were appraised using the AGREE II instrument. Guideline development methodologies, how the results were assessed, the recommendation formation, and work group composition were summarized.
Results: Overall, 10 clinical practice guidelines were identified that met our inclusion criteria. AGREE II domain scores were variable across the included guidelines. The methodology utilized across the guidelines was heterogeneous regarding the evidence inclusion criteria, analysis of evidence results, formulation of clinical practice recommendations, and work group composition. The recommendations provided by the guidelines for intra-articular hyaluronic acid treatment for knee osteoarthritis are highly inconsistent as a result of the variability in guideline methodology. Overall, 30% of the included guidelines recommended against the use of intra-articular hyaluronic acid in the treatment of knee osteoarthritis, while 30% deemed the treatment an appropriate intervention under certain scenarios. The remaining 40% of the guidelines provided either an uncertain recommendation or no recommendation at all, based on the high variability in reviewed evidence regarding efficacy and trial quality.
Conclusion: There is a need for a standard "appropriate methodology" that is agreed upon for osteoarthritis clinical practice guidelines in order to prevent the development of conflicting recommendations for intra-articular hyaluronic acid treatment for knee osteoarthritis, and to assure that treating physicians who are utilizing these guidelines are making their clinical decisions on the best available evidence. At present, the inconsistent recommendations provided for intra-articular hyaluronic acid treatment make it difficult for clinical professionals to determine its appropriateness when treating patients with knee osteoarthritis.

Introduction

Clinical practice guidelines (CPGs) have been developed as a teaching tool to help direct the treating healthcare professional in the care of their patients. They were initially developed heavily based on expert opinion. Although CPGs still involve an expert panel, they are increasingly evidence based. Hence, CPGs have a growing influence on clinical practice due to a movement toward the use of evidence-based medicine in clinical decision making [1]. Increasing healthcare costs are also a driving influence for the development of CPGs for clinical decision making, as a tool for limiting healthcare expenditure on treatments not proven to be effective [2]. Every patient requires treatment decisions based on their specific situation. CPGs are designed to provide information from available evidence to be considered by the treating physician and their patients when making a treatment decision, but they are not intended to create uniformity and replace treatment decisions of individual patients [3]. Hence, CPGs are intended to provide clinical benefit by educating physicians, other caregivers, and patients on the most effective documented available treatment methods. Unfortunately, there are limitations in the development

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and utilization of currently available guidelines [4]. These limitations are accentuated when more than one set of CPGs are developed on a condition.

Differences in the methods used in the development of the CPG often lead to inclusion of different evidence and techniques used in development of recommendations, creating inconsistent recommendations between guidelines for the same treatment [5]. In general, new CPGs are developed by a designed literature review with guidelines developed by a working group. The working group provides expert opinion on the integration of standards of clinical practice with a literature review. However, the expert opinions from the CPG working group can interject bias in recommendations based on anecdotal personal experience, or misinterpretation of the available evidence [4]. The potential for bias and misinterpretation from the CPG can be reduced but is not eliminated by utilizing a robust, multidisciplinary working group [6]. A potential area of bias is when patient preferences (an important factor in clinical decision making [7]) are not considered when guideline recommendations are formed. This could result in treatment recommendations that are developed based on low-cost implications or other societal impacts, not the sole demonstration of efficacy for the patient [4].

CPGs may vary in their quality, and the differentiation between high- and low-quality CPGs is essential in the dissemination of appropriate recommendations to clinical decision makers. Unfortunately, a lack of defined and generally accepted methodologies for CPG formation makes this differentiation difficult [5].

There has been a surge of CPG development on osteoarthritis (OA) treatment, perhaps reflecting the increasing prevalence of OA as a cause of disability, particularly in developed countries [1]. Several organizations developed their own CPGs for knee OA, and the quality of these guidelines is highly variable. Assessment tools such as the AGREE II tool have been created to aid in the evaluation of guideline quality [8], yet there is still no "standard" methodology for a group to utilize when formulating a CPG [5]. An example of the variable methodology used in guideline development with different conclusions and recommendations is evident in the proposed guidelines for the treatment of knee OA with intra-articular hyaluronic acid (IA-HA) [9–18].

The inconsistencies between CPG recommendations for the IA-HA treatment have brought the variability of methodology behind these guidelines into question [19]. In addition, the conflicting recommendations have led to confusion among treating physicians. This study aims to analyze the methodology used by the current CPGs for knee OA treatment using IA-HA, and compare the recommendation formulation process used by each of these CPGs. The treating physician can be better informed and directed by understanding the strengths and weaknesses of the present IA-HA guidelines for OA. We will attempt to bring some clarity to this issue.

Methods

Selection of guidelines

We conducted a comprehensive search of PubMed (Table 1) and multiple online sources to identify published guideline recommendations on the use of IA-HA treatment for the management of knee OA (Fig. 1). Specifically, we conducted additional online searches using Google, Yahoo, and National Guideline Clearinghouse. We used the following keywords in each of our searches: hyaluronic acid/hylan/hyaluronate/viscosupplementation, guideline, recommendation, and knee osteoarthritis. We then searched reference lists of the guidelines and articles identified and contacted multiple experts in order to attempt to ensure that we did not miss any relevant guidelines.

Table 1
PubMed search strategy

PubMed	Found articles
1. Osteoarthritis (title)	16,963
2. Treatment OR Recommendations (title)	8,371,303
3. Humans AND Osteoarthritis (MeSH terms)	38,960
4. Knee	117,257
5. 1 AND 2 AND 3 AND 4	4238
6. Guideline OR Recommendation	184,951
7. 5 AND 6	155

Guidelines were defined as "a set of systematically developed statements to assist practitioner and patient decisions about appropriate healthcare for one specific clinical condition or disease area" [20]. Publications that did not include recommendations for clinical practice on the management of knee OA (e.g., systematic reviews and service documents) were excluded. Since guidelines could change based on current information, only the most recent version of each guideline was included.

Assessment of quality of reporting

The AGREE II instrument was used to assess the quality of each guideline [8]. The AGREE II instrument was developed by the Appraisal of Guidelines Research and Evolution (AGREE) Collaboration. The AGREE instrument addresses 23 questions under six domains: (1) scope and purpose, (2) stakeholder involvement, (3) rigor of development, (4) clarity and presentation, (5) applicability, and (6) editorial independence. The AGREE instrument uses

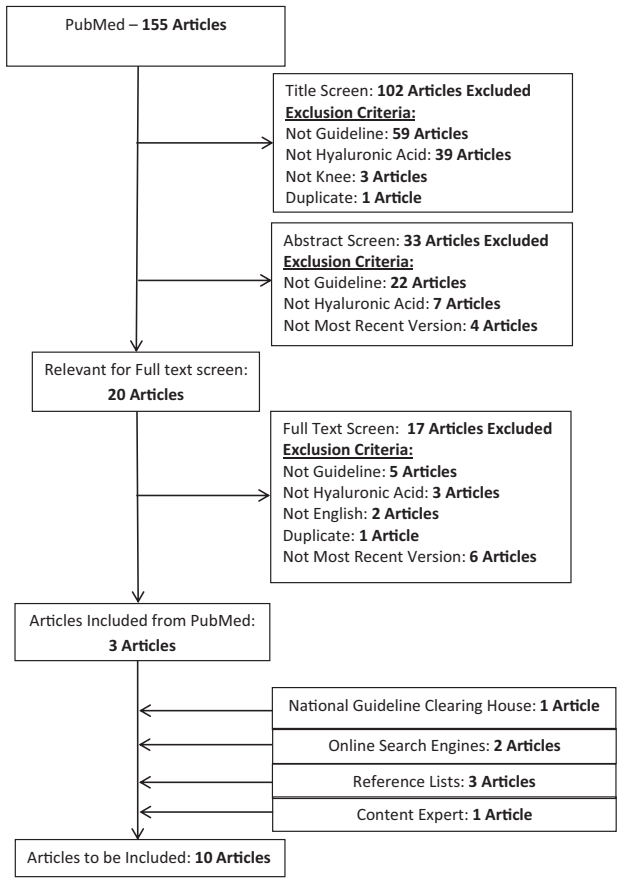


Fig. 1. Screening Process.

a 7-point Likert scale: ranging from "strongly agree" to "strongly disagree" [8].

In addition to the AGREE II criteria, the following variables were assessed with respect to recommendations for the use of IA-HA: (1) the strength of the clinical evidence included in the guideline, (2) model used for recommendation formation, (3) measurement tool of clinical significance, (4) consideration of patient opinion in formulating the recommendation, and (5) professions represented in the recommendation formulation group. The strength of the recommendation for the use of IA-HA for the treatment of knee OA was documented. Two reviewers (M.P. and E.N.) independently reviewed each guideline, and any disagreements were resolved via consensus. If consensus could not be reached, a third reviewer was consulted.

Analysis

For each guideline, mean scores for each of the six AGREE II domains were calculated as per the recommendations by the developers. The scores were standardized as a percentage of the maximum possible score for each domain using the following formula [20]:

$$\frac{(\text{score obtained} - \text{minimum possible score})}{(\text{maximum possible score} - \text{minimum possible score})} \times 100$$

As suggested by the instructions for the use of the AGREE II instrument, a single quality score was not derived for each guideline from the individual domain scores. Each domain of the AGREE II tool is reported independent from one another, as it is felt to be inappropriate to merge the scores into a single quality score [8]. Additionally, the aforementioned variables were analyzed and summarized for each guideline.

Results

Guideline characteristics and results

Our search strategy identified 10 guidelines focusing on the use of IA-HA for the management of knee osteoarthritis that met our inclusion criteria [9–18]. The guidelines were published between 2003 and 2014, and they were published in the United States (USA) (6 guidelines), United Kingdom (2 guidelines), Australia (1 guideline), and France (1 guideline) (Table 2). The publishing associations of the guidelines provide their services and guidelines to a variety of different member demographics: Osteoarthritis Research Society International (OARSI) has 1151 members distributed globally; American Academy of Orthopaedic Surgeons (AAOS) has 38,000 orthopedic surgeon members (86.5% US and 13.5% international); American College of Rheumatology (ACR) has 9317 members; American Academy of Family Physicians (AAFP) has 115,900 family physician members from the USA; Royal Australian College of General Practitioners (RACGP) has 26,000 members (over 22,000 of these members are general practitioners); National Collaborating Centre for Chronic Conditions (NCC-CC) is a department within the Royal College of Physicians, which has 29,472 members; and European League Against Rheumatism (EULAR) has

Table 2
Knee OA guideline details

Association	Year	Country	Recommendation	Members	Brief mission statement
Osteoarthritis Research Society International (OARSI)	2014	USA	Uncertain—varying quality of evidence and conflicting results	1151 Members distributed globally	Prevention and treatment of osteoarthritis through the promotion and presentation of research, education, and the worldwide dissemination of new knowledge
National Institute for Health and Care Excellence (NICE)	2014	UK	Do not recommend—uncertainty and varying quality throughout evidence. Hyaluronic acid is deemed to not be cost-effective	N/A, does not provide membership	Improve outcomes for people using the NHS and other public health and social care services
Veterans Affairs/ Department of Defense (VA/DoD)	2014	USA	Uncertain–insufficient evidence available; however, IA-HA may be considered if other treatment options are unsuccessful	N/A, does not provide membership	N/A, no applicable mission statement
American Academy of Orthopaedic Surgeons (AAOS)	2013	USA	Do not recommend—based on a lack of IA-HA efficacy, not potential harm. High variability in the quality of current evidence noted.	38,000 Orthopedic surgeons 86.5% US and 13.5% international	Serving (orthopedics) to provide the highest quality musculoskeletal care
American College of Rheumatology (ACR)	2012	USA	No recommendation made regarding the use of IA-HA for initial knee OA management; however, IA-HA is recommended for patients $\geq$75 that have not had satisfactory clinical response to acetaminophen	9317 Members	Advancing rheumatology
American Academy of Family Physicians (AAFP)	2012	USA	Recommended as a consideration for severe knee OA cases when other treatment options have been unsuccessful	115,900 Family physicians from USA	To improve the health of patients, families, and communities by serving the needs of members with professionalism and creativity
Royal Australian College of General Practitioners (RACGP)	2009	Australia	Grade C recommendation—there is some evidence to suggest that IA-HA is of some benefit for OA of the knee	26,000 Members > 22,000 GPs	To improve the health and well-being of all people in Australia by supporting GPs, general practice registrars, and medical students
National Collaborating Centre for Chronic Conditions (NCC-CC)	2008	UK	Do not recommend—Highly variable evidence regarding IA-HA efficacy, deemed not cost-effective	A department of the Royal College of Physicians, which has 29,472 members	A collaborative, multiprofessional center undertaking commissions to develop clinical guidance for the NHS in England and Wales
Agency for Healthcare Research and Quality (AHRQ)	2008	USA	Uncertain—due to variability in trial quality and unclear significance	N/A, does not provide membership	To produce evidence to make healthcare safer, higher quality, more accessible, equitable, and affordable
European League Against Rheumatism (EULAR)	2003	France	No recommendation made regarding the use of IA-HA for initial knee OA management; however, acknowledgement of potential efficacy	19 Healthcare organizations from various countries within Europe	To stimulate, promote, and support the research, prevention, treatment, and rehabilitation of rheumatic diseases

USA—United States of America, UK—United Kingdom, N/A—not applicable, GP—general practitioner, IA-HA—intra-articular hyaluronic acid, and OA—osteoarthritis.

provided memberships to 19 healthcare organizations throughout Europe. The Agency for Healthcare Research and Quality (AHRQ), Veterans Affairs/Department of Defense (VA/DoD), and National Institute for Health and Care Excellence (NICE) organizations do not provide membership options (Table 2). These associations have varying target audiences, with the primary focus including orthopedic surgeons, rheumatologists, and general practitioners.

Recommendations regarding the use of IA-HA varied across the guidelines (Table 2). Three of 10 (30.0%) guidelines recommend against the use of IA-HA in the treatment of knee OA [9,11,12]. Two of the guidelines that recommend against the use of IA-HA did so because the treatment was deemed "not cost-effective," as opposed to a lack of efficacy or potential harm [11,12]. The third guideline that strongly recommended against the use of IA-HA based on their recommendation on a lack of efficacy, not potential harm of the treatment [9].

Three of 10 (30.0%) guidelines recommended use of IA-HA in the treatment of knee OA [13,14,16]. The recommendations were based on specific scenarios in two of the guidelines: IA-HA is to be considered for patients $\geq$75 years old who have not had satisfactory clinical response to acetaminophen treatment [13], and IA-HA is to be considered for moderate to severe cases of knee OA when other treatment options have been unsuccessful [14]. The third guideline states that IA-HA should be considered as a knee OA treatment due to the representation of some clinical benefit within the reviewed evidence [16].

Three of 10 (30.0%) guidelines describe their recommendation of IA-HA as "uncertain" [10,17,18]. These guidelines do not definitively recommend for or against IA-HA due to the high variability in the available evidence regarding efficacy and trial quality, as well as the lack of available evidence. Additionally, one of the 10 (10.0%) guidelines did not provide any recommendation regarding the use of IA-HA as a treatment for knee OA [15]. This guideline did acknowledge the potential efficacy of IA-HA within the evidence but did not include an explicit recommendation for its use.

AGREE II guideline appraisal

Each guideline was independently appraised by two reviewers (M.P. and E.N.), using the AGREE II appraisal tool [8]. The mean scores and standard deviation for all 6 domains within the AGREE II instrument were calculated as outlined in the methods (Table 3). Most guidelines scored poorly in the "Applicability" domain, while most guidelines scored well in the "Scope and Purpose" domain. Scores were variable across the guidelines with respect to each domain, suggesting a high variability in guideline quality. Typically the OARSI, NICE, AAOS, and NCC-CC guidelines scored higher than the other guidelines. The NICE and NCC-CC guidelines scored highest in the "Applicability" domain mainly due to the inclusion of resource implications within these two guidelines, while most other guidelines did not provide this information. The generally low scores in the "Applicability" domain also arose from a lack of reporting of facilitators and barriers for guideline application.

Review of guideline development methodology

The developers of each of the guidelines utilized different methodologies, which may account for the different recommendations. The inclusion criteria for each guideline are variable, resulting in inconsistent evidence pools used to determine recommendations. Fig. 2 provides a summary of the evidence used by each guideline in comparison to the evidence found in the 2012 systematic review by Rutjes et al. [21], in the 2006 systematic review by Bellamy et al. [22], and in a comprehensive search of trial reference lists (considered to be "All Available Evidence" in Figure 1). The "All Available Evidence" pool consists of 25 systematic reviews and 110 RCTs. The evidence used by each guideline to form their recommendations was as follows: OARSI used three systematic reviews as the basis for their recommendation, NICE used one systematic review and 24 additional RCTs, VA/DoD used one systematic review and four RCTs, AAOS used 20 RCT's, ACR used three systematic reviews, AAFP used two systematic reviews, RACGP used one systematic review and three RCT's, NCC-CC used one systematic review and six RCT's, AHRQ used seven systematic reviews, and EULAR used eight RCTs (Fig. 2). The majority of the guidelines [8 of 10 (80.0%)] included the results from systematic reviews in their recommendation formulation [10–14,16–18], while two of 10 (20.0%) did not consider results from systematic reviews when determining their recommendation [9,15]. Figure 2 provides an overview of the evidence included in each of the systematic reviews within "All available evidence" [21–45]. Included evidence was highly variable across all guidelines, demonstrating that there are no standard inclusion criteria when formulating a guideline regarding the use of IA-HA (Fig. 3).

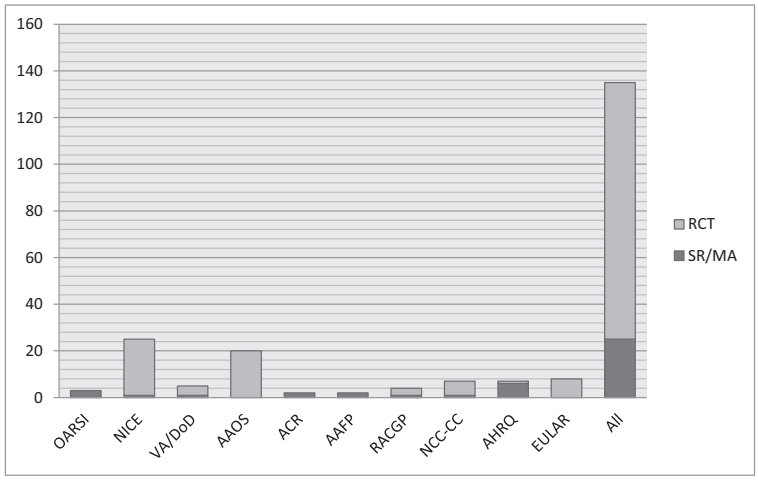
The reported limitations of the evidence of IA-HA treatment are presented in Table 4. Four of 10 guidelines (40.0%) indicate that a lack of inconsistent trial results limit the credibility of the body of evidence [10,14,17,18]. Six of 10 (60.0%) guidelines describe high variability in trial quality as a limitation in the evidence [9–12,16,17]. Inadequate differentiation between the results of specific IA-HA products was reported to be a limitation of the evidence in three of 10 (30.0%) guidelines [15–17]. One of 10 (10.0%) guidelines presented variability of safety data for IA-HA as a limitation in the body of evidence [10].

The guideline developers also utilized a variety of methodological assessments to formulate their recommendations

Table 3
AGREE II checklist scores for knee OA guidelines

Guideline	Scope and purpose (mean %, SD)	Stakeholder involvement (mean %, SD)	Rigor and development (mean %, SD)	Clarity of presentation (mean %, SD)	Applicability (mean %, SD)	Editorial independence (mean %, SD)
Osteoarthritis Research Society International (OARSI)	86.11 ± 19.64	80.55 ± 19.64	86.46 ± 4.42	100 ± 0	22.915 ± 32.41	100 ± 0
National Institute for Health and Care Excellence (NICE)	100 ± 0	100 ± 0	91.66 ± 0	88.88 ± 7.85	70.83 ± 5.89	95.83 ± 5.89
Veterans Affairs/Department of Defense (VA/DoD)	80.55 ± 11.78	75.00 ± 11.79	59.38 ± 1.48	77.78 ± 0	29.17 ± 0	58.34 ± 11.79
American Academy of Orthopaedic Surgeons (AAOS)	94.44 ± 7.86	86.11 ± 3.92	93.75 ± 0	100 ± 0	22.92 ± 20.62	100 ± 0
American College of Rheumatology (ACR)	77.78 ± 31.43	74.99 ± 3.92	72.22 ± 7.86	72.22 ± 23.57	18.75 ± 26.52	50 ± 0
American Academy of Family Physicians (AAFP)	27.78 ± 23.57	13.89 ± 11.79	27.08 ± 0	55.55 ± 31.42	35.4 ± 20.65	37.5 ± 17.68
Royal Australian College of General Practitioners (RACGP)	88.89 ± 15.72	88.89 ± 7.86	86.46 ± 10.32	97.22 ± 3.93	33.33 ± 11.78	75 ± 35.36
National Collaborating Centre for Chronic Conditions (NCC-CC)	83.33 ± 23.57	94.44 ± 0	80.21 ± 4.42	94.44 ± 0	77.08 ± 20.62	70.83 ± 29.46
Agency for Healthcare Research and Quality (AHRQ)	100 ± 0	66.66 ± 39.29	67.71 ± 16.20	41.66 ± 35.36	25 ± 11.79	75 ± 35.36
European League Against Rheumatism (EULAR)	91.67 ± 11.79	66.66 ± 31.42	72.79 ± 14.91	83.33 ± 15.71	43.75 ± 2.95	20.83 ± 29.46

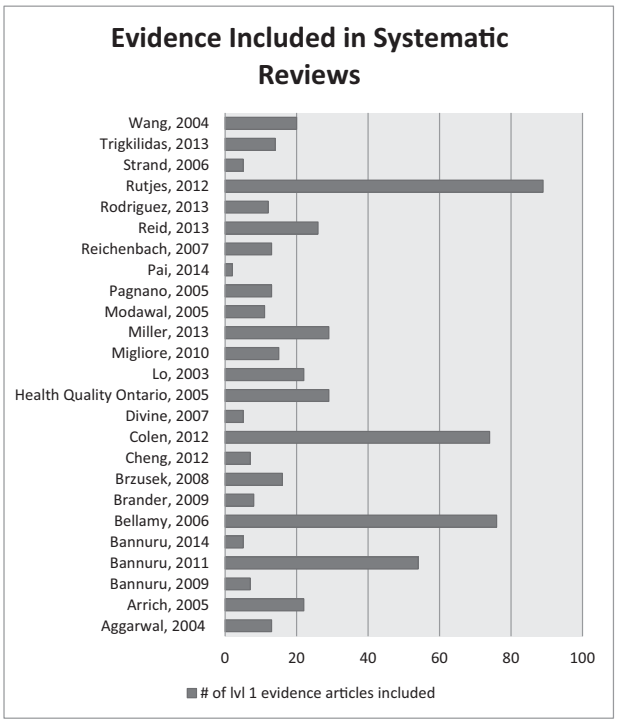
SD—standard deviation.



RCT – Randomized controlled trial, SR – Systematic review, MA – Meta-analysis, OARSI - Osteoarthritis Research Society International, NICE - National Institute for Health and Care Excellence, VA/DoD - Veterans Affairs/ Department of Defense, AAOS - American Academy of Orthopaedic Surgeons, ACR - American College of Rheumatology, AAFP - American Academy of Family Physicians, RACGP - Royal Australian College of General Practitioners, NCC-CC - National Collaborating Centre for Chronic Conditions, AHRQ - Agency for Healthcare Research and Quality, EULAR - European League Against Rheumatism
** All available evidence column derived from Rutjes, 2012[21] and Bellamy, 2006[22] , as well as hand-selected articles.*

Fig. 2. Evidence included in recommendation formation.
RCT—randomized controlled trial, SR—systematic review, MA—meta-analysis, OARSI—Osteoarthritis Research Society International, NICE—National Institute for Health and Care Excellence, VA/DoD—Veterans Affairs/Department of Defense, AAOS—American Academy of Orthopaedic Surgeons, ACR—American College of Rheumatology, AAFP—American Academy of Family Physicians, RACGP—Royal Australian College of General Practitioners, NCC-CC—National Collaborating Centre for Chronic Conditions, AHRQ—Agency for Healthcare Research and Quality, EULAR—European League Against Rheumatism.
*All available evidence column derived from Rutjes et al. [21] and Bellamy et al. [22], as well as hand-selected articles.

(Table 5), providing variable results from an inter-guideline analysis perspective. Half [5 of 10 (50.0%)] of the guidelines used a standardized mean difference as the measure of efficacy when forming recommendations [10,11,13,15,17]. Two of the 10 (20.0%) guidelines used a minimum clinically important improvement (MCII) to assess efficacy results [9,17], 2 of the 10 (20.0%) guidelines calculated a weighted mean difference [12,17], one (10.0%) guideline considered Quality Adjusted Life-Years (QALY) [12], one (10.0%) guideline used an expert review and opinion process to deem significance, and one (10.0%) guideline used the National Health and Medical Research Council (NHMRC) body of evidence assessment matrix to analyze the efficacy results from the evidence that met inclusion criteria [16]. One guideline (10.0%) did not provide any specific methodological assessments used when formulating their recommendations [14]. This variability in methodology suggests that there is not standard, universally accepted procedure for the evidence assessment for an association who is formulating guideline recommendations for knee OA.



lvl – level

Fig. 3. Evidence included in IA-HA systematic reviews and meta-analyses. lvl = level.

The guidelines also used multiple recommendation formulation tools when transitioning from the available evidence to a clinical recommendation (Table 5). The NICE and ACR guidelines used the GRADE recommendation tool to derive clinical recommendations [11,13], while the OARSI and EULAR guidelines used a Delphi method [10,15] (The OARSI guideline used a combination of RAND/UCLA Appropriateness method and Delphi methods). The VA/DoD guideline utilized the US Preventive Services Task Force (USPSTF) grading system. The AAOS guideline developed and utilized a unique system of evidence quality assessment and recommendation formation derived from their criteria and methodology [9]. The RACGP guideline used the NHMRC's "Additional levels of evidence and grades for recommendations for developers of guidelines" criteria. The NCC-CC guideline used recommendation methods taken from the 2007 NICE guideline manual, the "creating guideline recommendations" chapter. The AHRQ recommendations were derived on expert opinion regarding the pooled trial results from the included evidence, and the AAFP did not explicitly define their methodology in formulating IA-HA recommendations.

The guidelines were also inconsistent in their representation of all relevant clinical professionals within the recommendation work group (Table 5). The guidelines utilized experts from orthopedics [8/10 guidelines (80.0%)], rheumatology [9/10 guidelines (90.0%)], general practice/family medicine [8/10 guidelines (80.0%)], rehabilitation [6/10 guidelines (60.0%)], geriatrics [3/10

Table 4
Reported limitations within the IA-HA treatment body of evidence

Association	Inconsistent trial results	Variable trial quality	Inadequate differentiation between product results	Inconsistent safety profiles
Osteoarthritis Research Society International (OARSI)	Yes	Yes	No	Yes
National Institute for Health and Care Excellence (NICE)	No	Yes	No	No
Veterans Affairs/Department of Defense (VA/DoD)	Yes	No	No	No
American Academy of Orthopaedic Surgeons (AAOS)	No	Yes	No	No
American College of Rheumatology (ACR)	No	No	No	No
American Academy of Family Physicians (AAFP)	Yes	No	No	No
Royal Australian College of General Practitioners (RACGP)	No	Yes	Yes	No
National Collaborating Centre for Chronic Conditions (NCC-CC)	No	Yes	Yes	No
Agency for Healthcare Research and Quality (AHRQ)	Yes	Yes	No	No
European League Against Rheumatism (EULAR)	No	No	Yes	No

Yes—guideline has reported as a limitation, No—guideline did not report as a limitation.

guidelines (30.0%)], nursing [4/10 guidelines (40%)], and pharmacology [2/10 guidelines (20.0%)]. The ACR CPG also included a pain specialist [13]. In addition to the variability in work group composition, the inclusion of patient advocates within the work group was seen within four of 10 guidelines (40.0%).

Discussion

We identified and appraised 10 published CPGs for IA-HA treatment of knee OA, which provided inconsistent recommendations. The included guidelines varied greatly in terms of AGREE II domain scores, displaying inconsistent quality of reporting throughout the guidelines for this treatment. The primary limitation of most guidelines was within the "Applicability" domain of the AGREE II tool, as these guidelines generally lacked information regarding barriers to the guidelines application, potential resource implications of the recommendations provided, tools for putting the guideline into practice, and monitoring/auditing criteria. There was a large difference in scores between guidelines within the "Editorial Independence" domain, mainly due to the inconsistent reporting of competing interests of work group members. The inconsistent AGREE II scores for the guidelines within all six domains recorded demonstrate the wide range of quality within the available CPG literature regarding IA-HA injection for knee OA.

As well as inconsistent AGREE II scores, the methodological processes utilized in CPG development by each organization was

Table 5
Knee OA guideline methodology

Guideline	Measure of clinical significance	Model for recommendation formulation	Consideration of patient opinion	Clinical members of work group
Osteoarthritis Research Society International (OARSI)	SMD	RAND/UCLA Appropriateness method and Delphi method	Patient advocate included in work group	Rheumatologists, Orthopedic surgeons, physiotherapists, primary care physician, rehabilitation specialist, and patient advocate
National Institute for Health and Care Excellence (NICE)	SMD	GRADE-derived software "GRADEpro"	Patient advocate included in work group	Rheumatologists, Orthopedic surgeons, general practitioners, geriatrician, pharmacist, registered nurse, and patient advocates
Veterans Affairs/Department of Defense (VA/DoD)	Expert Opinion	USPSTF rating system	No patients in work group	Rheumatologists, orthopedic surgeon, registered nurse, nurse practitioner, rehabilitation specialist, chiropractor, and pharmacist
American Academy of Orthopaedic Surgeons(AAOS)	MCII	AAOS system of evidence quality assessment and recommendation formulation	No patients in work group	Orthopedic surgeons, rheumatologists, physiotherapist, and family physician
American College of Rheumatology (ACR)	SMD	GRADE approach	No patients in work group	Primary care physicians, rheumatologists, orthopedic surgeon, physiatrists, geriatricians, physical, and occupational therapists
American Academy of Family Physicians (AAFP)	Not defined within guideline	Not defined within guideline	No patients in work group	Single author and family physician
Royal Australian College of General Practitioners (RACGP)	NHMRC body of evidence assessment matrix	NHMRC additional levels of evidence and grades for recommendations for developers of guidelines	Patient advocate included in work group	Rheumatologists, general practitioner, registered nurse, physiotherapist, and patient advocate
National Collaborating Centre for Chronic Conditions(NCC-CC)	WMD and QALY	NICE guideline manual, 2007 "Creating guideline recommendations" methods	Patient advocate included in work group	Rheumatologists, general practitioner, physiotherapist, geriatrician, orthopedic surgeons, and patient advocate
Agency for Healthcare Research and Quality (AHRQ)	SMD, WMD, and MCII	Expert analysis of pooled trial results	No patients in work group	Orthopedic surgeons, rheumatologists, registered nurse, and family physician
European League Against Rheumatism (EULAR)	SMD	Five-stage Delphi questionnaire technique	No patients in work group	Rheumatologists and orthopedic surgeons

SMD—standardized mean difference, MCII—minimum clinically important difference, WMD—weighted mean difference, USPSTF—US Preventive Services Task Force, NHMRC—National health and medical research council, QALY—quality adjusted life year, NICE—National Institute for Health and Care Excellence, AAOS—American Academy of Orthopaedic Surgeons, RAND—Research And Development Company, UCLA—University of California Los Angeles, GRADE—grading of recommendations assessment, development, and evaluation.

highly heterogeneous. Comparisons between the recommendations provided and methodology of guidelines convey uncertainty as to the appropriateness of the methodology used. A highly heterogeneous pool of relevant evidence was included by each guideline, demonstrating a lack of universally accepted inclusion criteria for evidence when formulating a CPG for IA-HA treatment of knee OA. As a result of heterogeneous evidence inclusion throughout the guidelines, inconsistent recommendations regarding the efficacy and safety of IA-HA were formulated by the guidelines. The guidelines differ in their recommendations regarding safety, efficacy, evidence quality, and consistency of trial results. The AAOS, NICE, and NCC-CC guidelines all provided recommendations against the use of IA-HA; however, their reasoning for these recommendations is generally conflicting. The AAOS recommendation was based on a strong backing by a posthoc data analysis, demonstrating a lack of efficacy within the selected trials of IA-HA treatment [9]. In contrast, the NICE and NCC-CC guidelines suggested some potential efficacy of IA-HA treatment; however, the variability in trial quality made these results unclear. Instead, NICE and NCC-CC recommended against IA-HA treatment based on cost-effectiveness, and not efficacy [11,12]. It was generally agreed upon throughout the guidelines that the safety profile of IA-HA treatment was acceptable; however, OARSI suggested that a lack of definitive safety evidence was a factor in the work group's recommendation decision [10]. The heterogeneity of the evidence utilized by each guideline resulted in conflicting and inconsistent recommendations regarding the use of IA-HA treatment.

Further inconsistencies within the guidelines arose from variable methodologies in assessment of clinical significance from the included evidence. No clear “standard” method is available for assessing trial outcomes, leaving each organization to decide which assessment methodology they believe to be the most appropriate. This lack of a standard methodology results in conflicting opinions regarding the appropriateness of potential assessment methods. Although five of 10 guidelines used a standardized mean difference as an assessment of trial outcomes, there was not a consistent agreement on the most appropriate assessment. The AAOS described assessment of trial outcomes using minimum clinically important improvement (MCII) and minimum clinically important difference (MID) derived values from Tubach et al. [46] and Angst et al. [47] as the most appropriate method of trial outcome assessment [9,19]; however, the NICE guideline criteria explicitly states that its work group believed that MID values such as those from Tubach et al. [46] are not appropriate for the purposes of meta-analysis and guideline development [11]. Heterogeneity in recommendation formation was also noted, as the modes in which the working group formulated their clinical recommendations for each CPG were inconsistent.

In order to limit the potential for personal experience bias and evidence misinterpretation in CPG formation, it has been suggested that a robust and multidisciplinary working group should be used in CPG development [6]. The organizations that formed the included guidelines varied largely in what they believed to be a robust and multidisciplinary work group. The work groups varied with from the inclusion of one to seven represented clinical professions, demonstrating an unclear standard of professions to be included in the work group for knee OA CPGs. The consideration of patient values and preferences is a key factor in clinical decision making [4,7]; however, many guidelines neglected to include a patient advocate within the CPG formulation process.

Previous reports have highlighted the variability in knee OA CPG quality [48,49]. These reports have used the AGREE guideline appraisal tools to demonstrate that current CPGs are variable in their quality, which is consistent with the findings of our report. Previous work has described the differences in the methodologies utilized in CPG development for knee OA as well. The strengths and weaknesses of commonly used recommendation formation methodologies have been outlined [50]; however, consensus regarding the most appropriate methodology is lacking. The current report has aimed to address these issues for IA-HA CPG recommendations. Furthermore, other authors have reported that incorporation of patients in CPG development and making clear tools for recommendation implementation are important for increasing the validity and effectiveness of CPGs in knee OA [48,50]. It has also been suggested that in the guideline development process, working groups should follow the AGREE II checklist to ensure the resulting CPG will be of acceptable quality [48].

The current appraisal is limited by the low potential for reproduction of the search strategy used to identify relevant guidelines. A very general search was used to identify CPGs for knee OA that specifically addressed the use of IA-HA treatment. This search was used because of its efficiency in finding CPGs directly addressing IA-HA use, as systematic searches of databases provided numerous CPGs that did not address this treatment specifically. We believe that this search was successful, capturing the appropriate high-impact guidelines within the knee OA field. The current appraisal is strengthened by is its comprehensive analysis of the methodology used by current knee OA CPGs in addition to the use of the AGREE II assessment tool. Many of the previously published guideline appraisals utilize quality assessment tools such as the AGREE II system but do not report on the variability in trial methodology used throughout the guidelines. As the AGREE II tool does not address inter-guideline variability in methodology, this study provides a beneficial analysis of the heterogeneity in guideline development.

Conclusion

The general lack of a standard and consistent methodology in evidence inclusion, evidence assessment, recommendation formation, and work group composition for CPG development are seen to be the causes of inconsistent CPG recommendations, regarding IA-HA treatment for knee OA. The lack of consensus within the IA-HA treatment recommendations makes it difficult for clinicians to identify which guidelines should be followed when deciding to treat knee OA with IA-HA. Clinicians should use caution when adhering to CPGs that provide strong recommendations based on methodologies that are not consistent throughout the available CPG literature. Strong recommendations formulated using methodologies that have no consensus throughout available CPGs result in inconsistent opinions regarding the appropriateness of IA-HA treatment. The variability in opinion regarding IA-HA appropriateness caused by the inconsistent CPG methodologies and recommendations leads to confusion among clinicians, consequently leading to decreased patient access to available treatments. There is a need for an agreed upon standard “appropriate methodology” for OA CPG development in order to prevent the development of conflicting recommendations for IA-HA treatment for knee OA and assure that clinical professionals and patients utilizing these guidelines are making the most appropriate decisions as possible.

Disclosures

Roy Altman is a consultant for Cytori, DuPuy, Ferring, Flexion, Iroko, Novartis, Oletec, Pfizer, Q Med, Rotta, Strategic Science & Technologies, and Teva. Asheesh Bedi is a consultant for Smith & Nephew, and an A3 Shareholder. Emil Schemitsch is a consultant for Sanofi.

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