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An updated algorithm recommendation for the management of knee osteoarthritis from the European Society for Clinical and Economic Aspects of Osteoporosis, Osteoarthritis and Musculoskeletal Diseases (ESCEO)

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ABSTRACT

Objectives: The European Society for Clinical and Economic Aspects of Osteoporosis, Osteoarthritis and Musculoskeletal Diseases (ESCEO) sought to revisit the 2014 algorithm recommendations for knee osteoarthritis (OA), in light of recent efficacy and safety evidence, in order to develop an updated stepwise algorithm that provides practical guidance for the prescribing physician that is applicable in Europe and internationally.

Methods: Using the Grading of Recommendations Assessment, Development and Evaluation (GRADE) process, a summary of evidence document for each intervention in OA was provided to all members of an ESCEO working group, who were required to evaluate and vote on the strength of recommendation for each intervention. Based on the evidence collected, and on the strength of recommendations afforded by consensus of the working group, the final algorithm was constructed.

Results: An algorithm for management of knee OA comprising a stepwise approach and incorporating consensus on 15 treatment recommendations was prepared by the ESCEO working group. Both "strong" and "weak" recommendations were afforded to different interventions. The algorithm highlights the continued importance of non-pharmacological interventions throughout the management of OA. Benefits and limitations of different pharmacological treatments are explored in this article, with particular emphasis on safety issues highlighted by recent literature analyses.

Conclusions: The updated ESCEO stepwise algorithm, developed by consensus from clinical experts in OA and informed by available evidence for the benefits and harms of various treatments, provides practical, current guidance that will enable clinicians to deliver patient-centric care in OA practice.

Abbreviations: ASU, avocado soybean unsaponifiables, CS, chondroitin sulfate; IAHA, intra-articular hyaluronic acid; NSAIDs, non-steroidal anti-inflammatory drugs; OA, osteoarthritis; pCGS, prescription crystalline glucosamine sulfate; SYSADOAs, symptomatic slow-acting drugs for osteoarthritis.

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Introduction

Osteoarthritis (OA) is the most common form of arthritis, and is characterized by joint pain and stiffness leading to functional decline and loss in participation and quality of life [1,2]. The incidence of OA is rising due to the aging population and an increase in obesity [3]. Knee OA is the most common OA localization, and symptomatic knee OA is highly prevalent among people aged over 50 years, affecting more than 250 million people worldwide [4]. OA is a leading cause of pain in older people, and pain of the hip and knee results in physical disability and an increased risk of all-cause mortality [2,5]. Hip and knee OA together are the eleventh highest contributor to global disability: the years of life lived with OA-related disability increased by 64% from 1990 to 2010 reaching 17 million [6]. OA is a progressive disorder, with different degrees of severity, that requires long-term management with various treatment options over the course of the disease. The goals of treatment for OA are to reduce symptoms and ultimately slow disease progression, which may in turn reduce the impact of OA on the patient's mobility and quality of life, with consequent reduction in healthcare resource needs.

In 2014, the European Society for Clinical and Economic Aspects of Osteoporosis, Osteoarthritis and Musculoskeletal Diseases (ESCEO) published recommendations for the management of knee OA in the form of a treatment algorithm that provides practical guidance for the prioritization of interventions and guides physicians through progressive, logical steps [7]. The ESCEO algorithm differed from previous guideline development which had analyzed the level of evidence behind each intervention without prioritizing the interventions in a given sequence [8–11]. While the ESCEO guidelines were written predominantly from a European perspective, since 2014, the ESCEO algorithm has been well-received internationally, and endorsed by many societies worldwide with translation, adaptation to the local context, and publication in China, Russia and South-East Asia [12–15]. An update to the ESCEO algorithm was published in 2016 as a supplement to this journal, when further data for selected pharmacological interventions in OA and from real world analyses had become available [16]. Since publication of the 2014 algorithm, considerable new evidence has been published, particularly regarding the safety of many medications commonly used to treat OA. The ESCEO itself identified a need for comprehensive safety data, and commissioned several meta-analyses on different classes of anti-OA medications [17–21]. While conducting the safety meta-analyses, the extensive literature reviews revealed a lack of reporting of AE data and inconsistencies in the data reported, and a need for precise guidance on the reporting of AEs in clinical trials was identified. As a result, a recent consensus statement from the ESCEO provides specific, clear, practical and standardized guidance on the reporting of AE data in manuscripts reporting the outcomes of clinical trials assessing drugs for OA [22].

In this update, a working group of the ESCEO has revisited the ESCEO treatment algorithm recommendations in light of recent efficacy and safety evidence, and has developed new recommendations based upon application of the Grading of Recommendations Assessment, Development and Evaluation (GRADE) process [23]. To this end, the ESCEO working group now delivers an updated stepwise algorithm of recommendations in order to provide practical, current guidance that will enable clinicians to deliver patient-centric care in OA practice.

Methods

The ESCEO gathered an international working group of 18 members comprising rheumatologists, specialists in physical medicine and rehabilitation, clinical epidemiologists, endocrinologists, pharmacologists, orthopedic surgeons, geriatricians, specialists in public health and health economics, research scientists and patient representatives, all of whom are experienced in the performance, analysis and interpretation of clinical trial evidence related to OA. All experts in the working group were invited to a meeting held on March 20, 2018 in Geneva, Switzerland, where some members of the working group (OB, EC, GH-B. FR, DU, GH) gave presentations on a full review of the ESCEO 2014 algorithm recommendations and specific areas of knee OA treatment that required particular attention in light of new data on efficacy and safety. After the presentations, a comprehensive discussion was held within the group to address the areas requiring attention. Some members of the working group (NV, GH, EC, OB) were presented with the task of performing a full literature search on all interventions considered in the last algorithm and any other interventions subsequently approved or made available for knee OA, i.e. covering the period from publication of the last guidance document (2014) through to September 30, 2018. The purpose of the literature search was to identify the most recent, complete and representative systematic reviews and meta-analyses for each intervention that could support the development of specific questions to the working group with the intention of building the new version of the ESCEO algorithm recommendations. Particularly relevant randomized controlled trials (RCTs), especially if they were not included in any meta-analysis as yet, or other forms of clinical evidence, were also identified in the literature search. The search was conducted using a combination of keywords and controlled terms describing the study types (meta-analysis, systematic review, clinical trial) and the disease (OA). The following electronic databases were searched: MEDLINE (via Ovid), EMBASE, the Cochrane Central Register of Controlled Trials (Ovid CENTRAL) and the Cochrane Database of Systematic Reviews (CDSR via Ovid), adapting the search terms to each database vocabulary. When data on efficacy and/or safety outcomes were appropriate for analysis, the systematic reviews/meta-analyses were assessed using the GRADE system by two members of the working group (NV, GH) (http://www.gradeworkinggroup.org/) [23,24]. The findings of network meta-analyses were assessed by GRADE only if direct comparisons were reported. If this condition was not fulfilled, their general findings could not be analyzed by GRADE since the methods are not well developed as yet; in this case, their results were only reported descriptively. GRADE evidence profiles and quality assessments for suitable publications were created using the GRADEpro software (https://gradepro.org/) [25].

A Summary of Evidence document for each intervention was provided to all members of the working group and consisted of the following sections: (a) 2014 Status: a summary of the considerations that were included in the 2014 algorithm publication and led to the algorithm construction at that time, to be assessed before the updated literature search; (b) 2014–2018 Search Results: a description of the selected recent findings in the new literature search; (c) GRADE Evidence Profiles: consisting of the tables generated using the GRADE software for new qualifying studies and including the summary of findings and quality assessment by an explicit judgment of factors that determine the quality of evidence (certainty assessment) and the magnitude of effect for each outcome; (d) References.

All members of the working group were provided with the GRADE Grid (electronically) for all questions derived from the Summaries of Evidence. Recommendations were based on an integrated assessment of past and current evidence, including balance and magnitude of effect for important outcomes of both benefits and harms, quality of evidence (the higher the quality of evidence, the more likely a strong recommendation), value and preferences, costs (even if a formal assessment of costs was not provided to the panel members) [26], and position of the intervention within the algorithm. The instructions to the working group, the final Summary of Evidence documents and the GRADE Grid, are presented in **Appendices A, B** and **C**, respectively (**electronic supplementary material**). The votes of the ESCEO working group members were expressed anonymously to allow for free expression of views.

Consensus on each question/intervention was defined if at least 75% of the members of the working group were either "strongly" or "weakly" in favour or against the recommendation [26,27]. If this criterion was not met, a consensus could not be defined and a "No recommendation" was to be attributed to the question/intervention; however, this was never necessary. The strength of recommendation was determined as "strong" rather than "weak" if at least 75% of the working group members rated a recommendation as "strong".

Based on the evidence collected and on the strength of the recommendations by the working group (results of the GRADE process are presented in Table 1), the final algorithm was built and the draft manuscript prepared. This was submitted to all members of the working group through repeated rounds of comment and revision until a final version of the manuscript was accepted by all members of the working group.

Results

Non-pharmacological treatment: basic principles and core set

The combination of treatment modalities including non-pharmacological and pharmacological intervention remains key to the management of knee OA and it is the basic principle in the ESCEO algorithm, which provides advice for treatment prioritization and possible combination.

The core set of initial and continued measures that was endorsed in the ESCEO 2014 algorithm is still valid: information/education; weight loss if overweight [28]; and an exercise program (i.e. aerobic, strengthening, or resistance exercises) [7,29–32]. However, the working group acknowledges that there remains some debate regarding the optimal modalities of these approaches, their real effect size (ES) on pain and joint function [33,34], and their feasibility in the long term [35]. Further, it is recognized that such recommendations on exercise for knee OA also apply to subjects aged 70–80 years, even though there is a paucity of data on the benefit: risk of exercise and diet programs among older populations, particularly those aged ≥75 years [36].

GRADE recommendation: (1) The ESCEO working group affords a strong recommendation to the application of a core set comprising: information access/education, weight loss and an exercise program, which is applicable throughout the management of knee OA.

Other non-pharmacological interventions

In the 2014 version of the ESCEO algorithm, other non-pharmacological treatments for knee OA were briefly reviewed [7]. It was recommended that, in Step 1 of background treatment and after adhering to the basic principle and core set, patients should be referred to a physical therapist or another specialist for assessment of whether correction for varus/valgus malalignment is needed [37,38]. A correction with knee braces seems to be preferred to wedged insoles [38]. Moreover, during this step or afterwards and across steps at any time, this working group maintains the recommendation that assessment of whether other physical interventions may be useful for additional symptom relief in combination with pharmacological interventions should be carried out. A comprehensive review of non-pharmacological interventions goes beyond the scope of this article and was, in the meantime, performed by several specialized groups [10,29,30,32,39–41]. A non-comprehensive list of possible non-pharmacological interventions, supported by variable degrees of evidence, is listed in Fig. 1.

While the ES of non-pharmacological modalities may be measured as low, these interventions are generally considered as safe [10]. However, in practice, non-pharmacological treatments are under-utilized. Healthcare providers (HCPs: rheumatologists, orthopedic surgeons, physical therapists and general practitioners) report three main barriers impeding non-pharmacological, non-surgical care for patients with knee and hip OA including: lack of expertise of the healthcare professional (knowledge and skills); lack of evidence-based treatment (e.g. regarding weight management, and the intensity and dosage of physical exercise in the core set); and suboptimal organization of care [42]. To overcome these barriers, education focused on initiating and supporting lifestyle changes, promotion of interventions according to evidence-based recommendations, and improved organization of care is proposed [42]. For the patient, barriers also exist particularly for physical activity and exercises since patients are often experiencing a lot of pain, and preliminary pain relief is mandatory to allow for practicing exercises and physical activity. Barriers may be overcome through positive exercise experiences, changing beliefs, knowledge and attitudes, and by having the support of HCPs and social services. Lastly, the program should be personalized and adjusted to the characteristics of the patient [31] and their environment [43].

Pharmacological treatment

Step 1: background treatment

Paracetamol (acetaminophen) has been widely recommended as a first-line step for rescue analgesia, despite the fact that the effect of paracetamol on symptoms is minimal [8–11,44]. The ESCEO doubtfully recommended paracetamol on a regular basis in the 2014 algorithm version [7]. Paracetamol has a minimal ES on pain of 0.14 (95% confidence interval [CI] 0.05–0.22), which translates to no detectable clinical effect (<0.2), and no significant effect on stiffness and physical function in patients with knee OA [44–47]. Recent concerns over the safety profile of paracetamol raise questions over its routine chronic use, due to increasing evidence of gastrointestinal (GI), cardiovascular (CV), hepatic and renal adverse events (AEs) [48]. A systematic literature review of observational studies identified a considerable degree of liver and gastrointestinal toxicity associated with paracetamol, especially at the upper end of standard analgesic doses (up to 4 g/day) [49]. From 2 mortality studies, 1 showed a dose-response and increased relative rate of mortality from 0.95 (95% CI 0.92, 0.98) to 1.63 (95% CI 1.58, 1.68) [50], and the other a significantly increased standardized mortality ratio for patients prescribed paracetamol versus those not prescribed paracetamol [51]. Four studies reporting CV events all showed a dose-response with 1 reporting an increased risk ratio for all CV AEs from 1.19 (95% CI 0.81, 1.75) (325–650 mg/week) to 1.68 (95% CI 1.10, 2.57) (>4875 mg/week) [52]. One study reported a dose-response increase in upper GI AEs (ulcers, hemorrhages) with increased relative rate from 1.11 (95% CI 1.04, 1.18) to 1.49 (95% CI 1.34, 1.66) [50]. Three out of 4 studies reported a dose-response effect on renal function, with lifetime cumulative intake of 100–499 g associated with increased odds of reduced renal function (odds ratio [OR] 1.80; 95% CI 1.02, 3.18) [53], and a dose-response increase in OR of ≥30% decrease in estimated glomerular filtration rate (eGFR) and ≥0.3 mg/dL increase in serum creatinine [54].

A systematic review and meta-analysis found 3 RCTs that evaluated the results of liver function tests to detect AEs with paracetamol in participants with hip and knee OA. Participants taking paracetamol were nearly 4 times more likely to have abnormal results on liver function tests than participants taking placebo (weighted mean difference [WMD] 3.8; 95% CI 1.9, 7.4) [55]. Reports of hepatotoxicity and acute liver failure associated with chronic paracetamol dosing are a further cause of concern with widespread, unrestricted paracetamol use [56,57].

GRADE recommendations: Based on questionable efficacy and confirmed safety issues, (2) The ESCEO working group gives a weak recommendation that paracetamol (acetaminophen) should not be used on a regular basis as Step 1 long-term background pharmacological therapy for the management of knee OA.

Conversely, (3) The ESCEO working group gives a weak recommendation that paracetamol (acetaminophen) at doses no greater

Table 1
Results of the GRADE assessment and summary of ESCEO recommendations for the management of knee osteoarthritis

		Proportion of votes cast by ESCEO working group members completing the GRADE assessment ($N = 16$) (%)				
Number	Recommendation	Strong Do	Weak Do	No recommendation	Weak Don't	Strong Don't
1.	The ESCEO working group affords a strong recommendation to the application of a core set comprising: information access/education, weight loss, and an exercise program, which is applicable throughout the management of knee OA.	88%	12%	0	0	0
2.	The ESCEO working group gives a weak recommendation that paracetamol (acetaminophen) should not be used on a regular basis as Step 1 long-term background pharmacological therapy for the management of knee OA.	69%	25%	0	0	6%
3.	The ESCEO working group gives a weak recommendation that paracetamol (acetaminophen) at doses no greater than 3 g/day may be used as short-term rescue analgesia only, given on top of a background of Step 1 chronic therapy with SYSADOAs.	44%	56%	0	0	0
4.	The ESCEO working group affords a strong recommendation to the use of pCGS as Step 1 long-term background therapy for the management of knee OA, and discourages the use of other glucosamine formulations.	81%	19%	0	0	0
5.	The ESCEO working group affords a strong recommendation to the use of prescription CS as Step 1 long-term background therapy, as an alternative to pCGS, and the prescription drug should be distinguished from low quality OTC products.	81%	19%	0	0	0
6.	The ESCEO working group gives a weak recommendation that a combination of glucosamine and CS should not be used in Step 1 of background therapy, as there is no preparation containing both prescription products and no convincing evidence for existing non-prescription formulations.	56%	31%	6%	6%	0
7.	The ESCEO working group gives a weak recommendation to the use of SYSADOAs other than CS and pCGS (i.e. ASU and diacerein) as alternative Step 1 background therapy.	19%	69%	0	0	12%
8.	The ESCEO working group affords a strong recommendation to the use of topical NSAIDs as cyclic add-on analgesia in Step 1, for patients who are still symptomatic after the use of Step 1 background therapy, and prior to use of oral NSAIDs.	75%	19%	6%	0	0
9.	The ESCEO working group affords a strong recommendation to the use of oral NSAIDs (selective or non-selective) as Step 2 therapy, if used only intermittently or for longer cycles; the use of oral NSAIDs should be based on the patient risk profile.	94%	0	0	6%	0
10.	The ESCEO working group affords a weak recommendation to the use of IAHA in patients who have contraindications to NSAIDs, or if the patient is still symptomatic despite the use of NSAIDs.	56%	44%	0	0	0
11.	The ESCEO working group affords a weak recommendation to the use of IA corticosteroids, which are more effective than IAHA in the first few weeks of treatment in the same patient population; more severe pain may be a better predictor of this short-term efficacy than inflammatory signs.	69%	25%	6%	0	0
12.	The ESCEO working group gives a weak recommendation to the use of short-term weak opioids in Step 3 of the treatment algorithm as the last pharmacological attempt before surgery.	25%	75%	0	0	0
13.	The ESCEO working group gives a weak recommendation to the use of duloxetine as an alternative to weak opioids in Step 3 of the algorithm, especially in patients with pain from central sensitization.	19%	56%	0	25%	0
14.	The ESCEO working group affords a strong recommendation to total knee replacement surgery for end-stage knee OA patients, which is a highly selective and cost-effective procedure although not devoid of adverse outcomes; the role of other surgical procedures, especially unicompartmental knee replacement, should be further investigated.	81%	13%	6%	0	0
15.	The ESCEO working group gives a weak recommendation to the use of classical oral or transdermal opioids in end-stage knee OA patients for whom surgery is contraindicated.	38%	56%	0	6%	0

Note: Strong recommendation given when >75% of votes were cast in favor of "strong do"; Weak recommendation given when <75% of votes were cast in favor of "strong do".
ASU, avocado soybean unsaponifiables; CS, chondroitin sulfate; ESCEO, European Society for Clinical and Economic Aspects of Osteoporosis, Osteoarthritis and Musculoskeletal Diseases; GRADE, Grading of Recommendations Assessment, Development and Evaluation; IA, intra-articular; IAHA, IA hyaluronic acid; NSAIDs, non-steroidal anti-inflammatory drugs; OA, osteoarthritis; pCGS, prescription crystalline glucosamine sulfate; SYSADOA, symptomatic slow-acting drugs for OA.

than 3 g/day may be used as short-term rescue analgesia only, given on top of a background of Step 1 chronic therapy with symptomatic slow-acting drugs for OA (SYSADOAs).

SYSADOAs The recommended approach of the ESCEO working group to Step 1 treatment of knee OA is to initiate background therapy with chronic SYSADOAs (Fig. 1) [7]. However, there are many different agents in the class of SYSADOAs including glucosamine, chondroitin, diacerein, and avocado soybean unsaponifiables (ASU), which are supported by varying degrees of clinical efficacy data. Moreover, the availability of both over-the-counter (OTC) and prescription-grade SYSADOA products varies widely from country to country, which can make appropriate prescribing of SYSADOAs challenging.

Glucosamine, chondroitin and ASU are natural products. Exogenous glucosamine is administered as a salt. Glucosamine hydrochloride (GHCl) is a simple molecule obtained by extraction processes, and used as a nutraceutical or OTC product. Conversely, glucosamine sulfate is a more complex molecule, which can be obtained only by a proprietary semi-synthetic route and stabilization process and that is found only in the prescription drug product, i.e. prescription crystalline glucosamine sulfate (pCGS) [58]. Chondroitin is a high molecular weight, long chain polymer of repetitive units, which is obtained as chondroitin 4 and 6 sulfate (covalent binding) by different extraction processes. Thus, multiple formulations of these agents are available, both as prescription-grade products and nutritional supplements. However, while all preparations may claim to deliver a therapeutic level of glucosamine or chondroitin, not all are supported by clinical evidence [59–62]. Only pCGS is shown to deliver consistently high glucosamine bioavailability and plasma concentration in humans, which corresponds to demonstrated clinical efficacy [62–69]. Conversely, GHCl and non-characterized glucosamine sulfate products

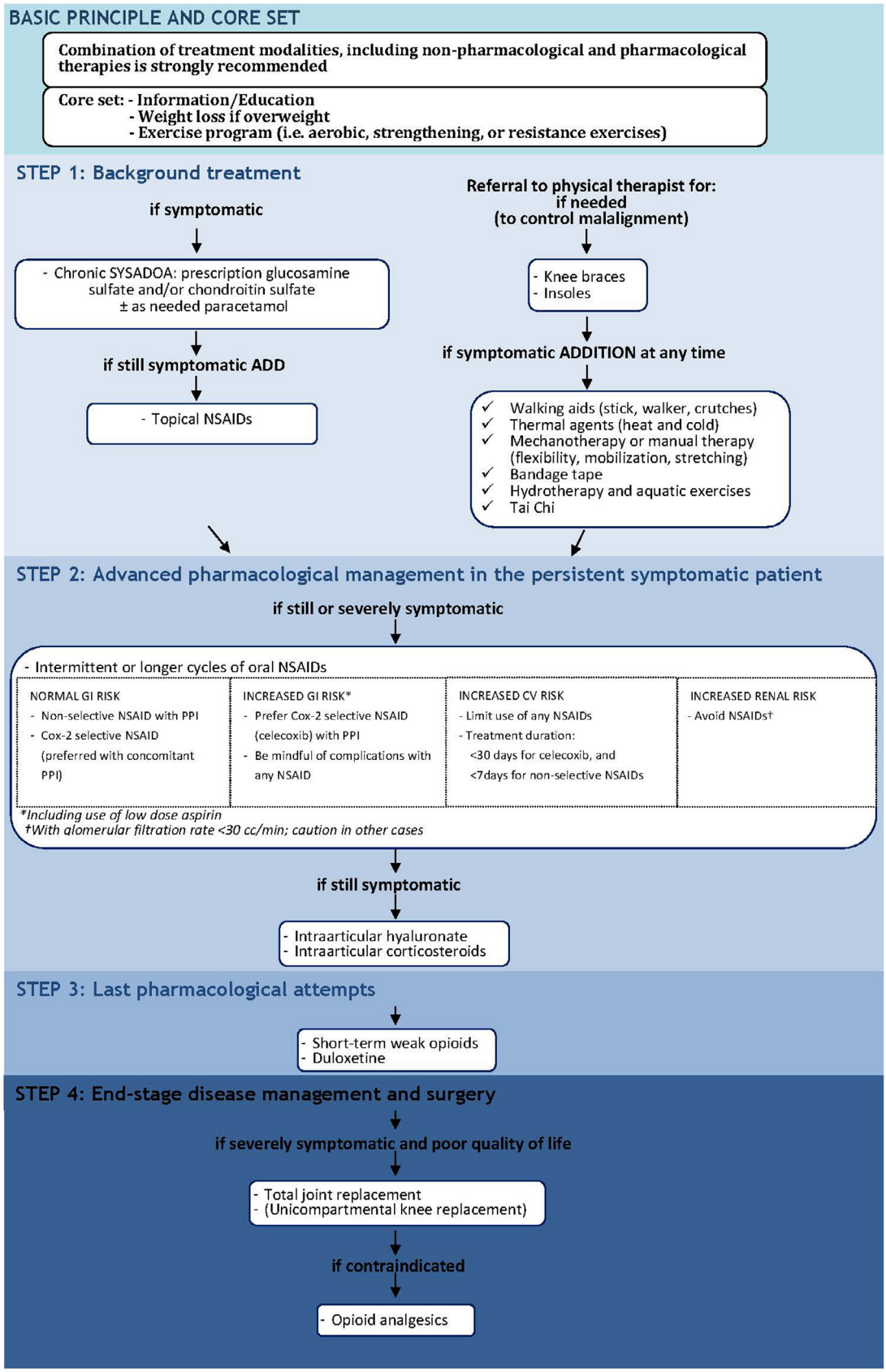

Fig. 1. Updated ESCEO stepwise treatment algorithm for knee osteoarthritis. COX-2, cyclooxygenase-2; CS, chondroitin sulfate; CV, cardiovascular; GI, gastrointestinal; GS, glucosamine sulfate; IA, intra-articular; NSAID, non-steroidal anti-inflammatory drug; PPI, proton pump inhibitor; SYSADOA, symptomatic slow-acting drugs in osteoarthritis; OA, osteoarthritis.

(usually consisting of GHCl with the addition of sodium sulfate to get a misleading "sulfate" labeling) are repeatedly demonstrated as ineffective in OA [62,64,70–72]. Similarly, only pharmaceutical-grade chondroitin sulfate (CS) has been evaluated for purity, content and physio-chemical parameters [73], and clinical evidence supports only pharmaceutical-grade CS [74–77].

Thus, among all glucosamine and chondroitin products available, the ESCEO recommends specifically the use of pharmaceutical-grade prescription glucosamine (pCGS) and chondroitin products, for which the evidence base is unequivocal [7]. In future, the ESCEO recommends that generic preparations of complex molecules with biological activity such as pCGS may be treated as "biosimilars" akin to the European Medicines Agency (EMA) guidance on biological medicinal products (EMEA/CHMP/BMWP/42,832/05 Rev.1; 2014), for which data demonstrating comparability with the reference medicinal product using appropriate physico-chemical and in vitro biological tests, non-clinical studies and clinical studies must be presented [59]. It seems likely that for all other complex molecules classed as SYSADOAs, the recommendation to use only formulations clearly supported by the evidence-base should apply.

Glucosamine sulfate The ES of pCGS on pain is 0.27 (95% CI 0.12 to 0.43) [63,64], which although 'small', is greater than the effect of paracetamol (ES = 0.14) and similar to the ES measured for non-steroidal anti-inflammatory drugs (NSAIDs) (ES = 0.32; 95% CI 0.24, 0.39) [46,47,78]. Conversely, other glucosamine preparations were devoid of efficacy in high-quality trials [64], and in a recent meta-analysis of individual patient data [71]. pCGS also has a significant effect on function [63], and there is evidence for disease-modifying effects [65,66], reduction in need for concomitant OA medications [79,80], and a delay in need for total joint replacement (TJR) surgery ($p = 0.026$) [80]. In a new network meta-analysis including only long-term (>1 year) trials of any pharmacological intervention for knee OA, only pCGS had a disease-modifying profile, being consistently effective on knee OA pain (ES = 0.29,;95% credibility interval [CrI] 0.09, 0.49), physical function and joint structure changes [81]. Furthermore, non-prescription glucosamine formulations, including GHCl with or without the addition of sodium sulfate (to get a misleading "sulfate" claim), were not effective on any outcome. Glucosamine supplementation is generally considered as safe and is not associated with any increased odds of AEs versus placebo [18,62,67,82,83].

GRADE recommendation: (4) The ESCEO working group affords a strong recommendation to the use of prescription crystalline glucosamine sulfate (pCGS) as Step 1 long-term background therapy for the management of knee OA, and discourages the use of other glucosamine formulations.

Chondroitin sulfate The ES of chondroitin 4&6 sulfate (CS) on pain is reportedly variable [10, 61], and a recent meta-analysis found that CS provides a moderate benefit for pain, with greater effect on function in knee OA; albeit with large inconsistency [84]. A recent study showed that pharmaceutical-grade CS is not different to celecoxib in terms of efficacy in symptomatic knee OA [77]. It was also reported to provide beneficial effects on joint structure, as assessed by changes visualized using magnetic resonance imaging [85]. The ChONdroitin versus Celecoxib versus Placebo Trial (CONCEPT) was conducted in full accordance with the 2015 EMA guidelines on clinical investigation in OA (CPMP/EWP/784/97 Rev. 1) [86], and found that CS (800 mg/day) and celecoxib (200 mg/day) showed a greater significant reduction in pain and Lequesne Index than placebo [77]. CS is also shown to have an effect on joint structural changes that could be clinically relevant [74,75]. In the network meta-analysis of long-term trials of any medication in knee OA, prescription CS had a significant effect on joint structure changes [81]. CS has a good safety profile at doses up to 1200 mg per day, with no significant increased odds of AEs versus placebo [18,61,82,83].

GRADE recommendation: (5) The ESCEO working group gives a strong recommendation to the use of prescription chondroitin sulfate as Step 1 long-term background therapy, as an alternative to pCGS, and the prescription drug should be distinguished from low quality over-the-counter products.

Glucosamine and chondroitin combination Glucosamine and chondroitin are often found in combination as dietary supplements although the combined products may be of variable pharmaceutical quality [87], and trials provide conflicting results as to whether there is any additional benefit to be derived from the combination [61,88–90]. A recent RCT of 164 patients with Kellgren-Lawrence (KL) grade 2 or 3 radiographic knee OA and moderate-severe knee pain who received 6 months with CS (1200 mg) plus glucosamine sulfate (1500 mg) once-daily or placebo, failed to demonstrate superiority of the available glucosamine/chondroitin combination over placebo in terms of reducing joint pain and functional impairment in patients with symptomatic knee OA over 6 months [91]. These findings may be attributed to the fact that CS is known to interfere with the absorption of glucosamine, reducing its bioavailability by 50%–75% [92,93]. Thus, the combination of glucosamine and chondroitin may not be recommended.

GRADE recommendation: (6) The ESCEO working group gives a weak recommendation that a combination of glucosamine and chondroitin sulfate should not be used in Step 1 of background therapy, as there is no preparation containing both prescription products and no convincing evidence for existing non-prescription formulations.

Avocado soybean unsaponifiables (ASU) ASU is a complex mixture of many natural vegetable extracts taken from avocado and soybean oils; the identity of the active component(s) is not known and analysis of commercially-available ASU supplements demonstrates variation in the sterol content [94]. In clinical studies of 3 to 6 months, some improvement in pain, stiffness and physical function has been shown with ASU (300 mg/day) leading to reduced need for analgesia [95–97], but mixed results for the effect of ASU on disease progression were found in studies of 2–3 years' duration in patients with hip or knee OA [98,99]. A single article (that was not subject to peer-review) has raised some concerns of possible AEs affecting the skin, liver, GI system, and platelet aggregation without any clear investigation of the relationship of these AEs to ASU [100]. However, recent safety meta-analyses of a specific proprietary ASU product have found no significant differences for safety signals compared with placebo treatment from limited trial evidence of ASU using concomitant NSAIDs [18,101].

Diacerein is an anthraquinone derivative with anti-inflammatory activity [102]. In meta-analyses, diacerein has a small beneficial effect on pain for up to 3 years, equivalent to a 9% reduction in pain (95% CI −16% to −2%) [103], with an estimated ES of 0.24 (95% CI 0.08, 0.39) [104]. Limited benefit in delay of joint progression has been reported in hip OA [105], but significant long-term effects in knee OA are yet to be shown [106]. The safety of diacerein has been called into question following reports of severe diarrhea and rare cases of potentially serious hepatotoxicity [107]. In a recent safety meta-analysis, the odds of any AE with diacerein was more than twice that with placebo, with or without concomitant OA treatment, largely due to GI AEs (diarrhea, abdominal pain, soft stools, colitis) and urine discoloration [18]. This incidence of diarrhea after daily treatment with diacerein 100 mg reportedly varies from 2.3 to 45.9%; this wide ranging result may be partly explained by variability of products containing diacerein on the market [108].

Nonetheless, a report from the EMA concluded that the benefit-risk balance of diacerein remains positive for hip and knee OA in patients aged <65 years [107]. It is advised that patients start treatment on half the normal dose (i.e. 50 mg daily instead of 100 mg daily) and should stop taking diacerein if diarrhea occurs. Furthermore, a recent opinion-based report from the ESCEO supports diacerein as a background treatment of OA, which may be of particular benefit in patients with a contraindication to NSAIDs or paracetamol [109]. Thus, although scarcer evidence is available, diacerein and ASU seem to offer a good benefit: risk ratio in the management of knee OA.

GRADE recommendation: (7) The ESCEO working group gives a weak recommendation to the use of SYSADOAs other than CS and pCGS (i.e. ASU and diacerein) as alternative Step 1 background therapy.

Topical NSAIDs may be added to the treatment regimen in Step 1 if the patient is still symptomatic after establishing appropriate background pharmacological therapy with SYSADOAs, and rescue analgesia with paracetamol provides insufficient symptom relief. The short-term efficacy of topical NSAIDs in knee OA has been established in several RCTs, meta-analyses and real-life studies [110–115]. A recent network meta-analysis found that topical NSAIDs were superior to placebo for relieving pain (standardized mean difference [SMD] = −0.30; 95% CI −0.40, −0.20) and improving function (SMD = - 0.35; 95% CI −0.45 to −0.24) in OA, among which diclofenac patches were most effective for OA pain (SMD = −0.81; 95% CI −1.12 to −0.52) [116]. Evidence from head-to-head studies shows that topical NSAIDs are as effective as oral NSAIDs, with a pooled ES for pain relief of 0.44 (95% CI 0.27, 0.62) [110]. Topical NSAIDs are associated with a lower risk of systemic AEs compared with oral NSAIDs due to lower systemic absorption [117], albeit with an increased risk of local mild skin reactions compared with placebo [111,114,118]. A recent safety meta-analysis found that the increases in skin and subcutaneous tissue disorders observed with topical NSAIDs may be product specific, as notably higher rates were observed only with diclofenac [17]. For considerations of safety, topical NSAIDs may be used in preference to oral NSAIDs, particularly in OA patients aged ≥75 years, and those with co-morbidities or at an increased risk of GI, CV or renal AEs.

GRADE recommendation: (8) The ESCEO working group affords a strong recommendation to the use of topical NSAIDs as cyclic add-on analgesia in Step 1, for patients who are still symptomatic after the use of Step 1 background therapy, and prior to use of oral NSAIDs.

Step 2: advanced pharmacological treatment

Oral NSAIDs If Step 1 treatments show inadequate efficacy, or in patients presenting with moderate-severe pain, benefit may be obtained with advanced pharmacological treatments. Oral NSAIDs have a small to moderate effect on pain relief in OA, with ES ranging between 0.35 (95% CrI 0.31, 0.40) for OA approved daily doses of celecoxib 200 mg/day, and 0.57 (95% CrI 0.45, 0.69) or 0.58 (95% CrI 0.43, 0.74) for maximally-approved daily doses of diclofenac 150 mg/day or etoricoxib 60 mg/day [119]; cyclooxygenase-2 (COX-2) selective, partially-selective, or non-selective (ns) NSAIDs are shown to be similarly effective in controlling pain [117,120,121]. In recent meta-analyses, oral NSAIDs were found to be similar to opioids for relieving pain in OA [122,123]. A Cochrane review assessed celecoxib to be slightly better than placebo and some nsNSAIDs in reducing OA pain and improving function with high level of evidence [124]. However, in the network meta-analysis of long-term trials of pharmacological interventions in knee OA, NSAIDs were not associated with improved pain, function or joint structure changes, with the exception of celecoxib which had a very small and probably not clinically relevant ES on knee pain (SMD = 0.18, 95% CrI 0.01, 0.35), that was no longer significant when only high-quality trials were considered [81]. In previous guidance, the selection of appropriate NSAID has been driven by assessment of benefit: risk balance, in terms of variability in GI and CV safety profile between individual drugs, and individual patient characteristics affecting risk of AEs [7]. Recent meta-analyses of the safety of NSAIDs suggests that all nsNSAIDs and COX-2 inhibitors have the potential for GI and CV toxicity [125,126].

A meta-analysis of 280 trials of NSAIDs versus placebo (124,513 participants, 68,342 person-years) and 474 trials of one NSAID versus another NSAID (229,296 participants, 165,456 person-years) found that all NSAID regimens, including nsNSAIDs and COX-2 inhibitors, increase upper GI complications compared with placebo (COX-2 inhibitors rate ratio [RR] = 1.81; 95% CI 1.17, 2.81; diclofenac RR = 1.89; 95% CI 1.16, 3.09; ibuprofen RR = 3.97; 95% CI 2.22, 7.10; and naproxen RR = 4.22; 95% CI 2.71, 6.56) [125]. In response to a letter requiring an analysis of these data with respect to age categorization [127], the authors did not report any NSAID-specific increase in relative risk (RR) of GI or CV major event in addition to the standard age-related GI/CV risk [128]. Another meta-analysis revealed that COX-2 inhibitors were similar to nsNSAIDs in combination with the gastroprotectant proton pump inhibitors (PPIs) in regard to upper GI AEs, GI symptoms and CV AEs [129]. There was no difference in upper GI AEs between COX-2 inhibitors and nsNSAIDs with concurrent use of PPIs (RR = 0.61; 95% CI 0.34, 1.09). In terms of GI toxicity, celecoxib may be less toxic than nsNSAIDs. A retrospective pooled analysis of 21 RCTs of 9461 patients aged ≥65 years with OA, rheumatoid arthritis or ankylosing spondylitis found that the combined incidence of GI AEs (abdominal pain, constipation, diarrhea, dyspepsia, flatulence, nausea) were reported by fewer patients receiving celecoxib (16.7%) than with naproxen (29.4%), ibuprofen (26.5%), or diclofenac (21.0%) [130].

While it was previously thought that selectivity of the NSAID for the COX-2 enzyme governed the CV toxicity profile, recent results suggest that CV risk may be drug specific; rofecoxib is the only NSAID associated with an increased risk of CV events, while celecoxib is associated with a lower incidence of stroke compared with the other drugs in the NSAID class [131]. In a meta-analysis of 26 RCTs, the incidence of the composite CV endpoint was increased with rofecoxib when compared to all other NSAIDs (odds ratio [OR] = 1.61; 95% CI 1.31, 1.98), and to other COX-2 selective-NSAIDs (OR = 1.84; 95% CI 1.32, 2.55) [131]. The risk of myocardial infarction (MI) was increased with rofecoxib in comparison to all other NSAIDs (OR = 1.81; 95% CI 1.38, 2.38), while a lower risk of MI was detected with celecoxib (OR = 0.58; 95% CI 0.40, 0.86) and naproxen (OR = 0.61; 95% CI 0.38, 0.99) [131]. The incidence of stroke was increased by rofecoxib in comparison with all NSAIDs (OR = 1.49; 95% CI 1.03, 2.16), and decreased by celecoxib when compared with all NSAIDs (OR = 0.60; 95% CI 0.41, 0.89) [131]. A significant increased risk of hemorrhagic stroke was also found with diclofenac (RR = 1.27; 95% CI 1.02, 1.59) and meloxicam (RR = 1.27; 95% CI 1.08, 1.50) [132]. In the Prospective Randomized Evaluation of Celecoxib Integrated Safety vs Ibuprofen Or Naproxen (PRECISION) trial, celecoxib was found to be non-inferior to naproxen or ibuprofen for the primary composite outcome of CV death (including hemorrhagic death), nonfatal MI, or nonfatal stroke [133]. A population-based cohort study has estimated the absolute risk of MI associated with NSAID use at around 0.5% to 1% per year [134]. Although this absolute MI risk increase is small, NSAID use is very prevalent in older adults. In 2010, around 43 million adults (19.0%) took aspirin at least three times per week for more than 3 months (i.e. regular users), and more than 29 million adults (12.1%) were regular users of NSAIDs [135]. The odds of acute MI for exposure to NSAIDs taken for any duration of time, showed an increase in risk of 15% for celecoxib (200 mg), 25% for naproxen (500 mg), 35% for diclofenac (100 mg), 40% for ibuprofen (1200 mg), and 55% for rofecoxib (25 mg) [134]. Notably, the MI risk with celecoxib appeared to depend on continuously using the drug for more than 30 days, whereas for ibuprofen, rofecoxib, diclofenac, and naproxen, a heightened MI risk occurred within 7 days of use [134]. A recent safety meta-analysis of COX-2 inhibitors (celecoxib, rofecoxib, etoricoxib, and valdecoxib) found a significant increase in CV AEs, even when rofecoxib was excluded, specifically hypertension, congestive heart failure and peripheral and generalized edema [20], which is consistent with other findings for nsNSAIDs [136]. The risk of hospitalization due to heart failure is roughly doubled by all NSAID regimens (COX-2 inhibitors RR = 2.28; 95% CI 1.62, 3.20; diclofenac 1.85; 95% CI 1.17, 2.94; ibuprofen 2.49; 95% CI 1.19, 5.20; and naproxen 1.87; 95% CI 1.10, 3.16) [125].

All NSAIDs are also associated with an increased risk of acute kidney injury, which may be particularly high in the first 30 days after initiation of therapy [137,138]. Although patients with normal renal function are unlikely to develop acute kidney injury secondary to

taking NSAIDs, those with a history of hypertension, heart failure, or diabetes have higher chance of developing these complications [137].

Consequently, due to the risk of GI and CV events with all NSAIDs, the ESCEO recommended in 2014 that all NSAIDs are used at the lowest effective dose for the shortest period of time necessary to control pain, i.e. intermittently or in longer cycles rather than in chronic use [7]. The ESCEO working group considers that celecoxib (200 mg/day) may be the preferred oral NSAID, due to the balance between good short-term efficacy in OA at approved doses and its lower propensity for toxicity, especially at the GI level.

GRADE recommendation: (9) The ESCEO working group affords a strong recommendation to the use of oral NSAIDs (selective or non-selective) as Step 2 therapy, if used only intermittently or for longer cycles; the use of oral NSAIDs should be based on the patient risk profile, as described in Fig. 1.

Intra-articular interventions: hyaluronic acid and corticosteroids In the case of contraindications to NSAIDs, or if the patient is still symptomatic despite use of NSAIDs, intra-articular (IA) treatment may be considered. IA hyaluronic acid (IAHA) may be a good alternative to NSAIDs for knee OA, with a more favorable safety profile, especially for older patients or in those at greater risk for NSAID-induced AEs. Viscosupplementation with IAHA is an effective treatment for knee OA with beneficial effects on pain, function and patient global assessment [139]. There is good evidence for the effectiveness of HA from RCTs, numerous meta-analyses, and real-life experience [140–142]. In a network meta-analysis, IAHA had a measured ES of 0.34 on pain (95% Crl 0.26, 0.42) when compared with IA placebo at 3 months [44]. Moreover, IAHA was the most efficacious treatment for pain among all OA interventions [38], with superior efficacy to oral NSAIDs [143]. Accounting for the risk of bias in RCTs, the estimated ES of IAHA on pain has been reduced to - 0.30 (95% CI −0.36 to −0.23; $p < 0.001$) [144], and to −0.21 while retaining significance for reduction of pain intensity at 3 months versus IA placebo (SMD = −0.21; 95% CI −0.32, −0.10) [145]. Furthermore, systematic reviews of overlapping meta-analyses have confirmed that IAHA is a viable option for knee OA, and its use results in improvement in knee pain and function that can persist for up to 26 weeks [146,147]. HA has a slow onset of action, with efficacy on pain demonstrated by week 4, reaching a peak at 8 weeks that is maintained for up to 6 months [148–150]. Beyond 8 weeks post-injection IAHA demonstrates superior, longer-lasting efficacy than IA corticosteroids [151]. Studies demonstrate that a single injection of IAHA offers no benefit over placebo [152], that multiple injection courses are superior to a single injection (2–4 injections gave the largest ES on pain at 3 and 6 months) [153], and there appears to be no additional benefit given by a 5-injection course over a 3-injection course [154].

While the efficacy of IAHA injections has been demonstrated across meta-analyses [155], some heterogeneity is found between trials, with a few trials reporting no benefit over placebo [152,156], and the magnitude of clinical benefit is reportedly different for different HA products [139]. Low molecular weight (MW) HA may provide inferior efficacy to intermediate and high MW HA [157–159]. The occurrence of AEs may also be HA product-dependent; Cross-linked high MW HAs (hylans) have been associated with increased pseudo-septic reactions [160], and an increased risk of local adverse reactions (RR 1.91; 95% CI 1.04–3.49; I^2=28%) and flares (RR 2.04; 95% CI 1.18–3.53; I^2=0%) compared with intermediate or low MW HA [161].

Conflicting safety reports associated with IAHA have led to some concerns over its use [162] that were not endorsed by the ESCEO [7]. A recent meta-analysis found no significant increased odds for AEs at any organ or system level [19]; however, the level of the evidence was graded as “low” and “moderate”, as a lack of reporting of AEs with IAHA was acknowledged. There were increased odds for serious AEs found in the IAHA group versus placebo, particularly in studies with concomitant OA treatment allowed (OR = 1.78; 95% CI 1.10, 2.89), which may require further investigation [19]. Differences in the reporting of serious AEs, whether a causal relationship was established or not [163], may account for the disparate conclusions regarding the balance of benefits and harms [164]. A network meta-analysis of 74 studies of 18 HA products involving 13,042 patients aged 45 to 75 years found a very low incidence of AEs, of which the most commonly reported were transient local reactions such as pain, swelling and arthralgia (incidence 8.5%) [165]. None of the HA products were statistically significantly different from placebo, nor from each other with regard to incidence of AEs. Multiple courses of IAHA are shown to be safe up to 18 months, with an overall AE rate of 0.008 (95% CI 0.001, 0.055) [166], although further long-term studies of the safety of IAHA are warranted.

IAHA therapy remains efficacious over several years of treatment, and 80% of patients respond to repeat courses of IAHA injections over 3 years [167]. Retrospective database analyses demonstrating a reduced need for, or delay in need for total knee replacement (TKR) surgery of around 2 years, and up to 3.5 years with 5 or more courses of IAHA [168–173]. IAHA treatment also reduces the need for other pain medications such as NSAIDs, corticosteroids and opioids among patients with knee OA [174]. IAHA is positioned later in the treatment algorithm, unless NSAIDs are contraindicated, due to the requirement for repeated injections performed by a hospital practitioner, and the inherent higher cost of treatment. Further investigation to define the patient phenotypes associated with optimal benefit: risk for IAHA treatment is warranted [141], and long-term efficacy should be better substantiated in additional prospective RCTs. IAHA should only be administered in knee OA once the acute inflammatory flare has settled. In these patients, IA corticosteroids may be used to treat the knee effusion.

IA corticosteroids are more effective than placebo and IAHA in the short-term (2–4 weeks) and efficacy may be higher in patients with more severe pain [151,175,176]. Indeed, intramuscular glucocorticoid injection has shown a clinically relevant reduction in pain associated with hip OA for up to 12 weeks post-injection [177]. However, limited benefit of repeated courses of IA corticosteroids on symptoms has been demonstrated and no benefit on joint structure modification in the long term was seen in two 2-year studies [178].

GRADE recommendations: (10) The ESCEO working group affords a weak recommendation to the use of IAHA in patients who have contraindications to NSAIDs, or if the patient is still symptomatic despite the use of NSAIDs.

(11) The ESCEO working group affords a weak recommendation to the use of IA corticosteroids, which are more effective than IAHA in the first few weeks of treatment in the same patient population; more severe pain may be a better predictor of this short-term efficacy than inflammatory signs.

Step 3: last pharmacological treatment

Last pharmacological options for the severely symptomatic patient are represented by short-term weak opioids, such as tramadol, for which there is good evidence of analgesic benefit in knee OA [120,179]. Opioids significantly decrease pain intensity (ES −0.79; 95% CI −0.98 to −0.59) and have small benefit on function (ES −0.31; 95% CI −0.39 to −0.24), while the number needed to harm (NNT) was calculated as 5 compared with placebo [180]. The sustained release (SR) formulation of tramadol may be preferred to reduce AEs [181]; Furthermore, the slow upwards titration of tramadol SR from 50 mg up to 100 mg is recommended to improve tolerability and minimize treatment discontinuations due to AEs [182]. Meta-analyses have found small beneficial effects of non-tramadol opioids on OA pain and function but with increased safety issues, particularly in older people (>60 years) [183,184]. A recent safety meta-analysis of oral opioids used in OA found an increased risk of GI (dry mouth, oral ulceration, nausea, vomiting, dyspepsia, constipation), central nervous system (headache, dizziness, fatigue, somnolence), and dermatological AEs (rash or pruritus) compared with placebo for both

immediate-release and SR formulations [21]. Notably, treatment with opioids is not found to be superior to treatment with non-opioid medications for improving pain-related function [185].

The antidepressant duloxetine has been used in chronic pain syndromes and some evidence for an effect is shown in OA especially in patients with pain from central sensitization, albeit with a high rate of AEs (dizziness, risk of falls) [186–188]. Duloxetine is not widely used in Europe, although it may be prescribed for OA.

GRADE recommendations: (12) The ESCEO working group gives a weak recommendation to the use of short-term weak opioids in Step 3 of the treatment algorithm as the last pharmacological attempt before surgery.

(13) The ESCEO working group gives a weak recommendation to the use of duloxetine as an alternative to weak opioids in Step 3 of the algorithm, especially in patients with pain from central sensitization.

Step 4: end-stage disease management and surgery

Full review and advice on surgical procedures for the management of end-stage knee OA goes beyond the scope of the working group's commitment. However, TKR is appropriate when all previous modalities have failed, if the patient is severely symptomatic, and there is significant loss in quality of life [189–191]. The surgical techniques that may be employed include: total joint replacement, partial knee replacement, or osteotomy around the knee. Recent years have seen an increase in the number of joint replacement surgeries performed [192], due in part to the aging population, increasing demands of patients, and more joint replacements performed in younger patients [193,194]. A recent network meta-analysis suggests that function scores are improved by TKR, which has better long-term efficacy, while unicompartmental knee replacement and osteotomy have better efficacy in the short-term [195]. Although TKR is highly successful and cost-effective, it has several adverse outcomes; While unicompartmental knee replacement has a higher revision rate, it has a lower occurence of complications compared with TKR, including mortality [196]. TKR may give better results when patients are carefully selected and well informed, surgery is well performed, and rehabilitation is appropriate [11].

For severly symptomatic patients in whom surgery is cotraindicated, or if they are unwilling to undergo surgery, the last pharmacological resort may be classical oral or transdermal opioids which demonstrated small to moderate positive effects on OA pain and function albeit with an increased risk of AEs [197]; They should be prescribed following the guidelines for use of opioid analgesics in management of non-cancer pain [198].

GRADE recommendations: (14) The ESCEO working group affords a strong recommendation to total knee replacement surgery for end-stage knee OA patients, which is a highly selective and cost-effective procedure although not devoid of adverse outcomes; the role of other surgical procedures, especially unicompartmental knee replacement, should be further investigated.

(15) The ESCEO working group gives a weak recommendation to the use of classical oral or transdermal opioids in end-stage knee OA patients for whom surgery is contraindicated.

Discussion

The 2014 ESCEO stepwise algorithm of recommendations for management of knee OA was well-received internationally, and this article represents a timely update based upon assessment of the current literature (2014–2018) regarding efficacy and safety of all treatment modalities. The ESCEO believes that the combination of treatment modalities including non-pharmacological and pharmacological intervention remains key to the management of knee OA as outlined in the updated treatment algorithm. While the efficacy of non-pharmacological modalities may be considered as low, and data on cost-effectiveness of the interventions are limited and inconclusive due to trial quality issues [40], non-pharmacological interventions are generally considered as safe. Non-pharmacological treatments are currently under-utilized in clinical practice [42]. To overcome barriers to the wider acceptance of non-pharmacological modalities, including a perceived lack of expertise of the HCP, lack of evidence-based treatment, and suboptimal care organization [42], the promotion of interventions according to evidence-based recommendations, and improved organization of care is proposed.

As Step 1 pharmacological treatment, the ESCEO working group advocates the use of background therapy with chronic SYSADOAs, specifically pharmaceutical-grade pCGS and CS, for which the evidence is unequivocal. Recent concerns over the safety profile of paracetamol raise questions over its routine, chronic use, due to increasing evidence of GI, CV, and renal AEs [49]; thus, paracetamol should be reserved for short-term rescue analgesia only. Topical NSAIDs may be added to Step 1 background therapy as cyclic analgesia, or used in preference to oral NSAIDs, particularly in OA patients aged $\geq$75 years, and those with co-morbidities or at an increased risk of systemic AEs. If Step 1 treatments show inadequate efficacy, or in patients presenting with moderate to severe pain, benefit may be obtained with advanced pharmacological treatments, such as oral NSAIDs.

In previous guidance, the selection of an appropriate oral NSAID was driven by assessment of the benefit: risk balance; however, recent meta-analyses of the safety of NSAIDs suggests that all nsNSAIDs and COX-2 inhibitors have the potential for GI and CV toxicity. Oral NSAID selection should be based on the patient risk profile and consider the level of GI or CV risk associated with each NSAID; celecoxib (200 mg/day) may be the preferred NSAID due to its better overall safety profile.

IAHA may be a good alternative to NSAIDs for knee OA, especially for older patients or in those at greater risk for NSAID-induced AEs or when NSAIDs have failed, although the current evidence does not allow for a definitive conclusion. The ESCEO working group affords a weak recommendation to the use of IAHA injections for knee OA patients. IAHA should only be administered in knee OA once the acute inflammatory flare has settled, and for these patients, IA corticosteroids are afforded a weak recommendation to treat the knee effusion or for more severe pain.

Last pharmacological options for the severely symptomatic patient are represented by short-term weak opioids, such as tramadol, which are afforded a weak recommendation, as is duloxetine as an alternative to weak opioids, especially in patients with pain from central sensitization. Finally, total knee replacement surgery is appropriate when all previous modalities have failed, if the patient is severely symptomatic and there is significant loss in quality of life.

Future research efforts should focus on the identification of patient phenotypes in OA, especially in the early stages of the disease. An ESCEO-EUGMS (European Union Geriatric Medicine Society) working group has recently suggested possible patient profiles in OA, including the existence of 4 clinical phenotypes: biomechanical, osteoporotic, metabolic and inflammatory [199]. Characterization of these phenotypes will help to properly stratify patients with OA in clinical trials or studies, which may in turn lead to optimization of the design of individualized treatments for OA.

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Supplementary materials

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