Commentary on recent therapeutic guidelines for osteoarthritis

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ABSTRACT

Background: Despite availability of international evidence-based guidelines for osteoarthritis (OA) management, agreement on the different treatment modalities is lacking.
Method: A symposium of European and US OA experts was held within the framework of the Annual European Congress of Rheumatology to discuss and compare guidelines and recommendations for the treatment of knee OA and to reach a consensus for management, particularly for areas in which there is no clear consensus: non-pharmacological therapy; efficacy and safety of analgesics and non-steroidal anti-inflammatory drugs (NSAIDs); intra-articular (i.a.) hyaluronates (HA); and the role of chondroitin sulfate (CS) and/or glucosamine sulfate (GS).
Results: All guidelines reviewed agree that knee OA is a progressive disease of the joint whose management requires non-pharmacological and pharmacological approaches. Discrepancies between guidelines are few and mostly reflect heterogeneity of expert panels involved, geographical differences in the availability of pharmacotherapies, and heterogeneity of the studies included. Panels chosen for guideline development should include experts with real clinical experience in drug use and patient management. Implementation of agreed guidelines can be thwarted by drug availability and reimbursement plans, resulting in optimal OA treatment being jeopardized, HA and symptomatic slow-acting drugs for osteoarthritis (SySADOAs) being clear examples of drugs whose availability and prescription can greatly vary geographically. In addition, primary care providers, often responsible for OA management (at least in early disease), may not adhere to clinical care guidelines, particularly for non-pharmacological OA treatment.
Conclusion: Harmonization of the recommendations for knee OA treatment is challenging but feasible, as shown by the step-by-step therapeutic algorithm developed by the European Society for Clinical and Economic Aspects of Osteoporosis and Osteoarthritis (ESCEO). More easily disseminated and implemented guidance for OA treatment in the primary care setting is key to improved management of OA.

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Introduction

Osteoarthritis (OA) has been defined as "a progressive disease of synovial joints that represents failed repair of joint damage that results from stresses that may be initiated by an abnormality in any of the synovial joint tissues, including articular cartilage, subchondral bone, ligaments, menisci (when present), peri-articular muscles, peripheral nerves, or synovium" [1]. Even if OA can involve single and/or multiple peripheral joints, including the knee, hip, and hand [2], the knee is the most common joint localization of symptomatic OA [3].

While diagnosis of OA is mainly based on clinical and radio-logical features [4], pain represents the first and prevailing symptom that leads patients to seek medical advice. Stiffness is generally linked to physical inactivity, while loss of movement and function can limit the patient's daily activities. Symptomatic OA is often associated with depression and disturbed sleep, greatly reducing patients' quality of life [2].

The current treatment of OA is based on symptom management, primarily pain control, and relies on the combination of non-pharmacological and pharmacological approaches that are

generally tailored to the patient's needs and risk factors. While several international professional societies have published evidence-based guidelines for OA management [5–11], no complete agreement on the different treatment modalities exists, highlighting the need for a debate to try to understand the differences and to develop a general consensus for disease management.

A symposium devoted to the recent therapeutic recommendations for OA management was held on June 12, 2014, in the framework of the 2014 Annual European Congress of Rheumatology to review, compare, and discuss the most important guidelines and recommendations for the treatment of knee OA published by the European League Against Rheumatism (EULAR), the Osteoarthritis Research Society International (OARSI), the American College of Rheumatology (ACR), and the European Society for Clinical and Economic Aspects of Osteoporosis and Osteoarthritis (ESCEO).

This article summarizes the comparisons of the guidelines for knee OA treatment regarding four specific topics: the non-pharmacological therapy of knee OA, efficacy and safety of analgesics and non-steroidal anti-inflammatory drugs (NSAIDs), intra-articular hyaluronates, and the role of chondroitin sulfate (CS) and/or glucosamine sulfate (GS) in the management of knee OA for which no clear cut consensus is available.

The non-pharmacological therapy of knee osteoarthritis

Table 1 presents the recommendations for non-pharmacological treatments issued over the past 10 years. The different recommendations rely on evidence from both systematic reviews and randomized clinical trials (RCTs), with the main outcomes considered being pain and physical function. While in patients with knee OA the most agreed non-pharmacological modalities are patient access to information and education, weight loss, and exercise

programs, debate continues regarding the limited effects of these approaches on early symptoms; their feasibility in a long-term perspective, including the potential for disease modification; and their real effect size (ES) on pain and joint function. In fact, the ES of these non-pharmacological treatment modalities is generally low if used as stand-alone treatments; still, it must be remembered that these interventions are relatively inexpensive and generally devoid of side effects.

Information access and education, self-management programs, and changes in patient lifestyle should be introduced as early as possible, with the aim being to provide patients with the knowledge of their disease and objectives of the treatment. In fact, these simple measures have been demonstrated to have a great impact on further adherence to treatment [5]. Comprehensive guidance on the principles of information and education and lifestyle changes has been recently published [6]. A 5% weight loss within 6 months produces a small but significant benefit on physical function [5,12] and is therefore highly recommended for overweight patients. OARSI recommendations reported in 2007 specified the ES of the different non-pharmacological modalities [13], but only a few displayed moderate ES values (aerobic exercise and thermal modalities) (Table 1). Exercise (cardiovascular or resistance) was one of the "strong recommendations" for knee OA non-pharmacological treatment from the ACR [7]. Both land- and water-based exercise reduce pain and disability in patients with knee OA [14]. While it has been stated that the intensity and/or duration of the exercise should increase over time [6] for more prolonged beneficial effects, the optimal exercise regimen has not been identified yet. Experts agree that regular aerobic exercise, quadriceps strengthening, and strength training of the lower limb should be recommended to patients as a mixed-approach program [14]. In the recently released ESCEO algorithm for the management of OA [5] it is stated that, after the initial core set assessment, all patients should be referred to a physical therapist for advice on the possible physical measures to be adopted by the patients for

Table 1
Recommendation for the non-pharmacological treatment of knee osteoarthritis (OA)

	Type of non-pharmacological treatment	Type of recommendation/evidence/ES[a]	Refs.
EULAR (2003)	Regular education, exercise, appliances (sticks, insoles, and knee bracing), and weight loss.	Recommended	[8]
OARSI (2007 and 2008)	Regular aerobic, muscle strengthening, and different range of motion exercises. For pts with symptomatic hip OA, exercises in water can be effective.	Pain ES = 0.52 (aerobic), = 0.32 (strength)	[13, 45]
	Some thermal modalities may be effective for relieving symptoms.	Pain ES = 0.69 (−0.07, 1.45)	
	Acupuncture may be of symptomatic benefit in pts with knee OA.	Pain ES = 0.51 (0.23–0.79)	
OARSI (2010)	Acupuncture	ES = 0.52	[11]
ACR (2012)	Cardiovascular (aerobic) and/or resistance land-based exercise, aquatic exercise, and weight loss if overweight.	Strongly recommended	[7]
	Self-management programs, use of thermal agent and manual therapy with supervised exercises, tai chi programs, and use of walking aids.	Conditionally recommended	
EULAR (2013)	Overall, 11 recommendations were provided concerning the assessment, general approach, patient information and education, lifestyle changes, exercise, weight loss, assistive technology and adaptation, footwear, and work.	Level of evidence ranging from Ia to III	[6]
OARSI (2014)	Core treatment (land-based exercise, strength training, weight management, self-management, education, and water-based exercise).	Appropriate for all patients (land-based exercise: Pain ES = 0.34–0.63, Function ES = 0.25; strength training: Pain ES = 0.38, Function ES = 0.41; weight management: Pain ES = 0.20, Function ES = 0.23; and self-management and education: Pain ES = 0.06–0.29, Function ES = 0.41)	[9]
	Cane (walking stick).	Appropriate for knee OA	
ESCEO (2014)	Core set information education, weight loss if overweight, and exercises program including aerobic and strengthening.	Recommended for all patients	[5]

ACR, American College of Rheumatology; ES, effect size; ESCEO, European Society for Clinical and Economic Aspects of Osteoporosis and Osteoarthritis; EULAR, European League Against Rheumatism; OA, osteoarthritis; OARSI, Osteoarthritis Research Society International; pts, patients.

[a] ES, effect size is a standardized mean difference between a treatment and a control group for an outcome variable, i.e., pain and function.

symptom relief (such as correction of mal-alignment and adoption of walking aids).

Non-pharmacological approaches for knee OA management suffer from a deficit in their dissemination and implementation that is even worse than for pharmacological treatments. This could be partly due to the fact that most of the guidelines are addressed to specialist doctors, and their application by general practitioners could be more problematic, as recently illustrated by the finding that only 30% of general practitioners would provide exercise advice for OA [15]. OA represents the second most common reason for consulting a doctor and, in most countries, it constitutes up to 10–20% of the visits to primary care practice [16]; nevertheless, general practitioners are not well educated on optimized management of these patients. Indeed, for most of them, the only general education in musculoskeletal disease is received during medical school [17]. Specific training in musculoskeletal disease during physician training is urgently warranted and should be advised by all of the international societies to ensure successful correct implementation of the guidelines for the management of OA, as recently introduced in the EULAR objectives.

Analgesics and non-steroidal anti-inflammatory drugs (NSAIDs)

Pharmacological treatment aims to reduce pain, which is one of the earliest symptoms of the disease. Traditionally, pain relief has mainly relied on the use of analgesics and NSAIDs. Table 2 summarizes the recommendations for the use of this class of compounds in the management of knee OA. There is general agreement that paracetamol should be used as the initial analgesic for the management of symptomatic OA at the recommended daily dose of no greater than 3 g/day, given, for example, as a 1000-mg dose three times per day. Despite the general consensus on its use, the reported ES of paracetamol on pain is quite small (less than 0.20), with no significant effect on stiffness or physical function in patients with knee OA, as reported by the OARSI guideline update [11]. A recent meta-analysis questioned the role of chronic paracetamol treatment, because in most of the clinical studies, paracetamol was administered for less than 6 months [18]. Moreover, concerns on the safety profile of paracetamol have been recently raised, as it is associated with an increased risk of hypertension, gastrointestinal (GI) bleeding, hepatotoxicity, and renal impairment in patients taking the drug regularly even at low dosage [19]. In the USA, paracetamol is one of the most frequent causes of drug-induced liver damage, with over 50% of the cases being due to an unintentional overdose.

In patients with knee OA, paracetamol may be combined with, or replaced by, topical NSAIDs (Table 2). Topical NSAIDs are active and have a moderate ES on pain relief, as established in RCTs [20]. The efficacy of topical NSAIDs is similar to that of their oral counterparts. However, topical NSAIDs show a better safety profile because of their lower systemic absorption that makes them more suitable for treating elderly patients, who often have co-morbidities, or patients with an increased risk of cardiovascular (CV), GI, or renal side effects. Studies with topical diclofenac have shown that its blood level is 0.4–2.2% of the maximum serum concentration achieved with oral diclofenac, resulting in significantly lower systemic exposure [21].

Topical capsaicin has been shown to be more efficacious than control in knee OA, and it is recommended for knee OA patients without co-morbidities as the initial local therapy; however, it is not recommended in both the ACR guidelines and the ESCEO algorithm [5,7] due to limited evidence. In fact, topical NSAIDs, if available and reimbursable, should probably be preferred.

All of the guidelines recommend the use of oral NSAIDs in patients with persistent symptoms that have not responded adequately to paracetamol with or without topical NSAIDs (Table 2) or, in the ESCEO recommendations, to glucosamine sulfate (GS) or chondroitin sulfate (CS). The reported ES of NSAIDs for pain is moderate (ES = 0.29) [22], greater than that of paracetamol [23], and they were shown to be more appropriate in patients with severe pain; in addition, NSAIDs are preferred to paracetamol by patients [24]. Cyclo-oxygenase-2 (COX-2)-selective, partially selective, or non-selective NSAIDs are similarly effective in controlling pain [25], so the drug choice is generally dictated by both the confidence of the physician with the drug and the presence of risk factors such as concomitant diseases and medical therapies, always weighing risks versus benefits (briefly summarized in Table 3) as well as the cost of the drug. The ESCEO algorithm stresses that "longer cycles" of continuous NSAID use are preferable to "chronic" use, because of safety concerns and the relative lack of data from long-term trials [5]. NSAID treatment is associated with serious side effects, mainly upper GI complications (UGIC) (i.e., peptic ulcer perforation, obstruction, and bleeding) [26]. Recently, a meta-analysis reported that high daily doses of several NSAIDs were associated with a 2- to 3-fold increase in the relative risk (RR) of UGIC compared with low-to-medium doses, except for celecoxib, for which no dose–response relationship was found [27], providing a strong rationale for the use of low drug dosages. COX-2 inhibitors, of which celecoxib and etoricoxib are the only two remaining in the market in Europe, are contra-indicated in patients with known CV thrombotic disease (including

Table 2
Recommendations of the use of analgesics and non-steroidal anti-inflammatory drugs (NSAIDs) for knee osteoarthritis (OA)

	Paracetamol	Topical NSAIDs	Oral NSAIDs	Refs.
ACR	Conditionally recommended for initial therapy at a maximal dose of 3000 mg/day	Conditionally recommended for initial therapy either alone or with paracetamol	Conditionally recommended for initial therapy; strongly recommended in patients unresponsive to paracetamol	[7]
EULAR	Recommended as initial therapy; no dose recommendation	Topical NSAIDs have efficacy and are safe	Consider in patients unresponsive to paracetamol	[8]
OARSI	Appropriate for individuals without relevant co-morbidities, with conservative dosing and treatment duration	Appropriate for individuals with knee OA only (with or without co-morbidities)	Appropriate for individuals without relevant co-morbidities; uncertain for those with moderate co-morbidity risk	[9]
NICE	Offer paracetamol in regular doses for pain relief	Consider ahead of oral NSAIDs or opioids; can be used with paracetamol	Use when paracetamol and/or topical NSAIDs are ineffective	[51]
ESCEO	Recommended as rescue analgesia with SySADOAs as background therapy	Recommended with paracetamol or SySADOAs when patients have insufficient pain relief	Recommended when paracetamol or SySADOAs and/or topical NSAIDs are not adequately effective	[5]

ACR, American College of Rheumatology; ESCEO, European Society for Clinical and Economic Aspects of Osteoporosis and Osteoarthritis; EULAR, European League Against Rheumatism; NICE, National Institute for Health and Care Excellence; NSAID, non-steroidal anti-inflammatory drug; OA, osteoarthritis; SySADOAs, symptomatic slow-acting drugs for osteoarthritis.

Table 3
Recommendations for the selection of non-steroidal anti-inflammatory drugs (NSAIDs) for the treatment of osteoarthritis (OA) according to patients' risk factors

Normal GI risk	Non-selective NSAIDs with PPI Cox-2-selective NSAIDs (consider PPI)
Increased GI risk[a]	Cox-2-selective NSAIDs with PPI Avoid non-selective NSAIDs
Increased CV risk	Prefer naproxen Avoid high-dose diclofenac and ibuprofen (if on low-dose aspirin) Caution with other non-selective NSAIDs Avoid Cox-2-selective NSAIDs
Increased renal risk	Avoid NSAIDs[b]

Cox-2, cyclo-oxygenase-2; CV, cardiovascular; GI, gastrointestinal; NSAID, non-steroidal anti-inflammatory drug; OA, osteoarthritis; PPI, proton pump inhibitor.
 [a] Including use of low-dose aspirin.
 [b] With glomerular filtration rate < 30 cc/min; caution in other cases GI.

peripheral arterial disease) in Europe, while in the USA this warning label applies to all prescription NSAIDs. In 2013, following a Europe-wide review of CV safety, warnings were given for diclofenac not to be prescribed to patients with ischemic heart disease, peripheral arterial disease, cerebrovascular disease, or established congestive heart failure [28]. Risk of serious CV events (i.e., myocardial infarction, stroke, and cardiac death) is a matter of debate in the use of NSAIDs. Naproxen has been associated with a lower risk of CV thrombovascular events compared with other NSAIDs, likely due to its sustained suppression of platelet aggregation [29]. Even the risk of CV events seems not to be related to the patient's baseline CV risk [29], although it is recommended that high doses of selective and non-selective NSAIDs should not be used in patients with a high CV risk [5]. However, if an NSAID is to be used in this patient population, naproxen should be preferred for its possible lower CV risk; it should always be co-prescribed with a proton pump inhibitor because of the risk of UGIC [29,30].

Hyaluronates

Hyaluronic acid (HA) is a natural biological substance, a high-molecular-weight glycosaminoglycan. It is a major component of ligament, tendon, and cartilage structure and of synovial fluid, maintaining the visco-elastic properties of the latter. Since depolymerization of HA in the synovial fluid has been reported in OA, the mechanism of intra-articular (i.a.) HA administration is visco-supplementation. Preclinical and clinical evidence support the hypothesis that this treatment modality can be useful, and indeed, i.a. injections of HA have been shown to reduce pain and improve joint function in OA in some studies [31–33]. Table 4 summarizes the recommendations for its use in the treatment of knee OA. The EULAR supported the efficacy of i.a. HA based on level 1B evidence

for both pain reduction and joint functional improvement [8] prior to the availability of recent high-quality meta-analyses. It was, however, pointed out that even if the pain relief could last for several months, it was associated with a slower onset of action and with the need for 3–5 weekly injections with the associated logistic and cost issues. Minimal evidence for disease modification was also reported in one study [8]. Despite overtly recommending it in previous versions, the 2014 OARSI guidelines surprisingly contained an "uncertain" recommendation for i.a. HA in patients with knee-only OA, with benefit scores very close to risk scores [9]. Conversely, both the ACR guidelines [7] and the more recent ESCEO therapeutic algorithm [5] recommend i.a. HA treatment in patients whose symptoms have persisted after prior treatments including oral NSAIDs: this recommendation is based on two recent meta-analyses [34,35]. Longer-lasting pain control has been reported with i.a. HA compared with i.a. corticosteroids [36], possibly delaying the need for total joint replacement [37]. No significant differences have been reported in symptom efficacy between i.a. HA and oral NSAIDs [38], suggesting that i.a. HA might be a good alternative to oral NSAIDs in older patients with knee OA or in those at a higher risk for NSAID-induced side effects. A combination of i.a. HA and a corticosteroid is often administered in the clinical setting, based on the different mechanisms of action and trajectories of the two compounds: the rapid effect of corticosteroids and the long-term effect of HA. However, no clinical data are yet available from RCTs supporting such combined treatment. The safety profile of i.a. HA has recently been questioned by a meta-analysis that reported a risk of side effects (serious adverse events and local adverse events) in addition to therapeutic effects that barely reached significance when the analysis was limited to a selected fraction of trials [35]. It is appropriate to point out that the considered studies were of poor methodological and reporting quality, rendering questionable the final conclusion that i.a. HA is not safe. Furthermore, this analysis is also in complete disagreement with the clinical setting, where only sporadic flares and no severe systemic side effects have been reported after i.a. HA treatment.

Role of chondroitin sulfate (CS) or glucosamine sulfate (GS) in the management of OA

CS and GS are natural compounds, consisting of glycosaminoglycans (CS) or a glycosaminoglycan unit component (GS), that belong to the pharmacological class known as symptomatic slow-acting drugs for osteoarthritis (SySADOAs). They have demonstrated symptomatic effects and potential disease-modifying effects based on the measurement of radiological joint space narrowing (JSN) in some studies [39–43]. Despite the large quantity of published evidence, the efficacy of this class of compounds is still controversial and under debate. The main source of controversy derives from the fact that the regulatory status and labeling of these medications substantially differ in

Table 4
Recommendations of intra-articular (i.a.) hyaluronate for knee osteoarthritis (OA)

	Recommendation	Refs.
EULAR	Evidence to support efficacy. Limitations: logistic and cost issues.	[8]
ACR	No recommendation in the initial management. Conditionally recommended if no satisfactory response to prior treatments.	[7]
OARSI	Uncertain but possible for knee-only OA. Not appropriate for multi-joint OA.	[9]
ESCEO	Recommended for advanced pharmacological management in persistent symptomatic patients if still symptomatic after intermittent or longer cycles of oral NSAIDs.	[5]

ACR, American College of Rheumatology; ESCEO, European Society for Clinical and Economic Aspects of Osteoporosis and Osteoarthritis; EULAR, European League Against Rheumatism; i.a., intra-articular; NSAID, non-steroidal anti-inflammatory drug; OA, osteoarthritis; OARSI, Osteoarthritis Research Society International.

different countries or regions of the world. In Europe, Latin America, and some Asian countries, SySADOAs are prescription drugs whose clinical effects have been investigated in appropriate RCTs conducted with Good Clinical Practice standards and according to the regulatory requirements. On the other hand, in other countries, including the USA, the only available products containing CS and/or glucosamine [mainly as glucosamine hydrochloride (G–HCl), which is a different substance than GS and has a different efficacy profile] are foods or nutritional supplements that do not reach the same level of purity as the prescription formulations, are not bioequivalent with them, and often do not even contain the amount of the substance claimed in the label. Unfortunately, this often applies also to other generics or over-the-counter (OTC) formulations of CS and GS that may be available worldwide and have been used in inconclusive clinical studies instead of the pivotal trials of the prescription medications. In fact, CS and GS generics/OTCs/food and nutritional supplements differ substantially from the original prescription products in their molecular forms, pharmaceutical formulation, purity, and even dose regimens. In this respect, OTC GS is generally given in divided daily doses (e.g., 500 mg tid), whereas prescription GS is given as a single high and bioavailable daily dose (e.g., 1500 mg od) that has a proven pharmacological effect [44]. The interpretation and comparison of efficacy trials is difficult when different drug formulations (prescription drugs versus generics/OTCs/food and nutritional supplements) are used. With this background, it is conceivable that despite compelling evidence of the efficacy of prescription glucosamine or chondroitin formulations in knee OA, there is no universal agreement on when and where to use these drugs.

Table 5 reports the convoluted history of the different recommendations on the use of GS and CS in knee OA over the years. The EULAR [8] recommended both CS and GS for symptomatic treatment on the basis of their high level of evidence (1A). Until 2010, the different versions of the OARSI guidelines not only recommended both CS and GS for symptom modification but also acknowledged a joint structure-modifying effect with long-term treatment [11,13,45]. The 2012 ACR guidelines [7] did not recommend GS or CS for knee OA, and in the latest OARSI guidelines [9], surprisingly, the former recommendations changed from "recommended" to "uncertain" for pain control and to "not appropriate" for disease modification, despite the fact that the panel had agreed on the good safety profile of treatment with these SySADOAs. The rationale behind the unfavorable recommendation by the ACR and the changes in the recommendation in the new OARSI guidelines

was based on (i) the lack of availability of prescription medications in the USA; (ii) the apparent lack of a significant effect on pain in high-quality studies when all formulations and trials are pooled [46]; (iii) the presence of large heterogeneity in favorable meta-analyses, especially for glucosamine; (iv) the lack of effect on pain in a network meta-analysis [47]; (v) the reported negative results of the NIH-supported trial of US nutritional supplements (GAIT study) [48]; and (vi) the reported mixed results of both glucosamine and chondroitin on structure modification [49,50].

The interpretation of these studies that led to the above recommendations has, however, been biased by different factors. First, no distinctions were made between prescription drugs and OTCs/food supplements used in the considered clinical studies. Second, when only the high-quality studies in which prescription GS was used were considered, the clinical effects on both pain and function were indeed significant in the specific Cochrane review quoted [46] and clinically relevant when the ES was appropriately calculated [44] (respectively, 0.27 and 0.33 in long-term studies, i.e., importantly, similar to the ones reported in short-term trials of oral NSAIDs [22]). Third, two out of the three high-quality studies considered for CS were designed to assess its structure-modification effect over 24 months, and the effects on symptoms could not be properly analyzed [40,41]; however, when pain data were assessed at the 6- to 9-month end points, the results were positive. In addition, if all the studies with prescription CS are considered, the ES on pain is 0.75 (ranging from 0.50 to 1.01); the high heterogeneity can be explained by the different study designs and durations [37]. Fourth, the network meta-analysis by Wandel et al. [47] has been highly criticized for severe methodological flaws by the scientific community, including the journal editor, who withdrew the article's negative conclusion [51]. Fifth, in the GAIT study [48], an inefficient formulation of 500 mg of G-HCl three times daily was used; this glucosamine molecular form and dose regimen have a poorer pharmacokinetic profile compared with the prescription GS 1500 mg once-daily formulation approved in Europe [44]. Finally, in the meta-analysis by Lee et al. on structure modification, GS did not show a significant effect versus controls on minimum joint space narrowing (JSN) over the first year of treatment, but, after 3 years of treatment (long-term), a small to moderate protective effect on minimum JSN could be observed, as could be expected when investigating the disease-modifying activity of an agent [50]. Similar positive results were reported for CS in mild-to-moderate disease, with a pain ES ranging from small to

Table 5
Recommendation for use of symptomatic slow-acting drugs for osteoarthritis (SySADOAs) in the treatment of OA

	SySADOAs	Level of evidence or ES	Final recommendation	Refs.
EULAR (2003)	Chondroitin sulfate and glucosamine sulfate	Highest level of evidence (1A), highest strength of recommendation (A)	Recommended for symptomatic effect and might modify structure	[8]
OARSI (2007, 2008, and 2010)	Chondroitin sulfate	Pain ES = 0.75 (0.5–1.01)	Recommended for OA symptoms	[11, 13, 45]
	Glucosamine sulfate	Pain ES = 0.58 (0.3–0.87)	Recommended for OA symptoms	
	Glucosamine HCl	Pain ES = −0.02 (−0.15 to 0.11)	Not recommended	
ACR (2012)	Chondroitin sulfate and glucosamine		Conditional recommendation NOT to use	[7]
OARSI (2014)	Chondroitin sulfate	Pain ES = 0.13 (0.00–0.27) to 0.75 (0.50–0.99)	Recommendation for symptom modification: uncertain	[9]
		mJSW[a] ES = 0.26 (0.14–0.38) to 0.30 (0.00–0.59)	Recommendation for disease modification: not appropriate	
	Glucosamine	Pain ES = 0.17 (0.05–0.28) to 0.47 (0.23–0.72)	Recommendation for symptom modification: uncertain	
		mJSW[a] ES = 1st year: 0.08 (−012 to 0.27); 3rd year: 0.43 (0.24–0.63)	Recommendation for disease modification: not appropriate	
ESCEO (2014)	Glucosamine sulfate	Pain ES = 0.27; function ES = 0.32	Recommended as a background treatment in the initial pharmacological management	[5]
	Chondroitin sulfate	Pain ES from mild to moderate		

ACR, American College of Rheumatology; ES, effect size; ESCEO, European Society for the Clinical and Economic Aspects of Osteoporosis and Osteoarthritis; EULAR, European League Against Rheumatism; OA, osteoarthritis; OARSI, Osteoarthritis Research Society International; SySADOAs, symptomatic slow-acting drugs for osteoarthritis.

[a] mJSW = minimum radiological Joint Space Width, the gold standard surrogate for disease modification.

moderate [9] and long-term data showing hints of structure modification with sustained effects on symptoms [39]. In the recently published ESCEO algorithm recommendations, the experts agreed that based on these data, SySADOAs should be considered a safer and more complete approach than continuous paracetamol as the first step of knee OA management, i.e., as pharmacological background (with paracetamol as needed for rescue analgesia) before initiating more advanced and less well-tolerated treatments if the disease progresses.

As noted above, prescription GS and CS are different from generics/OTCs/dietary supplements in terms of chemistry, pharmaceutical formulations and quality, dose regimens, and pharmacokinetics. When only the data for the prescription formulations are considered, the effects of GS and CS on pain and function are clinically relevant and similar to those of NSAIDs, especially during long-term treatment. These data are even more important when considering the safety profile of these SySADOAs and the side effects associated with long-term use of NSAIDs in chronic conditions like OA.

Discussion and concluding remarks

All of the guidelines reviewed during the debate agree that knee OA is a progressive disease of the joint whose management requires both non-pharmacological and pharmacological approaches. A close review of the different recommendations suggests that there are discrepancies between the guidelines. However, these are few and mostly reflect the heterogeneity of the expert panels involved in their production, differences in the availability of pharmaceutical-quality prescription drugs between countries and regions, and the heterogeneity of the studies considered, including different inclusion criteria, subsets of patients, and study designs. The panels chosen for the development of recommendations should involve experts with a variety of clinical experience; however, it often happens that the ones with greater clinical experience are the ones whose potential conflicts of interest preclude their inclusion in the expert panel. This means that in some cases, the guidelines rely on the data interpretation and opinion of "experts" who have no real clinical experience in drug use or in patient management, at least for the specific topic discussed.

The implementation of the agreed guidelines could also be problematic. In fact, the availability of pharmaceutical-quality prescription drugs, their approval by the appropriate regulatory agencies, and their reimbursement differ between countries and could greatly jeopardize the treatment of patients with OA: this has to be kept in mind in guideline implementation. Intra-articular HA and SySADOAs are indeed clear examples of compounds whose availability and prescription can greatly vary from country to country. In addition, widespread implementation of the guidelines could be hampered by the fact that primary care providers, who are generally responsible for the management of OA patients, are not practicing based on clinical care guidelines. This has been clearly shown for the non-pharmacological treatment of OA [15].

Although harmonization of the different recommendations for knee OA treatment could be challenging, it is indeed feasible. An important step toward this aim has been, for example, the therapeutic algorithm developed and recently suggested by the ESCEO [5]. This algorithm's recommendation suggests a step-by-step treatment in knee OA. This will hopefully allow a more easily disseminated and implemented guide for the OA treatment in the primary care setting favoring the general practitioners, who, as a rule, are the ones directly involved in the management of patients with OA, at least at the beginning.

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