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# An algorithm recommendation for the management of knee osteoarthritis in Europe and internationally: A report from a task force of the European Society for Clinical and Economic Aspects of Osteoporosis and Osteoarthritis (ESCEO)

Olivier Bruyère, PhD[a,*], Cyrus Cooper, MD, PhD[b,c], Jean-Pierre Pelletier, MD, PhD[d], Jaime Branco, MD[e], Maria Luisa Brandi, MD[f], Francis Guillemin, MD, PhD[g], Marc C. Hochberg, MD, PhD[h,i,j], John A. Kanis, MD[k], Tore K. Kvien, MD, PhD[l], Johanne Martel-Pelletier, PhD[d], René Rizzoli, MD, PhD[m], Stuart Silverman, MD[n,o], Jean-Yves Reginster, MD, PhD[a]

[a] *Support Unit in Epidemiology and Biostatistics, Department of Public Health, Epidemiology and Health Economics, University of Liège, CHU Sart Tilman, 4000 Liège, Belgium*
[b] *MRC Lifecourse Epidemiology Unit, University of Southampton, Southampton, UK*
[c] *NIHR Musculoskeletal Biomedical Research Unit, University of Oxford, Oxford, UK*
[d] *Osteoarthritis Research Unit, University of Montreal Hospital Research Centre (CRCHUM), Montreal, Quebec, Canada*
[e] *CEDOC, Department of Rheumatology, Faculdade de Ciências Médicas, Universidade Nova de Lisboa/CHLO, EPE—Hospital Egas Moniz, Lisbon, Portugal*
[f] *Department of Internal Medicine, University of Florence, Florence, Italy*
[g] *Université de Lorraine, Université Paris Descartes, Nancy, France*
[h] *Division of Rheumatology & Clinical Immunology, Department of Medicine, University of Maryland School of Medicine, Baltimore, MD*
[i] *Geriatric Research, Education and Clinical Center, Baltimore, MD*
[j] *Health Care System, Baltimore, MD*
[k] *WHO Collaborating Centre for Metabolic Bone Diseases, University of Sheffield, Sheffield, UK*
[l] *Department of Rheumatology, Diakonhjemmet Hospital, Oslo, Norway*
[m] *Service of Bone Diseases, Geneva University Hospitals and Faculty of Medicine, Geneva, Switzerland*
[n] *Cedars-Sinai Medical Center, Los Angeles, CA*
[o] *OMC Clinical Research Center, Beverly Hills, CA*

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ABSTRACT

*Objectives:* Existing practice guidelines for osteoarthritis (OA) analyze the evidence behind each proposed treatment but do not prioritize the interventions in a given sequence. The objective was to develop a treatment algorithm recommendation that is easier to interpret for the prescribing physician based on the available evidence and that is applicable in Europe and internationally. The knee was used as the model OA joint.

*Methods:* ESCEO assembled a task force of 13 international experts (rheumatologists, clinical epidemiologists, and clinical scientists). Existing guidelines were reviewed; all interventions listed and recent evidence were retrieved using established databases. A first schematic flow chart with treatment prioritization was discussed in a 1-day meeting and shaped to the treatment algorithm. Fine-tuning occurred by electronic communication and three consultation rounds until consensus.

*Results:* Basic principles consist of the need for a combined pharmacological and non-pharmacological treatment with a core set of initial measures, including information access/education, weight loss if overweight, and an appropriate exercise program. Four multimodal steps are then established. Step 1 consists of background therapy, either non-pharmacological (referral to a physical therapist for re-alignment treatment if needed and sequential introduction of further physical interventions initially and at any time thereafter) or pharmacological. The latter consists of chronic Symptomatic Slow-Acting Drugs for OA (e.g., prescription glucosamine sulfate and/or chondroitin sulfate) with paracetamol at-need; topical NSAIDs are added in the still symptomatic patient. Step 2 consists of the advanced pharmacological management in the persistent symptomatic patient and is centered on the use of oral COX-2

* Corresponding author.
*E-mail address:* olivier.bruyere@ulg.ac.be (O. Bruyère).

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selective or non-selective NSAIDs, chosen based on concomitant risk factors, with intra-articular corticosteroids or hyaluronate for further symptom relief if insufficient. In Step 3, the last pharmacological attempts before surgery are represented by weak opioids and other central analgesics. Finally, Step 4 consists of end-stage disease management and surgery, with classical opioids as a difficult-to-manage alternative when surgery is contraindicated.

*Conclusions:* The proposed treatment algorithm may represent a new framework for the development of future guidelines for the management of OA, more easily accessible to physicians.



## Introduction

Osteoarthritis (OA) is the most common form of arthritis and a major cause of disability [1]. The most prevalent OA localization is the knee joint, and symptomatic knee OA affects 24% of the general population [2]; thus, it represents the model for the development of treatment guidelines. Recommendations for the management of knee OA have been issued by national, continental, or global scientific authorities, including, among others, the European League Against Rheumatism (EULAR) [3]; the American College of Rheumatology (ACR) [4]; and the Osteoarthritis Research Society International (OARSI) [5–8]. The UK National Institute for Health and Clinical Excellence (NICE) has also issued a guideline document for the management of OA in adults [9,10].

The European Society for Clinical and Economic Aspects of Osteoporosis and Osteoarthritis (ESCEO) has promoted the creation of different expert working groups in the field of OA to analyze and generate consensus documents on disease management [11,12]. With respect to treatment guidelines, ESCEO felt the need to find a common denominator to the published guidelines and recommendation documents from different sources and generate a treatment algorithm applicable throughout Europe and elsewhere. Most of the existing practice guidelines analyze the evidence behind each proposed treatment but do not (often deliberately) prioritize the interventions because few clinical trials have been designed to study the effect of a given treatment in patients in whom initial therapies have failed and/or when and how new treatments should be introduced. Therefore, treatment remains based on the individualized assessment of the patient, taking into account patients' needs and preferences, or the subjective interpretation of the evidence by the physician. On the other hand, careful analysis of the evidence actually allows one to prioritize interventions and guide physicians into progressive and logical steps. In addition, it was necessary to synthesize the recommendations for the European situation, adapting global guidelines [6–8] to it or using what is applicable from other continental guidelines [4] and broadening the perspective of some national guidelines [9,10], providing an initial update of current European guidelines [3], that can be used virtually universally. Finally, the present effort may represent a new framework for the development of recommendations for the treatment of OA that is more practical and intuitive for practicing physicians than a mere exposition of the available and often contradicting evidence.

## Methods

ESCEO gathered an international task force of 13 members, consisting of 11 rheumatologists (8 from Europe, 2 from USA, and 1 from Canada), 1 clinical epidemiologist, and 1 clinical scientist, all of whom are experienced in the performance, analysis, and interpretation of the clinical trial evidence related to OA.

One member of the task force (O.B.) was entrusted with the task to collect the principal guidelines considered, including the most recent drafts released for consultation [3,4,6–10], and circulate them to the task force. Afterwards, an initial list of all interventions considered in the different documents was compiled, preparing a first and very schematic flow chart for possible prioritization of the different interventions, to the extent possible based on the information within the documents. For each intervention, a complete literature search was performed to identify new or additional randomized controlled trials and systematic reviews/meta-analyses, if any, not used in the existing guidelines. The MEDLINE (PubMed) database was searched using each intervention as a search term together with "osteoarthritis," limiting results to " humans," "randomized controlled trial," "meta-analysis," "review" and "systematic review," and "guideline." A similar search was adapted for the Embase database and each intervention was also searched in the Cochrane Central Register of Controlled Trials, the Cochrane Database of Systematic Reviews, and the Centre for Reviews and Dissemination of the University of York. The reference list of relevant retrieved articles was handsearched for additional resources, while members of the task force were interrogated for their knowledge on articles or congress abstracts in press. A free web search was also performed and considered. Searches were performed from the year 2000 and updated until February 2014, with the additional evidence constantly provided to the task force members for selection of the best evidence according to the panel.

Initial material was presented to the task force, together with the first schematic draft flow chart, in a 1-day meeting at the end of September 2013. During a detailed discussion, the initial flow chart was shaped to the treatment algorithm. Each step and intervention within the steps were discussed and amended until consensus agreement was achieved within the task force. A first draft of the final algorithm and the supporting evidence was then prepared (O.B.); three rounds of consultation occurred by electronic communication between December 2013 and February 2014 on the draft manuscript: all corrections and suggestions by each member were shared with the rest of the task force and included till final consensus with the third consultation round.

ESCEO is a not-for-profit organization dedicated to providing practitioners with the latest clinical evidence in the field of bone, joint, and muscle disorders: the development of practice recommendations is within the institutional scope of the organization to allow specialist and non-specialist practitioners to organize their daily clinical activity in an evidence-based medicine perspective, with a cost-conscious perception. ESCEO receives Unrestricted Educational Grants from several pharmaceutical companies that do not influence the institutional activities of the organization. In particular, the present recommendations were developed independently of any of the funding sources that had no role in the decision to prepare this document and its implementation, revisions, and approval for publication. In addition, each member of the task force individually agreed to declare their potential conflict of interest, if any, in the process of article submission.

## Results

*Basic principles and core set for a treatment algorithm in knee OA*

Appropriate diagnosis of knee OA is an essential pre-requisite to treatment; in this respect, EULAR recently published updated recommendations [13].

Virtually all existing practice guidelines agree that combination of treatment modalities, including non-pharmacological and pharmacological intervention, is strongly recommended. It was the firm opinion of the task force that this basic principle is valid and makes the effort to develop a treatment algorithm an absolute priority in order to prevent physicians from being confused as to how treatments should be prioritized and possibly added on for combination therapy.

The core set proposed by NICE [9] was adopted and expanded by the task force to represent the initial measures and interventions that every patient with knee OA should undergo. In particular,

(1) *Information access and education* consists in providing to the patient the necessary knowledge about the nature of the disease and the objectives of treatment. If necessary, the physician should prompt changes in the patient's lifestyle toward behaviors that may have a beneficial impact on joint protection or at least not worsen the progression of the disease or of its symptoms. It is recognized that these measures have minimal effect on OA symptoms, but they are essential for treatment adherence. EULAR has recently published comprehensive recommendations for the non-pharmacological management of hip and knee osteoarthritis that provided extensive guidance on the principles of information and education, as well as of lifestyle changes [14].
(2) *Weight loss if overweight.* Analysis of the available evidence indicates that at least 5% weight loss within 6 months induces a small but well-substantiated symptomatic benefit, more evident on physical function than on pain, where the effect is less predictable [15]. The task force strongly felt that a threshold should be indicated and, based on previous evidence [15] and a recent high-quality trial [16], weight loss should be targeted to at least 10% to achieve significant symptom benefit. A similar degree of weight loss has also been indicated to improve the quality and thickness of medial femoral compartment cartilage [17].
(3) *Exercise program.* Education should include information about exercise and physical activity [14] since exercise produces benefit on both pain and function in patients with knee osteoarthritis by different delivery modes (individual, group-based, or home programs) [18]. Although the optimal exercise dosing and rate of progression in its application remains unclear, expert opinion suggests that the intensity and/or duration of exercise should be increased over time [14]. There is good evidence that water-based exercise is effective on both pain and function [19]. However, specific quadriceps strengthening exercises or strength training for the lower limb, together with aerobic training such as walking, remain the best documented exercise approaches [18]: experts suggest that mixed programs (to include muscle strengthening, aerobic capacity, and flexibility/range of motion) should be recommended [14] as long as minimal intensity requirements are met [18]. Recent evidence suggests that tai chi is also effective in relieving symptoms [20].

*OA treatment algorithm: Beyond the core set*

It is a common clinical experience that core therapies are usually insufficient to fully control symptoms after diagnosis has been made and with disease progression. In agreement with the basic principle of treatment recommendation, which requires combination of treatment modalities, parallel addition of sequential non-pharmacological and pharmacological therapies should be established. The consequent treatment algorithm that was derived from the present effort is depicted in the Figure and can be described as follows.

*Step 1: Background treatment*

During Step 1, which follows the core set, further background physical remedies should be established as needed. In parallel, and if the patient is still symptomatic, background pharmacological therapy should be started and progressively moved toward combination treatment as soon as the clinical response is not satisfactory.

*Step 1-a: Non-pharmacological background treatment.* During Step 1, the patient should be referred to a physical therapist for assessment to determine whether physical treatments should be introduced. In particular, the physical therapist should first evaluate whether correction for malalignment is necessary. Moreover, he/she should also assess, during Step 1 and throughout steps thereafter at any time, whether other physical measures may be useful for additional symptom relief in parallel to the pharmacological interventions established by the physician.

Varus or valgus malalignment is a risk factor for knee OA and its progression. Therefore, there is a theoretical rationale for using biomechanical interventions such as braces or insoles in patients with unicompartmental tibiofemoral OA to reduce malalignment, to reduce the consequent articular stress, and thus to improve pain and function, or even retard disease progression. Despite significant heterogeneity and poor trial quality, there is reasonable evidence to suggest that knee braces actually improve biomechanical imbalance [21] and may improve knee OA symptoms [22]. The same may apply with multi-modal re-alignment treatment that includes braces, foot orthoses, and appropriate footwear [23]. Among foot orthoses, there are many studies on laterally wedged insoles in medial compartment knee OA aimed to increase foot pronation, thereby reducing medial compartment loading. Their biomechanical effects are more inconsistent [21] and the clinical efficacy is controversial; in particular, a recent high-quality meta-analysis found a significant effect on pain in all randomized controlled studies combined, but no effect when the more reliable higher quality trials were considered [24]. There are fewer studies on laterally wedged insoles with subtalar strapping and on medially wedged insoles for unicompartmental lateral OA, although they tend to show efficacy [22,24]. There is insufficient evidence to determine whether braces or insoles affect the progression of knee OA. EULAR did not recommend the use of insoles among non-pharmacological treatments for knee OA, also in view of an increased risk of adverse effects [14]. On the other hand, appropriate footwear (including shock-absorbing soles, foot arches support, and control for foot pronation if necessary, while avoiding raised heels) should be recommended [14].

Ideal patients for bracing are younger individuals, more physically active, not severely obese, with unicompartmental symptomatic tibiofemoral OA and malalignment that is reducible by valgus or varus stress maneuvers on physical examination. For laterally wedged insoles, patients should also probably have early and mild disease.

Among additional physical remedies, access to walking aids is an important help in providing security to patients: although appropriate clinical studies are scarce, a recent randomized trial confirmed that use of a cane improves symptoms in knee OA [25]. Referral to a physical therapist may also include assessment for the use of thermal therapies, such as ultrasound, for which there is

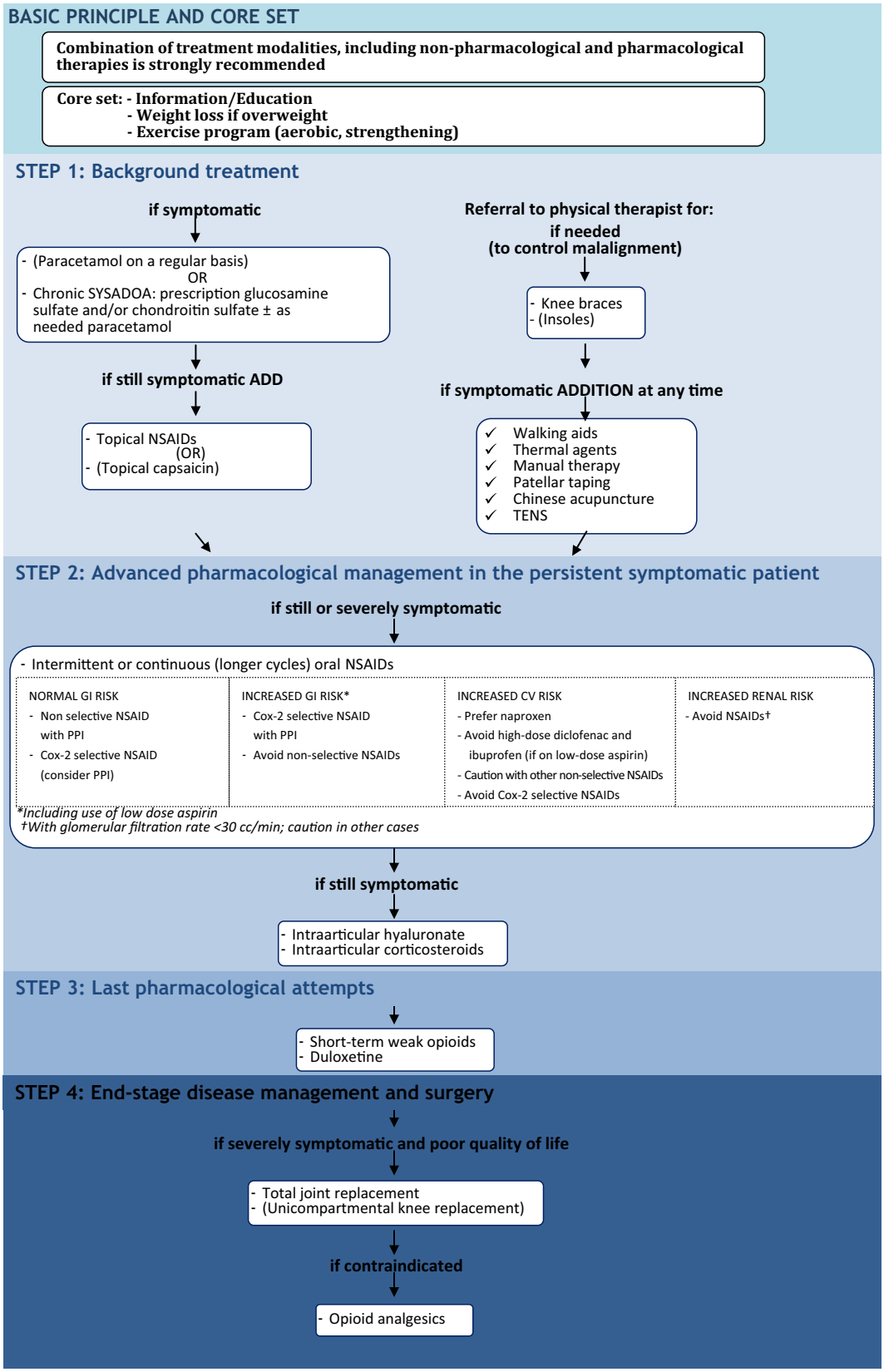


**Fig.** Knee osteoarthritis treatment algorithm. COX-2, cyclooxygenase-2; CV, cardiovascular; GI, gastrointestinal; NSAIDs, non-steroidal anti-inflammatory drugs; PPI, proton pump inhibitor; SYSADOA, Symptomatic Slow Acting Drugs in Osteoarthritis.

some evidence of efficacy, albeit in low-quality studies [26]. Indeed, more recent randomized trials failed to show additional improvement of ultrasound over a sham procedure [27], or for manual therapy in combination with exercise, or patellar taping where needed. Balneotherapy and, especially, acupuncture ranked high in a recent network meta-analysis of all physical treatments

for knee OA [28]. On the other hand, other studies suggest that the benefit of acupuncture is small, especially compared with sham acupuncture [29], and possibly due to expectation or placebo effect [30]. Finally, Transcutaneous Electric Nerve Stimulation (TENS) is also a possible physical intervention; the evidence is scarce, especially because of the availability (as it often happens for physical remedies) of mainly small and low-quality studies [31]. However, a recent larger randomized trial suggested that TENS may reduce the need for analgesic medications [32]. Interestingly, the recent ACR guidelines [4] suggested an approach that would advise reserving acupuncture and TENS as a non-pharmacological alternative to surgery when this is contraindicated or the patient is unwilling to undergo surgery. There are no specific studies in this respect and thus it is correct that both acupuncture and TENS are listed here and considered throughout the algorithm flow including, but not necessarily, as an alternative to surgery.

*Step 1-b: Pharmacological background treatment.* The aim of Step 1 pharmacological treatment is to establish a first chronic therapy that may improve or control symptoms or at least provide rescue analgesia.

Paracetamol at doses no greater than 3 g/day on a regular basis is recommended as an initial pharmacological approach in most clinical guidelines, despite its minimal effects on symptoms but in the presumption of acceptable safety and affordable price. However, a recent meta-analysis [33] outlined that the vast majority of clinical trials (of either immediate release or extended release formulations) were performed over durations of less than 6 months, thus questioning paracetamol chronic treatment role; indeed, the only placebo-controlled study of 6-month duration found a significant effect on function but not on pain [34]. This meta-analysis also confirmed the small effect size, less than 0.20, detected in a previous OARSI guideline update [7] and confirmed in large trials or those analyzed by intention-to-treat [33]. In addition, there is accumulating evidence for an increased risk of gastrointestinal adverse events with paracetamol use, with significant elevation in liver enzymes [7]. Indeed, paracetamol is the most frequent cause of drug-induced liver injury in the United States and over half of such cases are due to unintentional ingestion.

A safer and more sensible approach would be to use as a background therapy, chronic Symptomatic Slow-Acting Drugs for Osteoarthritis (SYSADOAs), with as needed paracetamol for short-term, rescue analgesia. Among SYSADOAs, prescription glucosamine sulfate should be differentiated from other glucosamine preparations. The latest update of a specific Cochrane Review [35] clearly showed that while the overall pain benefit of all glucosamine formulations together is jeopardized by high heterogeneity, subgroup analysis of non-prescription glucosamine high-quality trials showed no benefit versus placebo [35]. Conversely, high-quality trials of the patented prescription formulation approved in Europe and elsewhere (crystalline glucosamine sulfate) showed that it was superior to placebo in the treatment of pain and functional impairment [35]: all three pivotal trials [34,36,37] are long-term studies of 6 months to 3 years treatment in patients with mild-to-moderate pain and the calculated global effect size, without heterogeneity, is 0.27 (95% CI: 0.12–0.43) on pain and 0.33 (95% CI: 0.17–0.48) on function [38], i.e., in about the same range of short-term trials of oral non-steroidal anti-inflammatory drugs (NSAIDs) [39]. A recent network meta-analysis, again mixing all formulations [40], was criticized for severe methodological flaws [41] and the journal editor withdrew the article's negative conclusions [42]. The ACR guidelines did not recommend glucosamine because they noted that glucosamine is not a prescription drug in the USA, but only dietary supplements exist whose quality has not been evaluated by the FDA [4]. In addition, such dietary supplements often contain glucosamine hydrochloride and a large, NIH-sponsored trial showed no benefit of this preparation [43], similar to other studies of glucosamine hydrochloride [7,9]; indeed, these formulations have a different pharmacokinetic profile than prescription glucosamine sulfate 1500 mg once daily approved in Europe [44], and appropriate bioequivalence studies should be conducted before recommending glucosamine generic or OTC products [35]. Long-term prescription glucosamine sulfate may delay joint structure changes [36,37], suggesting potential benefit beyond symptom control when used early in the management of knee OA as recommended here.

Chondroitin sulfate may offer similar benefits on joint structure changes in patients with mild-to-moderate disease [45–47] using prescription chondroitin 4&6 sulfate. It should, however, be acknowledged that joint structure modification is not an approved indication for either prescription chondroitin or glucosamine sulfate but a potential benefit when they are used for long-term symptom control. In this respect, the data on chondroitin sulfate have been reported as conflicting [48], but the effect size on pain in meta-analyses ranges from 0.13 (0.00–0.27) to 0.75 (0.50–0.99) [8]. On the other hand, full data of one pivotal trial on chondroitin 4&6 sulfate have been published more recently and show chondroitin sulfate to reduce joint structural changes with a symptomatic effect that could be clinically relevant [46], as confirmed in another recent study [49]. The prescription drug used in this study [46] should be distinguished from low-quality OTC products available outside of Europe. As for glucosamine sulfate, the negative conclusions of a recent network meta-analysis [40] were withdrawn by the editor [42].

Beside their efficacy record, both glucosamine sulfate and chondroitin are safe medications, with no difference in adverse effects compared with placebo [35,46], which would also strengthen their role as chronic background treatments. Glucosamine and chondroitin sulfate are often used in combination as dietary supplements. Unfortunately, there are no published trials of the two pharmaceutical-grade prescription preparations combined. On the other hand, the previously mentioned NIH-sponsored trial [43], while finding no overall benefit, described a significant symptomatic effect in an exploratory analysis of patients with moderate-to-severe pain receiving a glucosamine hydrochloride and chondroitin sulfate combination [43]. Indeed, a similar combination has been shown to have comparable efficacy to celecoxib after 6 months in knee OA patients with moderate-to-severe pain (Hochberg et al., abstract presented at OARSI 2014). More interestingly, and following preliminary data from the Osteoarthritis Initiative database [50], a recently published trial from Australia found significant and clinically relevant joint structure modification after 2 years with a non-prescription or pharmaceutical-grade chondroitin/glucosamine sulfate combination, with apparently no effects on symptoms given the very mild and placebo responsive population studied [51].

The evidence for efficacy of other SYSADOAs, such as avocado soybean unsaponifiables (ASU) and diacerein, is more scarce [52,53]. With respect to diacerein, the European Medicines Agency (EMA) recently informed that despite the most recent meta-analysis showing some degree of efficacy without heterogeneity, safety issues may outline a negative benefit/risk ratio and a re-assessment was recommended [54]. Furthermore, newer drugs are gaining credit for their possible role as disease-modifying agents in OA, e.g., strontium ranelate (SR), a chemical entity currently marketed for the treatment of postmenopausal osteoporosis and osteoporosis in males. SR exhibited effects on subchondral bone and cartilage, which may be suggestive of a beneficial effect on OA progression. A recent high-quality 3-year placebo-controlled trial showed that SR decreases radiological progression of knee OA,

together with improving symptoms [55]. The drug was well tolerated in this trial, but the EMA recently restricted the use of SR to the treatment of severe osteoporosis due to a possible increase in cardiovascular risk [56]; therefore, the role of the drug in the management of OA will need further reassessment.

If the patient is still symptomatic after establishing appropriate background pharmacological therapy with SYSADOAs and rescue analgesia with paracetamol is insufficient, topical NSAIDs may be added to the pharmacological background and in parallel with non-pharmacological treatment. The efficacy of topical NSAIDs was established in several randomized trials that were systematically reviewed in 2004 [57]; the evidence shows a moderate effect size in the relief of OA pain [9] with high heterogeneity possibly due to differences between topical products. Recent randomized trials confirmed that there is no significant difference between topical NSAIDs and their oral counterpart, with topical formulations showing better gastrointestinal safety but more local cutaneous reactions, including in large studies [58,59] and as discussed in a comprehensive systematic review [60]. However, most of the studies were for $\leq$12 weeks, which would confirm topical NSAIDs' role as cyclic add-on analgesics if the background treatment leaves the patient symptomatic. Only one study performed in general practice [61] confirmed similar findings over 1 year, but the study did not meet all quality standards of a rigorous randomized controlled trial and was not blinded [61].

While topical rubefacients containing salicylates did not show efficacy compared with placebo in OA, with increased risk of local adverse reactions [62], there is no particular reason to recommend topical capsaicin instead of topical NSAIDs when all the available evidence is reviewed [60]. In fact, despite some evidence of efficacy against placebo, there is increased risk of local adverse reactions and no comparative trials with topical or oral NSAIDs.

*Step 2: Advanced pharmacological management in the persistent symptomatic patients*

The task force agreed that patients with mild-to-moderate pain due to knee OA can be appropriately managed by careful application of core set and Step 1 treatment modalities. However, if Step 1 shows inadequate efficacy or in patients arriving to the observation with moderate-to-severe pain, benefit may be achieved with advanced pharmacological treatment. However, these treatments are less manageable and/or prone to more severe adverse reactions.

In this respect, a central role within the pharmacological management of OA is traditionally represented by the use of oral NSAIDs. Recourse to oral NSAIDs may occur early for rescue analgesia in very short treatment cycles. In fact, oral non-selective or COX-2-selective NSAIDs provide better symptom relief than paracetamol [63], with an effect size on pain of 0.29 (0.22–0.35) [39], which is double the effect of paracetamol [63]. Indeed, patients show a higher preference for NSAIDs compared to paracetamol [64]. Although systematic reviews of head-to-head trials show no clear difference between glucosamine sulfate and oral NSAIDs for pain or function [60], with better safety of the former [35], the task force believes that based on the available clinical trial evidence, NSAIDs may be appropriate in patients with more severe pain, particularly if the SYSADOA has failed to effectively control symptoms. On the other hand, SYSADOAs may decrease NSAID use if adopted as a background therapy [65].

Oral NSAIDs may be used intermittently or continuously, although even the latter is not represented by chronic use but by longer cycles, because of safety concerns and the paucity of long-term trials. Recent systematic reviews of the many, mostly short-term, clinical trials show no clear differences in efficacy between COX-2 selective, partially selective, or non-selective NSAIDs [60]. Drug choice within available NSAIDs is therefore dictated by their safety profile according to the different risk factors and patients' concomitant diseases and medical conditions.

While COX-2-selective agents are associated with fewer gastrointestinal ulcer complications than non-selective NSAIDs over short-term use, this is not clear over longer periods of treatment [60], in particular for celecoxib [66] or etoricoxib [67], which are the only COX-2-selective agents left in the market in Europe. Indeed, recent evidence suggests that coxibs significantly increase the risk of upper gastrointestinal complications compared to placebo, although at a lower rate than non-selective NSAIDs [68]. Thus, on one hand non-selective NSAIDs should always be co-prescribed with proton pump inhibitors (PPI). However, for the reasons described above and for recent cost-effectiveness evidence [69], the task force believes that in patients with normal gastrointestinal risk, physicians should consider whether a PPI should be co-prescribed also with COX-2-selective NSAIDs. In patients with increased gastrointestinal risk, non-selective NSAIDs should be avoided and COX-2-selective NSAIDs should be co-prescribed with a PPI [70]. Concomitant use of aspirin increases non-selective NSAID gastrointestinal risk and at least partially negates COX-2-selective NSAID improved gastrointestinal tolerance [71]: addition of a PPI is beneficial and reduces the risk in either case [60].

There is little doubt that all NSAIDs, selective and non-selective, increase the risk of serious cardiovascular events; however, naproxen is usually associated with lower risk for thrombotic cardiovascular events [60]. This was confirmed in a recent meta-analysis of individual patient data from 639 randomized controlled trials [68], in which coxibs and diclofenac were shown to increase major vascular events by a third, mainly because of increased major coronary events (including fatal and non-fatal myocardial infarction) that occurred also with ibuprofen but not with naproxen that did not increase the general vascular risk, probably due to its sustained suppression of platelet aggregation [68]. In 2012, EMA stated that data suggest that naproxen may be associated with a lower risk for arterial thrombotic events than COX-2 inhibitors and other NSAIDs, although a small risk cannot be excluded [72]. This latter opinion is shared by the FDA, which recently decided not to recommend changes in the cardiovascular warning for naproxen based on the totality of the evidence from systematic reviews of observational studies and randomized controlled trials (Hochberg MC, personal communication).

While earlier evidence suggested that the relative risk of cardiovascular events increases with increased baseline cardiovascular risk at the start of treatment with COX-2-selective NSAIDs [73], the most recent and comprehensive meta-analysis found that the proportional increase in risk was similar irrespective of baseline risk [68]; however, the excess absolute risk is in any case higher in patients at high risk of major cardiovascular events and receiving coxibs or diclofenac and, probably, ibuprofen [68]. For this reason, the task force suggests to avoid coxibs and high-dose diclofenac or ibuprofen in high cardiovascular risk patients. However, this may apply to other non-selective NSAIDs as well (naproxen being a possible exception), based on observational studies [74] where the risk is persistently elevated [75], suggesting much caution. On the other hand, naproxen, because of its possibly lower cardiovascular risk [68,75], may be the preferred agent if an NSAID should be used in patients at high cardiovascular risk. Concomitant use of low-dose aspirin did not attenuate the increased cardiovascular risk associated with COX-2-selective NSAIDs in placebo-controlled trials [76,77], while observational studies did not find increased cardiovascular risk when non-selective NSAIDs, other than ibuprofen, are added to low-dose aspirin [60]. Actually, this does not apply to ibuprofen, which has a

clinically relevant pharmacodynamic interaction with the actions of aspirin and should be therefore avoided [78].

The association of NSAIDs with increased cardiovascular risk is a complex issue that, besides being directly mediated by prostanoid imbalance [79], may have indirect causality linked to the increase in blood pressure, congestive heart failure, and renal dysfunction associated with all NSAIDs [80] that should be always considered by physicians. In particular, it may be useful to suggest avoiding oral NSAID use in patients with increased renal risk, such as chronic kidney disease with estimated glomerular filtration rate below 30 cc/min [4].

In case of contraindications to NSAIDs, or if the patient is still symptomatic despite use of NSAIDs or was severely symptomatic, intra-articular treatment may be applied.

The role of intra-articular hyaluronic acid injections has been controversial, but most meta-analyses have shown a significant benefit in knee osteoarthritis, which is small when restricted to high-quality trials [7]. However, a more recent meta-analysis showed an effect size of 0.34 (0.22–0.46), which is hindered by high heterogeneity but survives several sensitivity analyses based on trial quality and, importantly, the small effects last up to 6 months after treatment [81]. These favorable results are confirmed by another recent meta-analysis in which, on the other hand, the authors make negative conclusions based on selective, and questionable, evidence [82] and that this task force does not endorse. Indeed, intra-articular hyaluronic acid injections are relatively safe, although pseudoseptic reactions have been reported especially with cross-linked formulations of the highest molecular weight. In addition, hyaluronic acid induces longer-lasting pain control compared with intra-articular corticosteroids [83] and may delay total joint replacement [84]. In addition, recent findings suggest that there are no significant differences in symptom efficacy compared with oral NSAIDs [85]; indeed, intra-articular hyaluronic acid might be a good alternative to NSAIDs in knee OA in older patients or in those at greater risk for NSAID-induced adverse effects.

Intra-articular corticosteroids may be suggested in patients especially when there is an effusion, although this recommendation is more theoretical than based on actual evidence. Practically, joint aspiration of the synovial fluid is directly followed by intra-articular administration of corticosteroids, e.g., methylprednisolone acetate or triamcinolone hexacetonide. They indeed have higher efficacy than intra-articular hyaluronic acid over the first weeks after administration [83], but their effect on pain may actually last for only a few (1–3) weeks in controlled trials [86]. Safety is good, with some evidence also over repeated cycles [87] if scheduled because of the short-lasting analgesic effect.

*Step 3: Last pharmacological attempts before surgery*

A patient who has failed all the above sequential approaches may be considered as a candidate to surgery. Last pharmacological chances for the severely symptomatic patient may be represented by the recourse to short-term weak opioids. The efficacy of tramadol in relieving pain and improving function in knee osteoarthritis is small but significant [88]; adverse events are significantly increased over placebo and (although they may be mostly minor) they may lead to treatment withdrawal in a substantial proportion of patients [88]. In general, opioids used in arthritis patients are associated with significant morbidity and should be used with extreme caution [89]. Combination therapy with tramadol and paracetamol has been shown to be effective when added to NSAIDs in patients who have not adequately responded to the latter [90]. However, the safety issues seem to be the same for tramadol alone and it is unclear whether combining only paracetamol with NSAIDs in these patients would also result in improved efficacy but less adverse effects [91].

Antidepressants are commonly used in chronic pain syndromes because they alter pain neurotransmitters (i.e., serotonin and norepinephrine) centrally, which may to some extent be applicable also to tramadol. Indeed, central sensitization may play a role in the severity of osteoarthritis pain [92]. In this respect, evidence for the use of duloxetine in knee osteoarthritis derives mainly from two randomized, placebo-controlled trials of short-term, 13 weeks, duration showing benefit in clinically relevant outcomes but a similar likelihood to elicit adverse reactions, such as nausea, fatigue, constipation, dry mouth, and others [93]. In a similarly short-term study, duloxetine improved knee pain in patients with an inadequate response to NSAIDs [94], which would confirm the drug's possible role in advanced patient management. Additional and longer term evidence is needed before moving duloxetine to earlier steps in the management of the disease. Actually, early physical examination may allow recognition of patients with central sensitization [95] who thus may benefit from central analgesics earlier in the course of the disease management.

*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 task force's commitment. However, there is little doubt that total joint replacement is cost-effective when all previous modalities have failed and there is significant loss in quality of life, although this is based mainly on studies other than randomized controlled trials [96] for obvious reasons. Total joint replacement is very effective in relieving severe symptoms of knee OA and has a high benefit/risk ratio when patients are carefully selected, well informed, anesthesia and surgery are well performed, and rehabilitation is appropriate [10]. The latter is particularly important when started immediately after surgery and normal activities can be then resumed 6–12 weeks after the intervention, with 95% of all joint replacement prostheses expected to survive into the second decade after surgery; only around 20% of patients do not benefit following total joint replacement [10].

Unicompartmental knee replacement is effective when the disease is restricted to a single knee joint compartment and patients may experience fewer complications such as deep vein thrombosis [97]. Among other surgical procedures, there is some evidence for certain efficacy of high tibial osteotomy for medial compartment knee disease [98] and no favorable evidence for joint lavage/debridement [99].

For severely symptomatic patients in whom surgery is contraindicated or if they are unwilling to undergo surgery, the last pharmacological chance may be represented by classical oral or transdermal opioids, although their small to moderate efficacy is outweighed by the large increase in the risk of adverse events [100]. The guidelines for the use of opioid analgesics in the management of chronic non-cancer pain should be followed [101].

## Discussion

Among the many current recommendations and guidelines issued by respectful scientific societies worldwide for the management of osteoarthritis [3–10], this is the first effort to produce a detailed algorithm that guides the physicians through the different steps of treatment of an individual patient.

The only previous attempt to generate an algorithm was performed with the NICE guidelines [9,10]. However, this is limited by regulatory approvals in UK (not all drugs taken into consideration here have the same regulatory history in UK than in other European countries) and, especially, by considerations on sustainability by the UK National Health System (NHS). Indeed, there are a limited number of pharmacological options considered in the final

NICE documents. Most importantly, there are only two rings (given the particular shape of the NICE algorithm) after the core interventions (education, exercise, and weight loss) with low, if any, degree of prioritization in the third and most comprehensive step that spans from oral NSAIDs to joint arthroplasty. These limitations did not improve with the new NICE guideline update [10].

Other recently released recommendations, such as the American College of Rheumatology guidelines [4], as it may be the case in other countries, are also influenced by the incomplete local availability of all drugs considered in our present effort. In addition, the ACR panel deliberately decided not to develop an algorithm but to use a formal process to rate the available evidence. Such process led to the absence of what the process designated as "strong recommendation" for any pharmacological interventions for knee OA, except for oral NSAIDs in patients with an inadequate response to acetaminophen (paracetamol) and do not have contraindications to these agents. Almost all pharmacological treatments were rated with a "conditional (weak) recommendation" and some received "no recommendation." The ACR guidelines' authors acknowledged that while most of the recommendations will not be controversial, some may be met with disagreement [4].

Similar limitations are applicable to the new OARSI guidelines. OARSI has a strong tradition of detailed evidence-based analysis with clear recommendations on the use of a given intervention [5–7]. In the latest guidelines [8], OARSI has chosen a "minimalist" approach in which the evidence is only briefly, and often incompletely, substantiated, and interventions are put in a mere alphabetical order, with the majority of them being classified with an "uncertain" recommendation. Only a small proportion of them received an "appropriate" recommendation, and knee OA patients with co-morbidities (the vast majority within this elderly patient population) are left only with topical NSAIDs and intra-articular corticosteroids as recommended appropriate treatments, beside the possible use of biomechanical interventions and a walking cane [8]. Therefore, the ESCEO task force found not particularly compelling the differentiation between an "appropriate" and an "uncertain" recommendation, the latter being difficult to interpret for the prescribing physician.

The algorithm proposed here summarizes the evidence on all proposed treatments and puts them in the sequence suggested by the evidence itself. Although one major limitation consists in the lack, in the vast majority of cases, of appropriate clinical studies on treatment prioritization, it is the firm opinion of the task force that the evidence from available standard trials is sufficient to propose a given intervention at a certain step of the algorithm.

Following the core set that, in agreement with most existing recommendations and guidelines, includes information/education, weight loss if the patient is overweight, and the establishment of an appropriate exercise program, the algorithm proposes four multimodal steps. During Step 1, there is an attempt to better characterize the use of paracetamol as the initial pharmacological intervention. Given its limited efficacy and some recent concerns on its safety, the task force proposes that paracetamol may remain for rescue analgesia during a background treatment with SYSADOAs, such as glucosamine sulfate or chondroitin sulfate: both of the latter should be not only of pharmaceutical grade, but specific prescription drugs are approved in Europe and elsewhere and they are the only products the task force recommends on the basis of the strong clinical evidence, including safety and the possibility of additional benefit when used in the early steps of disease management [36,37,46].

Topical NSAIDs may be added for additional analgesia given their short-term symptomatic efficacy similar to that of their oral counterparts and good systemic safety. Moreover, during this first step, appropriate background non-pharmacological treatment should be established beyond the core set and added sequentially at any time throughout prosecution of the algorithm flow, according to patient's response.

Step 2 consists of the advanced pharmacological management in the persistently symptomatic patient. It is acknowledged here that the central role within this step is represented by the recourse to oral NSAIDs. Despite the unclear differentiation in the available direct comparisons between oral NSAIDs and SYSADOAs or topical NSAIDs, the task force believes that the former may be more effective in more severe patients. On the other hand, the most important safety considerations were reviewed here and brought to the recommendation that oral NSAIDs should not be used chronically, but intermittently or continuously in longer treatment cycles. Secondly, such safety considerations led to different selection principles among non-selective or COX-2-selective NSAIDS, depending on the underlying gastrointestinal, cardiovascular, or renal risk.

Intra-articular treatment represents a more advanced pharmacological measure. Indeed, both hyaluronic acid and corticosteroids have mainly been studied in patients who have failed prior analgesic or anti-inflammatory treatment. Both the treatments can be clinically differentiated by the duration of the induced benefit, which is stronger for intra-articular corticosteroids but short-lived (a few weeks following a single injection) compared to hyaluronate whose effect size is smaller (and more controversial) but lasting for up to 6 months after a 1–3 weekly treatment course.

Step 3 consists of the last pharmacological attempt before surgery and includes oral weak opioids or duloxetine, whose still partial evidence was obtained in non-responders to previous treatment; the mild efficacy is challenged by adverse reactions that may lead to frequent patient withdrawal and significant morbidity [89].

Finally, end-stage disease management is the last or fourth step within the algorithm and consists of surgical procedures mainly represented by total joint replacement, with classical opioids as a difficult-to-manage alternative for patients in whom surgery is contraindicated.

Importantly, the algorithm developed here is to our knowledge the first attempt to provide guidance on combination or multimodal therapy. In fact, first of all, the task force believes that the core set given here should always be enforced in all patients, similar to the background treatment foreseen in Step 1, which already provides advice for multimodal therapy by suggesting on one side addition at any time of non-pharmacological treatment modalities when needed and, on the other side, the addition of topical NSAIDs to chronic SYSADOAs (with paracetamol for rescue analgesia) for further pain control if appropriate. When patients are moved to Step 2 and thus to treatment with oral NSAIDs, the background treatment of Step 1 should not be withdrawn since it can still provide a different approach to disease and limit the use of NSAIDs. Similarly, the decision to start intra-articular hyaluronate or corticosteroids if the patient is still symptomatic should not lead automatically to abandon any of the previous treatment modalities. Things get more complicated when the patient enters Step 3 because of insufficient symptom control; it may be safe to say that while Step 1 modalities might continue because they may provide different long-term benefit, the extent to which treatments adopted in Step 2 should be replaced depends on the overall benefit/risk ratio. Obviously, Step 4 changes all the perspective, especially when it involves definitive surgical procedures.

The present effort is an expert consensus strongly based on the available evidence. Among scientific societies within the Rheumatology area, ESCEO is the only one devoted to two specific disorders, such as osteoporosis and osteoarthritis, given the many biological connections between the bone and the joint. While most experts in the present task force have actually clinical and research expertise in both diseases or predominantly in OA and have widely

published in this field, a small minority have a predominant research interest in osteoporosis. However, all of them are physicians specialized within rheumatological areas, have a huge expertise in the care of patients with OA, and sit on scientific boards devoted to OA and pharmacoeconomics of rheumatic disorders.

When looking at all treatment modalities considered, the task force believes that a complete overview has been provided for non-pharmacological background treatment while, as mentioned, a more extensive review of surgical procedures in Step 4 would have gone beyond the scopes of these recommendations. Conversely, virtually all pharmacological treatments available have been reviewed and included in the algorithm, with the relevant comments. Drug classes that have not been reviewed here include bisphosphonates, due to failure of the phase III clinical trials with risedronate in controlling symptoms and joint structure disease progression, despite favorable changes in some biomarkers [102]. Muscle relaxants have not been included as well, due to the lack of appropriate trials in osteoarthritis, while studies have concentrated in other rheumatological conditions (e.g., cyclobenzaprine in fibromyalgia).

As any guidance document the present effort suffers from the limitations imposed by the generation of new evidence that may accumulate in the meantime and will need periodic revisions. For the time being, it contains easy-to-follow and evidence-based advice on how and when establishing a treatment flow in patients with knee OA. In addition, this document represents the attempt for a new framework for the development of new international guidelines for the management of OA that is more easily accessible and understandable to specialists and practicing physicians.

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