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# A consensus statement on the European Society for Clinical and Economic Aspects of Osteoporosis and Osteoarthritis (ESCEO) algorithm for the management of knee osteoarthritis—From evidence-based medicine to the real-life setting

Olivier Bruyère, PhD[a,*], Cyrus Cooper, MD, PhD[b,c], Jean-Pierre Pelletier, MD[d], Emmanuel Maheu, MD[e], François Rannou, MD, PhD[f], Jaime Branco, MD[g], Maria Luisa Brandi, MD[h], John A. Kanis, MD[i], Roy D. Altman, MD[j], Marc C. Hochberg, MD, PhD[k,l,m], Johanne Martel-Pelletier, PhD[d], Jean-Yves Reginster, MD, PhD[n]

[a] *Support Unit in Epidemiology and Biostatistics, Department of Public Health, Epidemiology and Health Economics, University of Liège, CHU Sart Tilman, Liège 4000, 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] *Rheumatology Department, AP-HP, Saint-Antoine Hôpital, Paris, France*
[f] *Rehabilitation Unit, Rheumatology Department, Hôpital Cochin, AP-HP, INSERM UMR-S 1124, Université Paris Descartes, Paris, France*
[g] *CEDOC, Department of Rheumatology, Faculdade de Ciências Médicas, Universidade Nova de Lisboa/CHLO, EPE–Hospital Egas Moniz, Lisbon, Portugal*
[h] *Department of Internal Medicine, University of Florence, Florence, Italy*
[i] *WHO Collaborating Centre for Metabolic Bone Diseases, University of Sheffield, Sheffield, UK*
[j] *David Geffen School of Medicine, University of California, Los Angeles, CA*
[k] *Division of Rheumatology & Clinical Immunology, Department of Medicine, University of Maryland School of Medicine, Baltimore, MD*
[l] *Geriatric Research, Education and Clinical Center, Baltimore, MD*
[m] *Health Care System, Baltimore, MD*
[n] *Department of Public Health, Epidemiology and Health Economics, University of Liège, Liège, Belgium*

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## ABSTRACT

The European Society for Clinical and Economic Aspects of Osteoporosis and Osteoarthritis (ESCEO) published a treatment algorithm for the management of knee osteoarthritis (OA) in 2014, which provides practical guidance for the prioritization of interventions. Further analysis of real-world data for OA provides additional evidence in support of pharmacological interventions, in terms of management of OA pain and function, avoidance of adverse events, disease-modifying effects and long-term outcomes, e.g., delay of total joint replacement surgery, and pharmacoeconomic factors such as reduction in healthcare resource utilization. This article provides an updated assessment of the literature for selected interventions in OA, focusing on real-life data, with the aim of providing easy-to-follow advice on how to establish a treatment flow in patients with knee OA in primary care clinical practice, in support of the clinicians' individualized assessment of the patient. In step 1, background maintenance therapy with symptomatic slow-acting drugs for osteoarthritis (SYSADOAs) is recommended, for which high-quality evidence is provided only for the prescription formulations of patented crystalline glucosamine sulfate and chondroitin sulfate. Paracetamol may be added for rescue analgesia only, due to limited efficacy and increasing safety signals. Topical non-steroidal anti-inflammatory drugs (NSAIDs) may provide additional symptomatic treatment with the same degree of efficacy as oral NSAIDs without the systemic safety concerns. Oral NSAIDs maintain a central role in step 2 advanced management of persistent symptoms. However, oral NSAIDs are highly heterogeneous in terms of gastrointestinal and cardiovascular safety profile, and patient stratification with careful treatment selection is advocated to maximize the risk:

*Abbreviations:* CS, chondroitin 4&6 sulfate; GS, glucosamine sulfate; IA, intra-articular; HA, hyaluronic acid; pCGS, patented crystalline glucosamine sulfate; SYSADOAs, symptomatic slow-acting drugs for osteoarthritis.

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

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benefit ratio. Intra-articular hyaluronic acid as a next step provides sustained clinical benefit with effects lasting up to 6 months after a short-course of weekly injections. As a last step before surgery, the slow titration of sustained-release tramadol, a weak opioid, affords sustained analgesia with improved tolerability.



## Introduction

Osteoarthritis (OA) is a progressive disease of the synovial joints that causes joint pain and limitation of function resulting in considerable morbidity, impairment of quality of life, and social and economic burden [1,2]. 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 [3]. OA accounts for a substantial number of healthcare consultations and is a leading indication for use of prescription drugs, at around US $3000 per patient per year [4]. With the increasing aging population, OA is expected to become the fourth leading cause of disability by 2020 [1]. 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, and lead to a reduction in the need for rescue analgesia and joint replacement surgery in the long term, with consequent reduction in healthcare resource needs.

In 2014, the European Society for Clinical and Economic Aspects of Osteoporosis and Osteoarthritis (ESCEO) published a treatment algorithm for the management of knee OA, which provides practical guidance for the prioritization of interventions and guides physicians through progressive, logical steps [5]. This represents a significant advance in the preparation of recommendations for the treatment of OA, where previous guideline development has analyzed the level of evidence behind each intervention without prioritizing the interventions in a given sequence [6–9]. The ESCEO algorithm was developed by an international task force through analysis of the clinical trial evidence related to OA and detailed discussion to develop the algorithm. This article provides an updated assessment of the literature for selected interventions in OA, with particular focus on real-life data, with the aim of providing further practical guidance on the management of OA patients in primary care clinical practice, as was discussed at a meeting of the ESCEO task force in May 2015. Non-pharmacological background treatments were extensively reviewed previously and are not further examined here [5]. Pharmacological interventions for OA are discussed in some detail, and a simplified algorithm for the pharmacological management of OA has been developed by the ESCEO task force, which is presented here (Fig.). Further analysis of the evidence base in support of the interventions discussed here is provided in the four accompanying review articles included in this issue [10–13].

## Step 1: Pharmacological treatment

### *Paracetamol*

Paracetamol is widely recommended as a first-line step for rescue analgesia, despite the fact that the effect of paracetamol on symptoms is minimal [5–9], with only a small effect size (ES) on pain at 0.14 [95% confidence interval (CI): 0.05–0.22] and no significant effect on stiffness and physical function in patients with knee OA [14]. The persistent use of paracetamol, particularly in primary care, is largely due to the presumed safety of paracetamol and low cost. However, recent concerns over the safety profile of paracetamol raise questions over its routine, chronic use. Evidence is accumulating for an increased risk of upper gastrointestinal (GI) events with paracetamol use, and elevated risk of severe liver injury with high daily doses [15]. Treatment with high-dose paracetamol ( $>3$ g/day) is associated with a greater risk of hospitalization due to GI perforation, ulceration, or bleeding (PUB) than lower daily doses of paracetamol [hazard ratio (HR) = 1.20; 95% CI: 1.03–1.40] [16]. There is also evidence for loss of renal function in women following long-term consumption of high doses of paracetamol ( $>3$ g/day) [odds ratio (OR) = 2.04; 95% CI: 1.28–3.24], with a decline in glomerular filtration rate (GFR) $>30$ ml/min, and increase in hypertension in men [relative risk (RR) = 1.34; 95% CI: 1.00–1.79] and women (RR = 2.00; 95% CI 1.52–2.62) [17–19].

In primary care, paracetamol may still be used to treat pain in mild-moderate OA at daily doses up to 3 g/day. However, if paracetamol is ineffective or insufficiently effective, the physician should consider stopping and switching treatment, or adding-on other therapies.

### *SYSADOAs*

A preferential approach to Step 1 treatment of knee OA recommended by the ESCEO task force is to initiate background therapy with chronic symptomatic slow-acting drugs for osteoarthritis (SYSADOAs), with the addition of paracetamol as short-term rescue analgesia as needed (Fig.) [5]. Among SYSADOAs, the evidence is greatest for the effect of prescription-grade glucosamine sulfate (GS) and chondroitin 4&6 sulfate (CS). Other SYSADOAs, including diacerein, avocado-soybean unsaponifiable (ASU), collagen fragments, or plants extracts have been suggested as potential treatments for OA. Data from preclinical studies provide evidence that diacerein may impact abnormal articular tissue metabolism in OA [20]. Clinical evidence suggests that diacerein might have structure-modifying effects in hip OA [21], which provides a basis for further research particularly in knee OA that is lacking. For the other putative SYSADOAs, the evidence for any preclinical or clinical effect is limited [22].

### *Glucosamine sulfate*

A large amount of trials have investigated the efficacy of GS in the management of OA symptoms and potential disease-modifying effects through the delay of joint structural changes [23–27]. Numerous formulations of glucosamine as both sulfate and hydrochloride (HCl) salts are available as prescription-only, generic, over-the-counter (OTC) products and dietary supplements. However, it is apparent from careful consideration of the evidence base that only the patented crystalline glucosamine sulfate (pCGS) formulation (Rottapharm) [28] has proven efficacy in the treatment of OA [23–25]. A Cochrane review of randomized controlled trials (RCTs) concluded “only those studies evaluating the Rotta preparation showed that glucosamine was superior to placebo in the treatment of pain and functional impairment”. In fact, when this meta-analysis was restricted to studies with adequate concealment it failed to show any benefit of glucosamine for pain [standardized mean difference (SMD) = −0.16; 95% CI: −0.36 to 0.04] [23]. This finding was reflected in an analysis of only those RCTs employing any non-Rottapharm preparation of glucosamine,

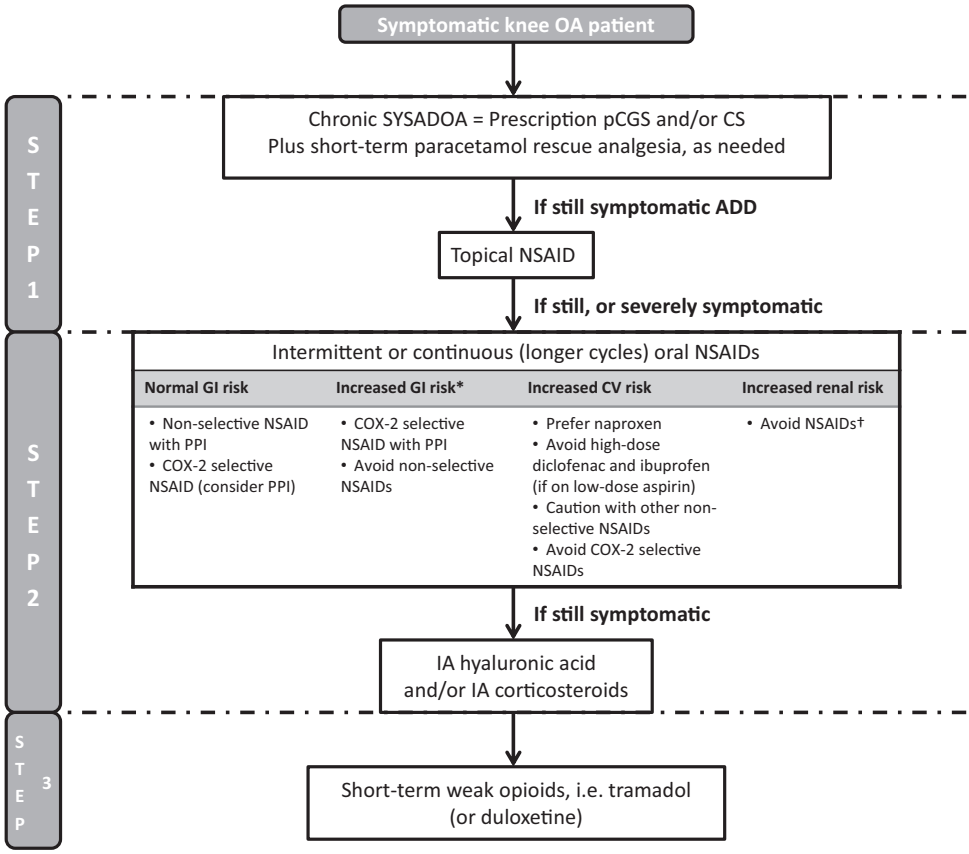


**Fig.** Simplified stepwise algorithm for the pharmacological management of knee osteoarthritis [5]. Modified from the ESCEO algorithm for treatment of knee OA [5]. For the full algorithm including non-pharmacological management, please refer to the original publication. *Including use of low-dose aspirin; †With glomerular filtration rate < 30 cc/min; caution in other cases, COX-2, cyclooxygenase-2; CS, chondroitin sulfate; CV, cardiovascular; GI, gastrointestinal; IA, intra-articular; NSAID, non-steroidal anti-inflammatory drug; pCGS, patented crystalline glucosamine sulfate; PPI, proton pump inhibitor; SYSADOA, symptomatic slow-acting drugs in osteoarthritis; OA, osteoarthritis.

which also failed to show any benefit over placebo for pain (SMD = −0.05; 95% CI: −0.15 to 0.05). Notably, when the RCTs using the pCGS formulation ("Rotta preparation" in the Cochrane review) were analyzed separately, pCGS was found to be superior for pain (SMD = −1.11; 95% CI: −1.66 to −0.57) and function (Lesquesne index SMD = −0.47; 95% CI: −0.82 to −0.12), albeit with high heterogeneity between trials ($I^2$ = 92%) [23]. To overcome the issue of heterogeneity, one may look only at the three pivotal trials of pCGS [26,27,29], which have been independently assessed as of the highest quality (Jadad score = 5) and with "low risk of bias" [24,25], thus falling within the studies with adequate concealment in the Cochrane review [23]. These studies have assessed the efficacy of pCGS on OA symptom management and functional outcomes for 6 months up to 3 years [26,27,29]. In independent meta-analyses, the calculated global effect size (ES) of pCGS on pain was 0.27 (95% CI: 0.12–0.43) without heterogeneity [24,25]. Although this effect size was moderate, it is greater than the effect of paracetamol (ES = 0.14), as confirmed in a head-to-head study [29], and similar to the effect size measured for non-steroidal anti-inflammatory drugs (NSAIDs) (ES = 0.32; 95% CI: 0.24–0.39) [14,30]. In addition, a significant effect on function for pCGS was demonstrated with an effect size of 0.33 (95% CI: 0.17–0.48) for Western Ontario McMaster Universities Osteoarthritis Index (WOMAC) function and 0.38 (95% CI: 0.18–0.57) for Lesquesne index [24].

The further benefit of chronic administration of pCGS is shown by long-term studies that demonstrate a significant reduction in joint space narrowing (JSN) as compared with placebo over 3 years of treatment [26,27]. Radiographic JSN of > 0.5 mm over 2–3 years is considered a reliable surrogate measure for total joint replacement (TJR) [31]: the proportion of patients with JSN of > 0.5 mm was significantly reduced in both pCGS pivotal 3-year trials [26,27]. The evidence for long-lasting disease-modifying effects of pCGS is further borne out by the real-life follow up of patients included in these long-term RCTs [32]. Treatment with pCGS for at least 12 months significantly delayed the need for TJR surgery ($p$ = 0.026); TJR occurred in twice as many patients from the placebo group in the 5 years of follow-up compared with those patients who had received pCGS (RR = 0.43; 95% CI: 0.20–0.92) [32].

The pharmacoeconomic benefits of long-term pCGS are demonstrated in real-life studies showing a reduction in need for concomitant NSAID use of 36–50% [32,33], and in reduction of the utilization of healthcare resources, including physician visits and examinations [32]. Further, cost-effectiveness analysis of a 6-month treatment trial using the incremental cost-effectiveness ratio (ICER) has shown pCGS to be a highly cost-effective therapy compared with paracetamol and placebo to treat patients with primary knee OA [29,34].

The ESCEO task force advocates the differentiation of prescription pCGS from other glucosamine preparations as a first-line SYSADOA for medium- to long-term control of knee OA symptoms (Fig.). Only pCGS is given as a highly bioavailable once-daily dose (1500 mg) with a proven pharmacological effect [35] that equates to a clear clinical benefit in trials and real-life studies of knee OA.

### *Chondroitin sulfate and SYSADOA combinations*

Studies using prescription-grade CS have shown that CS may offer similar benefits on joint structure changes in patients with

mild to moderate OA [36–38]. The effect size of CS on pain is reportedly variable [8]; although more recent studies and systematic reviews show that prescription-grade CS has an effect on joint structural changes that could be clinically relevant, with efficacy on symptoms of the disease that could be of similar magnitude to that of GS [38–40].

Glucosamine and CS are often used in combination as dietary supplements, which raises the question of whether there is any additional benefit derived from the combination. However, there are currently no trials of the combination of the two pharmaceutical-grade prescription preparations of CS and GS (as pCGS) compared with CS or pCGS alone, or to a comparator or placebo, to address this question. In the Glucosamine/Chondroitin Arthritis Intervention Trial (GAIT), although glucosamine hydrochloride (GH) or CS alone or in combination did not reduce pain effectively in the overall group of patients with knee OA, a positive trend for a symptomatic effect of the combination of CS plus GH was shown in the subgroup of patients with moderate-to-severe knee pain [41]. Moreover, the combination of pharmaceutical-grade CS plus GH is reported to provide an effect non-inferior to that of celecoxib [42], albeit in the absence of a placebo comparison. Since GH is demonstrated to provide an effect equivalent to that of placebo on symptomatic and structural management of OA [41,43] and its combination with CS decreases glucosamine bioavailability by 50–75% [35], any benefit of the combination of CS and GH is difficult to interpret and may be mainly attributable to CS.

Evidence for a disease-modifying effect of the combination is shown in a recent trial of once-daily non-prescription-grade GS (1500 mg) and CS (800 mg) which found a statistically significant reduction in JSN at 2 years compared with placebo (mean difference 0.10 mm; 95% CI: 0.002–0.20 mm; $p = 0.046$) [44]. Another study using the Osteoarthritis Initiative (OAI) cohort found a reduced loss of cartilage volume over 2 years with dietary supplement combinations of glucosamine and CS [45]. These data are in line with the earlier and stronger evidence for a disease-modifying effect of pCGS alone [26,27,32] or, pharmaceutical-grade CS alone [36–38]. Thus, there is limited evidence to suggest that combinations of non-prescription-grade glucosamine (including GH) and chondroitin should be preferred to either of the two single, pharmaceutical-grade prescription agents. Conversely, since both pCGS and CS are considered as safe medications, with no difference in adverse events (AEs) compared with placebo [23,38], and both are associated with long-term symptom-modifying effects [24,25,40], protection of joint cartilage and delay in disease progression [46], it may be wise to perform placebo-controlled RCTs to confirm the clinical benefit of the combination of the two prescription-grade agents beyond monotherapies alone.

*Topical NSAIDs*

Topical NSAIDs may be added to the treatment regimen if the patient is still symptomatic after establishing appropriate background pharmacological therapy with SYSADOAs, and rescue analgesia with paracetamol provides insufficient symptom relief. The efficacy of topical NSAIDs in knee OA has been established in RCTs and meta-analyses [47–50]. Evidence from head-to-head studies show that topical NSAIDs are as effective as oral NSAIDs, but with a lower risk for gastrointestinal (GI) AEs albeit with an increased risk of mild skin reactions [47]. The pooled effect size for pain relief with topical NSAIDs was calculated as 0.44 (95% CI: 0.27–0.62), although there is a heterogeneity of efficacy between products ($I^2 = 69\%$) [48]. Data for topical diclofenac showed the number needed to treat (NNT) for at least 50% pain relief over 8–12 weeks as six for the solution and 11 for the gel formulation [51]. However, recent studies of topical ketoprofen failed to demonstrate a benefit of treatment over placebo [52,53]. Good absorption through the skin and accumulation of the active agent in the target tissues are important factors, which contribute to the efficacy of topical NSAIDs, alongside low plasma levels to minimize systemic AEs and improve tolerability. The bioavailability of topical NSAID formulations varies, with etofenamate demonstrating the highest bioavailability at 21% [54], and accumulation in inflamed target tissues at levels 10-times that of the plasma concentration [55]. Topical diclofenac has also been shown to accumulate in the synovial tissue [56].

In real-life studies, topical NSAIDs demonstrated an equivalent effect on knee pain to oral NSAIDs over 1 year of treatment, with fewer AEs reported with topical NSAIDs [57]. In addition, the use of topical NSAIDs in inflammatory rheumatic diseases led to a 40% reduction in the need for concomitant oral NSAIDs, with a significant reduction in the reporting of GI AEs [58]. Studies of patient preference showed that 75% of patients would choose to use a topical NSAID in preference to an oral NSAID [57].

For considerations of safety, topical NSAIDs may be used in preference to oral NSAIDs due to their lower systemic absorption and consequent better tolerability profile. Topical NSAIDs may be considered as the preferred treatment option, particularly in OA patients aged 75 years or older, and those with co-morbidities, or those at an increased risk of GI, cardiovascular (CV), or renal side effects.

## Step 2: Advanced pharmacological treatment

*Oral NSAIDs*

If Step 1 treatments show inadequate efficacy and the patient is still symptomatic, or in patients presenting with moderate-severe pain, benefit may be obtained with advanced pharmacological treatments. Oral NSAIDs traditionally play a central role in the pharmacological management of OA. Oral NSAIDs have a moderate effect on pain relief, with effect size of 0.29 (95% CI: 0.22–0.35) that is greater than that of paracetamol (ES = 0.14) [14], and with demonstrated greater efficacy in patients with more severe OA accompanied by a higher degree of patient preference [59]. Cyclooxygenase-2 (COX-2) selective, partially selective, or non-selective NSAIDs are shown to be similarly effective in controlling pain [47]. In recent years, the widespread use of NSAIDs has been questioned due to the reporting of significant upper GI complications (UGIC) and CV AEs [9].

Oral NSAIDs are associated with a three- to five-fold increase in the risk of UGIC, including peptic ulcer perforation, obstruction, and bleeding [60,61]. However, there is considerable variability in UGIC and CV risk for individual NSAIDs [62,63]. The high risk of UGIC with indomethacin was attenuated by use of acemetacin, a prodrug, which is less active on the COX-1 enzyme in the gastric mucosa, resulting in a reduction in GI AEs of around one-third [64]. Celecoxib and ibuprofen have a low relative risk for UGIC compared with other NSAIDs [65], while nabumetone is associated with 10-fold fewer GI AEs than other NSAIDs [66,67].

The use of gastroprotective agents such as proton pump inhibitors (PPIs) can reduce the occurrence of UGIC by 50–60% [68]. While COX-2 selective inhibitors are associated with a lower risk of UGIC compared with non-selective NSAIDs, there is still a significant increase in risk compared with placebo [69]. The ESCEO task force recommends that in patients with low (normal) GI risk, it should be considered to prescribe either a non-selective NSAID with or without a PPI or a COX-2 selective NSAID based on the judgement of the clinician (Fig.) [5].

The choice of which NSAID to use in clinical practice depends on individual patient characteristics and medical history [5]. The ESCEO task force recommends that patients are assessed for risk

factors and the risk:benefit ratio of treatment is determined before making treatment decisions. Several patient factors have been identified to increase the risk of UGIC, including advanced age, a history of GI ulcer, and concomitant treatment with corticosteroids, aspirin, or anticoagulants [62,70]. In patients with high GI risk, which includes patients receiving concomitant low-dose aspirin, non-selective NSAIDs should be avoided and COX-2 selective NSAIDs should be co-prescribed with a PPI [71]. Patient preference is an important consideration, for example, of dosing regimen whether once daily or more frequent dosing is desirable.

There is little doubt that all oral NSAIDs, selective and non-selective, increase the risk of serious CV events [69] and should be avoided in high CV risk patients. Ibuprofen should not be used with concomitant low-dose aspirin due to clinically relevant pharmacological interaction [72]. Naproxen is the exception, and may be the preferred agent if an NSAID is required in patients at high CV risk, because of its lower risk of CV events [69,73], which may be due to its sustained suppression of platelet aggregation [69]. In patients with increased renal risk, such as chronic kidney disease with estimated GFR below 30 cc/min, the ESCEO task force recommends that oral NSAID use is avoided [5].

The ESCEO task force recommends that oral NSAIDs may be used intermittently or continuously in longer cycles rather than in chronic use, at the lowest effective dose and for the shortest time necessary to control symptoms, because of safety concerns and a lack of long-term trials [1]. In the event of insufficient control of symptoms with an NSAID, the combination of NSAIDs is not recommended by the ESCEO task force, as there is no evidence of additional benefit, and an increased risk of AEs, with additional cost of treatment. While switching NSAIDs may provide some benefit, the ESCEO task force does not recommend multiple successive rounds of NSAIDs before considering other treatment options. In the case of contraindications to NSAIDs, or if the patient is still symptomatic despite use of NSAIDs, intra-articular treatment may be considered (Fig.) [1].

*Hyaluronic acid*

Viscosupplementation with intra-articular (IA) hyaluronic acid (HA) is an effective treatment for knee OA with beneficial effects on pain, function, and patient global assessment [74]. There is good evidence for the effectiveness of HA from RCTs, with a high effect size of 0.63 when compared with oral placebo, found in a recent network meta-analysis [75]. IA HA was the most efficacious treatment for pain among all OA interventions. However, the IA delivery method itself had a significant effect size of 0.29 compared with oral placebo. This might be explained by the fact that injecting any fluid in the joint could potentially influence nociceptive response by affecting the peripheral nervous system. More importantly, when fluid is aspirated prior to HA injection, such a procedure might exert a mild anti-inflammatory effect by removing inflammatory cytokines or pain-modulating neuropeptides and other mediators [76]. Despite this, when compared with IA placebo, a statistically significant effect size of 0.34 [95% credible interval (CrI): 0.26–0.42] was shown for IA HA on pain at 3 months [75]. In trials directly comparing IA HA with continuous oral NSAID treatment, the effect size of IA HA on pain was not significantly different to that of NSAIDs up to 12 weeks [77]. IA HA demonstrated a more favorable safety profile, with injection site pain as the most common AE, compared with more frequent GI AEs with NSAID therapy. In this respect, IA HA may be a good alternative to NSAIDs for knee OA, especially for older patients or in those at greater risk for NSAID-induced AEs.

HA is not a rapidly acting agent, but rather the clinical effect on pain and function extends for a long time after administration, up to 6 months post-injection [78]. Analysis of US-approved IA HA injections found a significantly large treatment effect from 4 weeks up to 26 weeks for knee pain (SMD = 0.38) and knee function (SMD = 0.32) compared with placebo ($p < 0.001$) [78]. HA has a slow onset of action, with efficacy demonstrated by week 4, reaching a peak at 8 weeks that is maintained for up to 6 months [79]. In comparison, IA corticosteroids provide greater pain relief in the short-term up to 4 weeks, while beyond 8-weeks post-injection IA HA demonstrates superior, longer-lasting efficacy [80].

Real-life evidence for the long-term effectiveness of IA HA is reported in a study of over 300 patients with knee OA who received repeat cycles of IA HA injections (4 cycles of 5 weekly injections) [81]. After 40 months (12 months after the last treatment cycle), significantly more treatment responders were found in the treatment group compared with placebo according to OARSI 2004 criteria for pain, function, and patient global assessment (80.5% of responders with HA vs. 65.8% for placebo; $p = 0.004$) [81]. Notably, the number of responders to IA HA increased progressively after each treatment cycle, while response to placebo remained fairly stable. In other observational studies, IA HA injections in knee OA were highly effective in improving resting and walking pain with duration of symptom control up to 6 months, and a reduction in concomitant analgesia use of 30–50%. Few AEs were reported, mostly limited to mild or moderate local AEs of transient pain and swelling [82–84]. Furthermore, IA HA delayed the need for total knee replacement (TKR) surgery by approximately 2 years [85–87].

Most head-to-head clinical trials performed to date have found non-inferiority with respect to symptomatic efficacy between the HA preparations of various molecular weights (MWs) tested [88–92]. In a head-to-head clinical trial of intermediate MW HA vs. low MW HA, the intermediate MW HA provided statistically superior pain relief at 6 months ($p = 0.021$) [93]. Cross-linked high MW HAs (hylans) have comparable efficacy with intermediate MW HA [94], but are associated with increased safety concerns due to an increased rate of flares/non-septic post-injection arthritis [95]; hylans are twice as likely to cause 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 [94].

Although the exact mechanism of action of exogenous HA is unknown, the proposed mechanism occurs in 2 stages, a mechanical stage and a pharmacological stage [80,96]. Injection of a high concentration of HA provides viscosupplementation [97,98], while the induction of biosynthesis of endogenous HA and extracellular matrix components [99] can occur, which reduces proteoglycan loss in cartilage and apoptosis of chondrocytes [97,100]. The endogenous synthesis of HA by synovial fibroblasts is influenced by the concentration and MW of HA in the extracellular environment [99,101]. The optimal stimulation of HA biosynthesis occurs with intermediate MW HA binding to synovial fibroblast cell receptors; this binding may be limited by the steric volume of high MW HA, and only weak binding occurs with low MW HA [99]. The re-establishment of joint homeostasis through induction of endogenous HA production continues long after the exogenous injection has left the joint.

While further investigation into the OA patient types most likely to benefit from IA HA is warranted, the ESCEO task force recommends the use of IA HA in knee OA patients with mild-moderate disease, and for more severe patients who are either contraindicated to TKR surgery or wishing to delay the surgical procedure. IA HA should only be administered in knee OA once the acute inflammatory flare has settled. In these patients, IA corticosteroids may be used first line to treat the knee effusion. In this respect, it is useful to note that the combination of HA and IA corticosteroids could be contraindicated due to some meddling effects between them, unless pharmaceutical

compatibility between formulations has been shown. Although the treatment effect of IA HA is comparable with NSAIDs, IA HA is positioned later in the treatment algorithm, unless NSAIDs are contraindicated, due to the requirement for repeat injections usually performed by a trained, specialized practitioner (either rheumatologist or orthopedic surgeon). Nonetheless, IA HA is an effective and safe treatment for long-term management of knee OA and may be a cost-effective treatment (to be further studied).

### Step 3: Last pharmacological treatment

Last pharmacological options for the severely symptomatic patient may be represented by the use of short-term weak opioids. Opioids, in general, are associated with significant morbidity [102]. Conventional opioid analgesics may cause respiratory depression, dependence, and have the potential for drug abuse. However, weak opioids such as tramadol offer good analgesia with improved safety profile. Antidepressants, including duloxetine, have been used in chronic pain syndromes because they act centrally to alter pain neurotransmitters (serotonin and norepinephrine) and scant evidence of an effect is shown in OA albeit with a high rate of AEs [103,104]. Tramadol and duloxetine should not be used in combination, due to the overlapping mechanisms of action on central pain neurotransmitters.

#### *Tramadol*

Tramadol is a weak opioid that has small but significant efficacy for the relief of pain and improvement of function in knee OA [105]. Treatment of knee OA with short-term tramadol has been shown to reduce pain, reduce stiffness, and improve function and overall well-being, with significant results for patients' overall assessment of therapy compared with placebo [105,106].

Tramadol is a synthetic, centrally acting opioid agonist that acts through both weak opioid and non-opioid mechanisms [107]. Consequently, tramadol rarely causes the AEs of respiratory depression and physical dependence commonly associated with conventional opioid drugs. Tramadol use is also not associated with the GI and CV AEs attributed to NSAIDs [105]. The most frequently reported AEs with tramadol are nausea and headache, which may result in treatment withdrawal and sub-optimal pain management [108,109].

Sustained-release (SR) formulations may improve tramadol tolerability and reduce the incidence of AEs [110]. SR formulations of tramadol are associated with prolonged effective plasma levels of tramadol, while preventing the high plasma peaks associated with AEs with the immediate-release formulations [110,111]. The risk of AEs may be further attenuated by the slow upward titration of tramadol SR from 50 to 100 mg bid over 7 days, which affords a reduction in AEs and reduced frequency of treatment discontinuations [112].

The short-term use of tramadol may be considered for severely symptomatic OA patients and there is good evidence that tramadol works if prescribed properly. The SR formulation of tramadol is preferred and the slow upwards titration of tramadol SR is recommended to improve tolerability and minimize AE-related treatment discontinuations.

## Conclusions

Few clinical trials have been designed to study the effect of given treatment in patients in whom initial therapies have failed, and/or when and how new treatments should be introduced. However, the assessment of the evidence base by the international ESCEO task force has provided a stepwise multi-modal treatment algorithm for the practical management of knee OA [5]. Recent real-life studies provide additional evidence in support of pharmacological interventions, in terms of management of OA pain and function, avoidance of AEs, disease-modifying effects and long-term outcomes, e.g., delay of TKR surgery, and pharmacoeconomic factors such as reduction in healthcare resource utilization.

In clinical practice, treatment should be based upon the individualized assessment of the patient, taking into account a patient's needs and preferences, or the subjective interpretation of the evidence by the physician. In the future, identification of patient profiles may lead to more personalized healthcare, with more targeted treatment for OA [113]. For now, this stepwise approach to the pharmacological management of knee OA is advocated by the ESCEO task force. During step 1, background treatment with SYSADOAs using only the prescription formulations of pCGS or CS is recommended, with paracetamol as add-on rescue analgesia for short-term therapy. Topical NSAIDs may be included for additional analgesia given that their symptomatic efficacy is similar to the oral NSAIDs but with superior systemic safety. Oral NSAIDs maintain a central role in the step 2 advanced pharmacological management of the persistently symptomatic patient. NSAIDs as a class, including non-selective and COX-2 selective NSAIDs, are heterogeneous and there is wide disparity in the AE risk for GI and CV events between different oral NSAIDs. Patient stratification and careful selection of appropriate medication can help to minimize risks while maintaining clinical benefit of treatment. Intra-articular treatment represents the next stage in the stepwise treatment algorithm, for patients who fail to derive sufficient symptomatic benefit from prior treatments. IA HA can be clearly differentiated from IA corticosteroids by the duration of the induced benefit, lasting for up to 6 months after a short weekly injection course. Step 3 comprises the last pharmacological attempt before surgery and includes short-term weak opioids, such as tramadol. SR formulation and dose titration of tramadol can help to limit the side effects often associated with opioid treatment, and minimize treatment discontinuations while providing sustained efficacy.

Overall, this guidance provides evidence-based and easy-to-follow advice on how to establish a treatment flow in patients with knee OA, for practical implementation in real-world clinical practice.

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