gastrointestinal (GI) tract (constipation, fecaloma) were reported with both immediate-release (IR) and extended-release (ER) formulations of opioids versus placebo: IR opioids (relative risk [RR] = 5.20, 95% confidence interval [CI] 3.42, 7.89); ER opioids (RR = 4.22, 95% CI 3.44, 5.17). The risk of risk of nausea, vomiting or loss of appetite increased 4 to 5-fold with both IR (RR = 3.39, 95% CI 2.22, 5.18) and ER opioids (RR = 4.03, 95% CI 3.37, 4.83). An increased risk of dermatologic AEs (rash and pruritis) (IR opioids: RR = 3.60, 95% CI 1.74, 7.43; ER opioids: RR = 7.87, 95% CI, 5.20, 11.89). For COX-2 inhibitors, database searches identified 2149 records from which, after exclusions, 40 trials were included in the meta-analysis. The use of COX-2 inhibitors in OA was associated with a significantly increased risk of drug-related AEs compared with placebo (relative risk [RR] = 1.26, 95% CI 1.09, 1.46; $I^2 = 24\%$). The risk of upper gastrointestinal complications (including dyspepsia, gastritis, and heartburn) was significantly increased with COX-2 inhibitors versus placebo (RR = 1.19, 95% CI 1.03, 1.38; $I^2 = 0\%$). The risk of heart failure and edema was increased by nearly 70% with COX-2 inhibitors versus placebo (RR = 1.68, 95% CI 1.22, 2.31; 0%).

Conclusions: Our results confirm the concerns regarding safety and tolerability surrounding the use of opioids and COX-2 inhibitors in OA.

ESCEO5
SAFETY OF SYSADOAS, INTRAARTICULAR HYALURONIC ACID AND INTRAARTICULAR CORTICOSTEROIDS

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Objectives: In the absence of any treatments clearly established to modify the progression of OA, a number of products have been tested and/or promulgated for potential chondroprotective effects while providing symptom relief. These treatments could theoretically be preferable to traditional analgesic regimens through lower risk of toxicity. We comprehensively assessed the safety profiles of agents in this broad category in patients with knee and/or hip OA.

Material and methods: We searched Medline and the Cochrane Databases from inception through December 2017. We included randomized controlled trials (RCTs) of knee / hip OA that tested avocado soybean unsaponifiables (ASU), glucosamine (GC), chondroitin (CS), risedronate, calcitonin, diacerein strontium ranelate (SR), intra-articular hyaluronic acid (IAHA), intra-articular corticosteroids (IACS). Reference screening and extraction of adverse event data were undertaken by two independent reviewers. We calculated risk ratios and 95% confidence intervals using a random effects model. Data from knee OA, hip OA, and mixed knee/hip OA populations were analyzed separately.

Results: We identified 118 eligible RCTs involving 22,994 knee OA patients, 18 RCTs involving 1877 hip OA patients, and 2 RCTs involving 468 patients with knee and/or hip OA. In these RCTS, there were no significant increase in risk for adverse events compared to placebo for ASU, GC, CS, risedronate, or SR. Evidence of toxicity was evident in RCTs of calcitonin (more withdrawals, GI AEs, flushes); diacerein (diarrhea, withdrawals), IAHA (AEs, SAEs, and local reactions). There was no significant difference in safety outcomes observed between IACS and IA placebo in studies of up to 2 years, although one of these detected an increased rate of cartilage damage of uncertain clinical significance. Quality of toxicity reporting was generally low and in one instance inconsistent with post-marketing surveillance (SR).

Conclusions: Evaluation of toxicity profiles based on RCTs can be limited by methodologic problems, inconsistent reporting, small numbers of events (especially serious events) and issues of generalizability. However, no safety signals emerged for nutritional products promulgated for OA.

ESCEO6
THE 2014–2016 ESCEO ALGORITHM FOR THE MANAGEMENT OF KNEE OSTEOARTHRITIS

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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. 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 centred on the use of oral COX-2 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. Further analysis of real-world data for OA, published in 2016, provided 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. Since 2014, these guidance documents have received international endorsement, with translation, adaptation to the local context, and publication in China, Russia, and South-East Asia.

ESCEO7
NEW INSIGHTS IN THE MANAGEMENT OF OSTEOARTHRITIS

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Knee osteoarthritis (OA) affects around 4% of people worldwide and accounts for 17.1 million years of life lived with disability. It is expected to become the fourth leading cause of functional impairment by 2020, placing a huge burden on health services. Recommendations for the management of knee OA have been issued by several international and national bodies, including the European League Against Rheumatism (EULAR); the American Society for Rheumatology (ACR); and the Osteoarthritis Research Society (OARSI). These have recently been systematically evaluated by the European Society for Clinical and Economic Aspects of Osteoporosis and Osteoarthritis (ESCEO), to construct a treatment algorithm that might enhance OA management throughout Europe and worldwide. The initiative advanced existing practice guidelines, which typically evaluate interventions individually, by prioritizing these into a well- ordered series of practical steps which can be undertaken by physicians. The algorithm was constructed by an international taskforce experienced in the performance, analysis and interpretation of clinical trial evidence in OA. The core set of measures, which are applicable to all patients with knee OA include: (a) Access to information about the disease and education about the disorder; (b) Weight loss if adipose; and provision of (c) an exercise programme. The consequent treatment algorithm consists of four multimodal steps. Step 1 consists of background therapy, either non-pharmacological (referral to a physical therapist for realignment treatment if needed and sequential introduction of further physical interventions) or pharmacological. The latter consists of chronic symptomatic slow-acting drugs for OA (eg prescription of glucosamine sulphate with chondroitin sulphate) with paracetamol if required; topical NSAIDs are added in the still symptomatic patient. Step 2 consists of the advanced pharmacological management in the persistently symptomatic patient. It centres on the use of oral COX-2 selective or non-selective NSAIDs, chosen based o concomitant risk factors, with intra-articular glucocorticoids or hyaluronic acid derivatives for further symptom relief. Step 3 incorporates the remaining pre-surgical pharmacological measures including weak opioids and other central analgesics such as duloxetine; Step 4 progresses to surgical intervention, or classical opioids where surgery is contraindicated. This treatment algorithm represents a new framework for the development of future guidelines for OA management, which are more easily accessible to primary and secondary care physicians.

ESCEO8
THE UPDATED ESCEO ALGORITHM FOR THE MANAGEMENT OF KNEE OSTEOARTHRITIS: ASSESSMENT OF THE VARIOUS TREATMENT MODALITIES BY GRADE

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Objective: The European Society for Clinical and Economic Aspects of Osteoporosis, Osteoarthritis and Musculoskeletal Diseases (ESCEO) decided to revisit the 2014 algorithm recommendations for knee osteoarthritis (OA), using the Grading of Recommendations Assessment, Development and Evaluation (GRADE) process.

Material and methods: A Summary of Evidence document for each intervention was provided to all members of a dedicated working group and consisted of: a) 2014 Status; b) 2014–2018 Literature Search Results; c) GRADE Evidence Profiles: these tables included the summary of findings and quality assessment by a judgment of factors that determine the quality of evidence (certainty assessment) and the magnitude of effect for each