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EXPERT OPINION

Endorsement by Central European experts of the revised ESCEO algorithm for the management of knee osteoarthritis

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Abstract

Osteoarthritis (OA) is characterized by deterioration of the joints and associated with considerable pain and disability. OA is a chronic disease that requires intervention with both non-pharmacological and pharmacological treatment modalities and, inevitably, disease progression may necessitate successive treatments throughout the course of the disease. There is increasing data on the shortfalls of current pharmacological treatment of OA, and safety concerns associated with analgesic therapy use in OA arising from increasing evidence of gastrointestinal, cardiovascular, hepatic and renal adverse events with paracetamol and non-steroidal anti-inflammatory drugs (NSAIDs). Consequently, symptomatic slow-acting drugs for OA (SYSADOAs) may now be considered as a first-line treatment for knee OA, with a particular emphasis placed on the outstanding benefit: risk ratio of pharmaceutical-grade glucosamine and chondroitin sulfate formulations. In this short communication we review recent publications concerned with the safety of paracetamol, NSAIDs and SYSADOAs. Greater understanding of the benefits and limitations of current medications will lead to better disease management in OA. Furthermore, adherence to guideline recommendations across Europe and internationally, such as those from the European Society for Clinical and Economic Aspects of Osteoporosis, Osteoarthritis and Musculoskeletal Diseases (ESCEO), will promote evidence-based medicine and patient-centric care, ultimately leading to greater physician and patient satisfaction.

Keywords NSAID · Osteoarthritis · Paracetamol · Safety · SYSADOA

Abbreviations

ASU	Avocado soybean unsaponifiables
COX-2	Cyclo-oxygenase-2
CS	Chondroitin sulfate
NSAID	Non-steroidal anti-inflammatory drug
OA	Osteoarthritis
pCGS	Prescription crystalline glucosamine sulfate
SYSADOA	Symptomatic slow-acting drugs for osteoarthritis

Introduction

Osteoarthritis (OA) is a long-term chronic disease characterized by deterioration in joints resulting in pain and stiffness and impaired movement. OA is strongly, but not exclusively, associated with aging, and most-commonly affects the knees, hips, and hands. Across Europe, age-standardized self-reported, doctor diagnosed, OA ranges from 2.8% in Romania to 18.3% in Hungary, and globally it is estimated that 1 in 10 of the population aged 60 years or older have significant clinical problems that can be attributed to OA [1].

The European Society for Clinical and Economic Aspects of Osteoporosis, Osteoarthritis and Musculoskeletal Diseases (ESCEO) published recommendations for the management of knee OA as a stepwise treatment algorithm to guide physicians through progressive, logical steps [2]. These guidelines were well-received internationally and are used widely across Europe [3]. The ESCEO guidelines include a core set comprising the education of patients with

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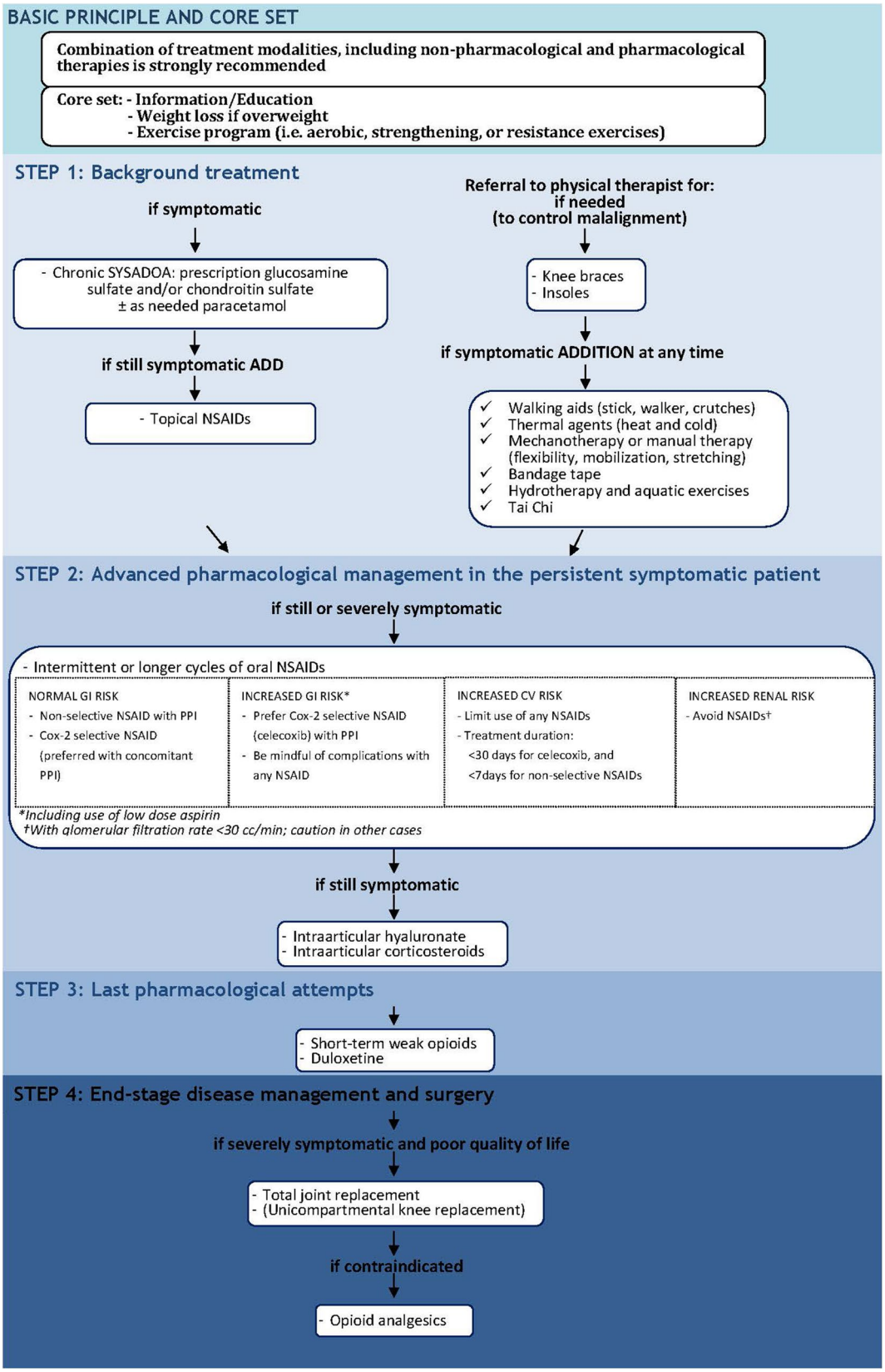
BASIC PRINCIPLE AND CORE SET
Combination of treatment modalities, including non-pharmacological and pharmacological therapies is strongly recommended
Core set: - Information/Education
- Weight loss if overweight
- Exercise program (i.e. aerobic, strengthening, or resistance exercises)
STEP 1: Background treatment
if symptomatic
- Chronic SYSADOA: prescription glucosamine sulfate and/or chondroitin sulfate ± as needed paracetamol
if still symptomatic ADD
- Topical NSAIDs
Referral to physical therapist for: if needed (to control malalignment)
- Knee braces
- Insoles
if symptomatic ADDITION at any time
✓ Walking aids (stick, walker, crutches)
✓ Thermal agents (heat and cold)
✓ Mechanotherapy or manual therapy (flexibility, mobilization, stretching)
✓ Bandage tape
✓ Hydrotherapy and aquatic exercises
✓ Tai Chi
STEP 2: Advanced pharmacological management in the persistent symptomatic patient
if still or severely symptomatic
- Intermittent or longer cycles of oral NSAIDs
NORMAL GI RISK
- Non-selective NSAID with PPI
- Cox-2 selective NSAID (preferred with concomitant PPI)
INCREASED GI RISK*
- Prefer Cox-2 selective NSAID (celecoxib) with PPI
- Be mindful of complications with any NSAID
INCREASED CV RISK
- Limit use of any NSAIDs
- Treatment duration: <30 days for celecoxib, and <7days for non-selective NSAIDs
INCREASED RENAL RISK
- Avoid NSAIDs†
*Including use of low dose aspirin
†With glomerular filtration rate <30 cc/min; caution in other cases
if still symptomatic
- Intraarticular hyaluronate
- Intraarticular corticosteroids
STEP 3: Last pharmacological attempts
- Short-term weak opioids
- Duloxetine
STEP 4: End-stage disease management and surgery
if severely symptomatic and poor quality of life
- Total joint replacement
- (Unicompartmental knee replacement)
if contraindicated
- Opioid analgesics

◂**Fig. 1** Updated ESCEO stepwise treatment algorithm for knee osteoarthritis. *COX-2* cyclooxygenase-2, *CS* chondroitin sulfate, *CV* cardiovascular, *GI* gastrointestinal, *GS* glucosamine sulfate, *IA* intra-articular, *NSAID* non-steroidal anti-inflammatory drug, *PPI* proton pump inhibitor, *SYSADOA* symptomatic slow-acting drugs in osteoarthritis, *OA* osteoarthritis Reprinted from Semin Arthritis Rheum 2019; April 30 online. https://doi.org/10.1016/j.semarthrit.2019.04.008. Bruyère O, et al. An updated algorithm recommendation for the management of knee osteoarthritis from the European Society for Clinical and Economic Aspects of Osteoporosis, Osteoarthritis and Musculoskeletal Diseases (ESCEO), Copyright 2019, with permission from Elsevier

disease information, recommended weight loss if overweight and an exercise program, along with a combination of treatment modalities including non-pharmacological and pharmacological interventions [2]. Since publication of the 2014 algorithm, considerable new evidence has been published particularly regarding the safety of many medications commonly used to treat OA. In preparation for a guideline update, a full literature search on all interventions for knee OA covering the period from 2014 through to September 30, 2018 was performed. In addition, the ESCEO identified a need for comprehensive safety data on anti-OA medications, and commissioned several safety meta-analyses on different classes of anti-OA medications, including symptomatic slow-acting drugs for osteoarthritis (SYSADOAs) and cyclooxygenase-2 (COX-2) inhibitors. The results of these safety meta-analyses were included alongside the literature search results in the analysis and formulation of revised guidelines, which are summarized in the modified treatment algorithm (Fig. 1) [4]. While it is recognized that OA management practices can vary slightly between "Western" and "Central" Europe, the ESCEO guidelines, which were originally drafted by a panel of physicians mainly from Western Europe, are also endorsed by the Central European authors here. Our article provides a summary of the new safety data identified for selected OA medications, namely paracetamol, SYSADOAs, and non-steroidal anti-inflammatory drugs (NSAIDs) alongside recommendations for the appropriate use of these medications in OA.

Paracetamol

Paracetamol (acetaminophen) is widely used as rescue analgesia for OA, despite having only minimal effect on pain (effect size [ES] 0.14, 95% CI 0.05–0.23) and no significant effect on stiffness and physical function in patients with knee OA [5]. Recent concerns over the safety profile of paracetamol raise questions over its routine chronic use, due to increasing evidence of gastrointestinal (GI), cardiovascular (CV), and renal adverse events (AEs), and increased mortality risk associated with paracetamol use [6]. A systematic literature review of observational studies identified a considerable degree of toxicity with paracetamol, especially at the upper end of standard analgesic doses (up to 4 g/day) [6]. Eight cohort studies included in the review investigated ≥ 1 of the AEs of interest with oral doses of paracetamol of 0.5–1.0 g every 4–6 h to a maximum 4.0 g/day. Two of the studies reported on mortality, of which one reported a dose–response increase in all-cause mortality and rate of gastrointestinal AEs or bleeds based upon low to high medication possession ratio (measured by repeat prescription frequency), and the other study reported an increase in standardized mortality ratio for patients prescribed paracetamol compared with those not prescribed paracetamol, regardless of specific cause of death, with a nearly doubled overall death rate [6]. Four studies included in the analysis showed a dose–response relationship between paracetamol use and risk of CV AEs, and three studies reported an increased risk of renal AEs with paracetamol [6]. Reports of hepatotoxicity and acute liver failure associated with chronic paracetamol dosing are a further cause of concern with widespread, unrestricted paracetamol use [7].

Consequently, when analgesic benefit is uncertain and with increasing safety issues, more careful consideration of paracetamol use is required. The ESCEO algorithm recommends that paracetamol be used as short-term rescue analgesia only (dose ≤ 3 g/day) given on top of a background of SYSADOAs [4].

SYSADOAs

There are many different agents in the class of SYSADOAs including glucosamine, chondroitin, diacerein, and avocado soybean unsaponifiables (ASU), and confusion may arise over appropriate prescribing and use of this class of agents. Multiple formulations of these agents are available, both as prescription-grade products and nutritional supplements. However, while all preparations may claim to deliver a therapeutic level of the active agent, not all are supported by clinical evidence [8, 9]. Only the prescription crystalline glucosamine sulfate (pCGS) is shown to deliver consistently high glucosamine bioavailability and plasma concentration in humans, which corresponds to demonstrated clinical efficacy [10–12]. Conversely, glucosamine hydrochloride and non-characterized glucosamine sulfate products are repeatedly demonstrated as ineffective in OA [12–14]. Similarly, only pharmaceutical-grade chondroitin sulfate (CS) has been evaluated for purity, content and physiochemical parameters [9], and clinical evidence supports only pharmaceutical-grade CS [15].

Both glucosamine and CS can be considered as safe treatments for patients with OA. A recent systematic review and meta-analysis found no statistically significant increase in odds between glucosamine or CS, each compared with

placebo, for any system organ class (SOC)-related disorders including: GI, cardiac, vascular, nervous system, skin and subcutaneous tissue, musculoskeletal and connective tissue, and disorders of the renal and urinary systems [16]. In addition, no difference in odds for severe and serious AEs, and for withdrawals due to AEs was found for glucosamine or CS versus placebo. Similarly, no safety issues were found with ASU, although only studies that included a single proprietary ASU product (Piascledine®) and allowed concomitant rescue anti-OA medications qualified for the analysis. Consequently, the safety of ASU as a whole requires further investigation.

Diacerein has a small beneficial effect on OA pain; however, the safety of diacerein has been called into question. In a meta-analysis, the odds of any AE with diacerein was more than twice that of placebo (odds ratio [OR] 2.22, 95% CI 1.58, 3.13) [16]. This was largely due to increased odds of GI AEs with diacerein versus placebo (OR 2.85, 95% CI 2.02, 4.04), of which diarrhea, abdominal pain, soft stools, and colitis were frequently reported, and a high increase in odds of renal and urinary disorders with diacerein (OR 3.42; 95% CI 2.36, 4.96), urine discoloration being the most reported effect. A significant increase in odds of dermatological disorders was found with diacerein versus placebo (OR 2.18, 95% CI 1.40, 3.42), specifically eczema, rash, pruritus, and urticaria.

Thus, among the SYSADOA products available, pharmaceutical-grade pCGS and CS are strongly recommended by the ESCEO as first-line SYSADOAs, for which the evidence base is unequivocal [4]. Other SYSADOAs (diacerein and ASU) may be used as alternative step 1 background therapy; however, the evidence for their efficacy and safety is scarcer than that of CS and pCGS.

NSAIDs

NSAIDs are one of the most widely used drugs in OA. Topical NSAIDs may be added to the treatment regimen in Step 1 therapy if the patient is still symptomatic, and may be used in preference to oral NSAIDs particularly in patients aged ≥ 75 years as they have similar efficacy to the oral medications in reducing pain (ES 0.44, 95% CI 0.27, 0.62) with a reduced risk of systemic AEs [4]. An increase in mild local skin reactions is observed with topical NSAIDs although this may be product-specific, and is notably higher with diclofenac [17]. Topical NSAIDs are recommended as add-on analgesia in Step 1 for patients who are still symptomatic, and prior to the use of oral NSAIDs [4].

Oral NSAIDs are included as step 2 treatment in the ESCEO algorithm for management of knee OA, in those with moderate to severe pain, and those unresponsive to Step 1 interventions [4]. Oral NSAIDs have a small to moderate effect on pain in short-term studies (ES 0.29, 95% CI 0.22, 0.35) [5]. Oral NSAIDs have been associated with wide-ranging AEs affecting, amongst others, the GI, CV and renal systems. GI toxicity is found with all NSAIDs which may be of particular concern when treating older patients with OA. All NSAID regimens, including non-selective (ns)-NSAIDs and COX-2-selective NSAIDs, are found to increase upper GI complications (COX-2 inhibitors Rate ratio [RR] 1.81, 95% CI 1.17,2.81; diclofenac RR 1.89, 95% CI 1.16, 3.09; ibuprofen RR 3.97, 95% CI 2.22, 7.10; and naproxen RR 4.22, 95% CI 2.71, 6.56) [18]. Gastric AEs associated with nsNSAIDs may be reduced by taking a concomitant gastroprotective agent (proton pump inhibitor), although intestinal AEs are not ameliorated [19].

CV risk exists for both nsNSAIDs and COX-2 inhibitors alike, and thus CV toxic effects may result from differences in physiochemical properties [18, 20]. A meta-analysis of 26 randomized controlled trials compared the incidence of CV endpoints between different NSAIDs finding the highest risk with rofecoxib among all NSAIDs [20]. Conversely, celecoxib has lower CV toxicity [21], and among nsNSAIDs naproxen has the lowest CV toxicity [18].

The absolute risk of myocardial infarction (MI) associated with NSAID use is estimated to be about 0.5–1% per year [22]; although small, the absolute risk is increased with all NSAIDs. In a recent safety meta-analysis, COX-2 inhibitors were associated with an increased risk of heart failure and edema (RR 1.68, 95% CI 1.22, 2.31) compared with placebo, which remained significant even when rofecoxib was removed from the analysis (RR 1.67, 95% CI 1.21, 2.29) [23]. While NSAIDs use overall is associated with only a small, but insignificant risk of hemorrhagic stroke, an elevated risk of hemorrhagic stroke is found with diclofenac (RR 1.27, 95% CI, 1.02, 1.59) and meloxicam (RR 1.27, 95% CI, 1.08, 1.50) [24].

All NSAIDs have the potential to induce acute kidney injury (AKI) and the risk of AKI is particularly high in the first 30 days after initiation of therapy. NSAID users have a threefold greater risk of developing clinical AKI compared with non-NSAID users in the general population and OA patients with co-morbid conditions including hypertension, heart failure and diabetes mellitus are at increased risk [25]. Oral NSAIDs may be partly responsible for the excess mortality seen in patients with OA and should be used judiciously in OA due to safety considerations.

Consequently, the ESCEO guidelines recommend that oral NSAID use be limited to the lowest effective dose for the shortest time necessary to control symptoms, either intermittently or in longer cycles rather than in chronic use [4].

Discussion

Greater understanding of the benefits and limitations of current medications will lead to better disease management in OA. Data is accumulating on the shortfalls of current pharmacological treatment of OA, highlighted by issues of safety arising with analgesic therapies including paracetamol and NSAIDs. Due to the safety issues with paracetamol, SYSADOAs are now a first-line treatment for knee OA, with a particular emphasis placed on the outstanding benefit: risk ratio of pharmaceutical-grade pCGS and CS. As a step 2 treatment in OA patients who are unresponsive, or have moderate-severe pain, oral NSAIDs may offer good analgesia in the short-term; however, chronic use is not recommended due to GI, CV and renal toxicity. As a last resort, pharmacotherapy with weak opioids may be considered, although a recent report of association of opioids with increased all-cause mortality among OA patients requires further investigation [26].

Non-pharmacological interventions are often underutilized, and more could be achieved through appropriate application of the core set principles (education, weight management and exercise) and the combination of non-pharmacological and pharmacological treatment modalities throughout the treatment plan. Patient, physician and pharmacist education is an essential element of successful OA management, which may be achieved through programs that promote knowledge and understanding within the medical profession through medical societies, and in the wider community through patient societies. Finally, adherence to guideline recommendations, such as the updated ESCEO treatment algorithm for knee OA, will promote evidence-based medicine and patient-centric care, ultimately leading to greater physician and patient satisfaction across Europe and internationally.

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Compliance with ethical standards

Conflict of interest Eugene J. Kucharz reports royalties for lecturing and expert fee from the following companies: AbbVie, Berlin Chemie, Biogen, Celgene, Egis, Eli Lilly Polska, MSD, Novartis, Pfizer, Polpharma, Roche, Sandoz, UCB Biopharma, outside the submitted work. S. Szanto reports personal fees from Roche, personal fees from MSD, personal fees and non-financial support from Abbvie, grants and personal fees from Pfizer, personal fees from Novartis, personal fees from KRKA, personal fees from Sager Pharma, personal fees and non-financial support from Mylan, outside of the submitted work; O. Bruyère reports grants from Biophytis, IBSA, MEDA, Servier, SMB, and Theramex, outside the submitted work. C. Cooper has received lecture fees and honoraria from Amgen, Danone, Eli Lilly, GSK, Kyowa Kirin, Medtronic, Merck, Nestlé, Novartis, Pfizer, Roche, Servier, Shire, Takeda and UCB outside of the submitted work. J-Y. Reginster reports grants from ELI LILLY, grants and personal fees from SERVIER, grants and personal fees from MEDA, grants and personal fees from CNIEL, grants and personal fees from IBSA GENEVRIER, personal fees from RADIUS HEALTH, grants and personal fees from PIERRE FABRE, personal fees from DAIRY RESEARCH COUNCIL, outside of the submitted work. J. Konstantynowicz reports non-financial support from Takeda/Shire and Mylan (travel and conference fee), outside of the submitted work. M. Ivanova Goycheva reports payment for lectures from Abbvie, Pfizer, Novartis, UCB, Mylan, Amgen, outside of the submitted work. Z. Kamenov reports lecturing fees, personal fees, and expert fees from Boehringer, Astra Zeneca, Mundipharma, NovoNordisk, Sanofi, Eli Lilly, Berlin Chemie, MSD, Novartis, Sandoz, Merck, MEDA, Mylan, Servier, outside the submitted work. M. Petronijevic reports non-financial support from Takeda/Shire, and non-financial support from Mylan, outside of the submitted work. R. Stoilov reports payment for lectures from Pfizer, Abbvie, UCB, MSD, Novartis, Mylan, Amgen, outside of the submitted work. M. Domzalski, G. Radunovic, R. Vrana, R. Stok, K. Simnovec, B. Steno, and L. Gallelli declare that they have no conflicts of interest.

Ethical approval All authors meet the ICMJE criteria for authorship for this manuscript, take responsibility for the integrity of the work as a whole, and have given final approval to the version to be published.

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