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FOREWORD

Importance of Safety in the Management of Osteoarthritis and the Need for Updated Meta-Analyses and Recommendations for Reporting of Harms

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Osteoarthritis (OA) is a chronic progressive disorder that typically requires multiple treatment modalities over the course of disease. Osteoarthritis occurs frequently in older age, and the incidence of OA is rising owing to an aging population and association with obesity [1]. Older patients often have comorbidities and are at an increased risk of cardiovascular, gastrointestinal (GI), and renal adverse events (AEs), which impact on the appropriate choice of anti-OA medication.

The contemporary model of evidence-based medicine is predicated on the principle that clinical decisions and recommendations are data driven. Recommendations are based on the balance of relative benefits and harms of the treatment and patients' values and preferences. Often, the choice of medication is reduced to a trade-off between desirable and undesirable outcomes.

While multiple guidelines exist for the treatment of OA [2–6], they contain varying levels of detail concerning the safety and side effects of OA therapies. Consequently, a summary of the current evidence base is timely. A working party was convened by the the European Society for Clinical and Economic Aspects of Osteoporosis, Osteoarthritis and Musculoskeletal Diseases (1 December, 2017) to discuss current knowledge on the safety of anti-OA medications. New systematic reviews and meta-analyses were presented by several members of the working party, and their research findings are reported in this supplement.

Paracetamol has long been widely used for analgesia in OA; its widespread use is driven largely by an assumption of relative safety and despite evidence for its poor efficacy in OA. In recent years, evidence is mounting for cardiovascular, GI, renal, and hepatic AEs occurring with long-term paracetamol exposure. In this issue, Conaghan et al. provide a critical review of the literature on paracetamol safety, recommending a cautious approach to the use of paracetamol for chronic pain management in OA [7].

Non-steroidal anti-inflammatory drugs (NSAIDs) play a central role in the management of pain in OA. While moderately effective on OA pain, NSAIDs are associated with wide-ranging toxicities affecting the GI, cardiovascular, and renal systems. In a narrative literature review, Cooper et al. [8] provide a synopsis of safety data on non-selective NSAIDs published since the Cochrane review of 2011 [9]. Gastrointestinal toxicity is found with all NSAIDs, which

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may be of particular concern when treating older patients with OA. Cardiovascular toxicity is associated with all NSAIDs to some extent and the degree of risk appears to be drug specific. All NSAIDs have the potential to induce acute kidney injury, and patients with OA with co-morbid conditions including diabetes mellitus, hypertension, and heart failure are at increased risk. Further details provided in this analysis will facilitate a better understanding of the risk:benefit of using NSAIDs in OA and aid treatment selection.

In an accompanying article, Curtis et al. present the results of a systematic literature review and meta-analysis of the safety of cyclo-oxygenase (COX)-2 inhibitors [10]. Although the COX-2 inhibitors were designed to avoid the GI toxicity associated with COX-1 inhibition and non-selective NSAIDs, the results of this meta-analysis show that an increased risk of upper GI AEs, especially abdominal pain, remains with the COX-2 selective inhibitor class. Cyclo-oxygenase-2 inhibitors have a known association with increased risk of cardiovascular AEs; notably, even with the removal of rofecoxib from this meta-analysis, the risk of heart failure and edema remained significant. Consequently, a cautious approach to the use of NSAIDs and COX-2 inhibitors in OA is advised, with selection of treatment tailored to the individual patient characteristics, and limited to intermittent or cyclical use rather than long-term treatment to minimize safety concerns.

Topical NSAIDs are generally recommended ahead of oral NSAIDs as an early option for the symptomatic management of OA. Topical NSAIDs have a moderate effect on pain with similar efficacy to oral NSAIDs, but with a better safety profile owing to lower systemic absorption [9]. The findings of a systematic literature review and meta-analysis presented by Honvo et al. in this issue confirm the favorable safety profile of the topical route of administration of NSAIDs [11]. A non-significant increase in skin and subcutaneous tissue disorders was found, largely driven by topical diclofenac, which may account for the higher withdrawal rate with topical NSAIDs vs. placebo. Nonetheless, topical NSAIDs may be considered as safe in the management of OA, especially with regard to low GI toxicity.

Symptomatic slow-acting drugs for OA (SYSADOAs) represent a class of diverse agents that offer benefit in managing the symptoms of OA, with evidence for a disease-modifying effect in the long term in some cases [12–14]. Symptomatic slow-acting drugs for OA include glucosamine sulfate, chondroitin sulfate, diacerein, and avocado soybean unsaponifiables, which are widely used and it is of primary importance to establish their safety profiles. While some SYSADOAs may be considered safe for use in patients with OA, some concerns have been raised about the safety profiles of other agents. Consequently, Honvo et al. have performed a systematic review and meta-analysis of the safety of SYSADOAs vs. placebo in OA, the findings of which are reported in this issue [15]. The SYSADOAs glucosamine sulfate and chondroitin sulfate are shown to be safe treatments for patients with OA. Indeed, only the pharmaceutical-grade prescription crystalline glucosamine sulfate and chondroitin sulfate are recommended as safe and effective SYSADOAs [2, 16]. Limited evidence is available for unsaponifiables, which comprise multiple products containing a complex mixture of many natural vegetable extracts; however, the safety of one proprietary product is demonstrated in this new analysis. Diacerein is also available in several products and is associated with some safety signals [17]; consequently, the usefulness of diacerein in OA should be assessed for each patient after consideration of the nature of the product, appropriate dosage, and patient characteristics [18].

Intra-articular hyaluronic acid (IAHA) is recommended as a treatment option in the case of a contraindication to NSAIDs, e.g., in older patients with comorbidities, and patients who did not respond to earlier treatment [2]. Despite mounting evidence for the efficacy of IAHA, particularly for knee OA, and the widespread use of IAHA in clinical practice, controversy still persists regarding the risk:benefit of IAHA largely because of mixed reports on safety. The findings of a systematic review and meta-analysis presented in this issue by Honvo et al. did not identify any safety issue with IAHA [19], although the evidence was associated with only "low" to "moderate" certainty owing to a lack of safety data reporting for IAHA, which requires further studies. It is possible that some reports of serious AEs associated with IAHA are due to the concomitant use of NSAIDs, which should be further investigated.

The use of opioid analgesia may be considered as a last-resort pharmacologic therapy in OA when the pain is severe, when patients have not responded to other therapies, and when surgery is not deemed appropriate [2]. The results of a systematic review and meta-analysis presented here by Fuggle et al. confirm that there are considerable safety and tolerability issues surrounding the use of opioids in OA [20]. Oral opioids are associated with an increased risk of GI-, dermatologic-, and central nervous system-related AEs, regardless of whether the immediate- or extended-release formulation is used. These findings support recommendations to use opioids in OA after other analgesic options and only for short time periods.

Last, in preparation of the meta-analyses of the safety of anti-OA medications, the extensive literature review revealed a lack of reporting of AE data and inconsistencies in the data reported. This identified a need for precise disease-specific guidance on the reporting of AEs in clinical trial manuscripts. To close this gap, a consensus statement from the European Society for Clinical and Economic Aspects of Osteoporosis, Osteoarthritis and Musculoskeletal

Diseases Working Group published in this supplement provides specific, clear, practical, and standardized guidance on the reporting of AE data in manuscripts reporting the outcomes of clinical trials assessing drugs for OA [21], which will complement existing recommendations [22–24]. Ultimately, we hope that the findings of these new safety analyses will add to the evidence base from which future guideline updates may provide further clarity on the appropriate selection of anti-OA medications tailored to the individual patient.

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