Drugs
https://doi.org/10.1007/s40265-025-02162-4

SYSTEMATIC REVIEW

Safety of Anti-osteoarthritis Medications: A Systematic Literature Review of Post-marketing Surveillance Studies

Germain Honvo[1] · Laetitia Lengelé[2] · Majed Alokail[3] · Nasser Al-Daghri[4] · Jean-Yves Reginster[3] · Olivier Bruyère[1]

Accepted: 10 February 2025

Abstract

Background Several meta-analyses of phase 3 randomized controlled trials (RCTs) were published in 2019, reassessing the safety of most anti-osteoarthritis (OA) medications, mainly on the basis of data from full safety reports. The current systematic review (SR) intends to provide complementary insights into the safety of anti-OA medications, using evidence from post-marketing safety surveillance studies.

Methods The review protocol was registered with PROSPERO database (registration no. CRD42021227872). We followed the Cochrane methodology for SRs of interventions and comprehensively searched the Medline, CENTRAL, Scopus and TOXLINE databases from inception to November 2023, to include all post-marketing safety surveillance studies on any anti-OA medications. The outcomes of this SR were any adverse events (AEs) reported in the included studies.

Results The literature search yielded 16,990 studies, of which 59 articles were ultimately included in the review. Most studies investigated non-steroidal anti-inflammatory drugs (NSAIDs, 27 studies, 28 reports) and intra-articular hyaluronic acid (IAHA, 16 studies). Symptomatic slow-acting drugs for osteoarthritis (SYSADOAs) were assessed in seven studies (one of which also assessed NSAIDs), and corticosteroid injections in four studies, while opioids and "herbal mixtures and other compounds" each were investigated respectively in three and two studies. Most of the studies were cohort studies ($n = 44$), others were case reports or case series ($n = 12$), RCTs ($n = 2$ reports of the same trial), or a case–control study ($n = 1$). The most commonly reported AEs with NSAIDs from cohort (sample sizes varied between 129 and 22,938 patients), RCT (21,645 patients with OA), and case–control (174 cases and 926 control patients with OA) studies were gastrointestinal (GI) and/or cardiovascular (CV) AEs, with specific AEs varying with individual NSAIDs. Where comparisons between NSAIDs were made, the overall literature shows a better or similar safety profile for celecoxib (at a daily dose of 200 mg, where dosage was reported) compared with other NSAIDs in regards to GI, CV and renal events. Other anti-OA medications with most common AEs reported from cohort studies were: IAHA (injection site pain); diacerein (GI AEs and reddish urine); avocado–soybean unsaponifiables (GI AEs); non-pharmaceutical-grade glucosamine and chondroitin (allergic reactions, GI disorders); opioids (hip fracture associated with long-term tramadol use among older adults; GI and nervous system disorders with hydrocodone); corticosteroid injections (increased risk of OA progression); herbal mixtures and other compounds (GI AEs). There were case reports or case series of specific AEs with various anti-OA medications that require further investigations in well-designed cohort studies before any definitive conclusions can be reached.

Conclusions This SR confirms previous evidence on the safety of anti-OA medications from meta-analyses of phase 3 RCTs. Beyond the evidence here reported, the limitations of this research highlight the urgent need of a reporting guideline for post-marketing safety surveillance studies. Importantly, real-life safety surveillance of anti-OA medications should be strengthened with large cohort studies with control groups, and results should be disaggregated by disease populations for drugs common to several conditions.

✉ Olivier Bruyère
Olivier.Bruyere@uliege.be

[1] Division of Public Health, Epidemiology and Health Economics, University of Liège, Liège, Belgium

[2] Metabolism and Nutrition Research Group, Louvain Drug Research Institute, UCLouvain, Université catholique de Louvain, 1200 Sint-Lambrechts-Woluwe, Belgium

[3] Protein Research Chair, Biochemistry Department, College of Science, King Saud University, Riyadh, Kingdom of Saudi Arabia

[4] Chair for Biomarkers of Chronic Diseases, College of Science, King Saud University, Riyadh, Kingdom of Saudi Arabia

Published online: 17 March 2025

Key Points

This systematic review confirms previous evidence on the safety of anti-osteoarthritis medications from meta-analyses of phase 3 randomized placebo-controlled trials.

Some additional safety concerns have been reported on specific drugs, mainly from case reports and case series, which require further investigations in large cohort studies before any definitive conclusions can be reached.

The limitations of this research highlight the urgent need of a reporting guideline for post-marketing safety surveillance studies.

1 Introduction

Osteoarthritis (OA) is the most common joint disease and a major public health issue, particularly in the context of global population growth and ageing, representing a significant burden for patients, societies and healthcare systems [1–3]. In the absence of recognized disease-modifying drugs, the management of OA relies on combinations of pharmacological and non-pharmacological treatments, with the aim of relieving the pain induced by the disease and improving the functional status and quality of life of patients [4]. In such a context, the safety of these drugs is of paramount importance, as patients may need to take anti-OA medications for several years.

Recently, the European Society for Clinical and Economic Aspects of Osteoporosis, Osteoarthritis and Musculoskeletal Diseases (ESCEO) commissioned a series of systematic reviews and meta-analyses that reassessed the safety of various anti-OA medications, providing up-to-date evidence on safety using data from phase III randomized placebo-controlled clinical trials (RCTs) [5–9]. For more accuracy of estimates, many of these meta-analyses used as much as possible data from full safety reports, instead of safety data reported in clinical trial manuscripts [5–7].

Although evidence from meta-analyses of RCTs is the highest-level evidence in epidemiology and evidence-based medicine, such evidence is limited for assessment of drug safety and therefore needs to be complemented by post-marketing surveillance data. Limitations of RCTs in providing strong evidence on drug safety include sample size restrictions, selective patient population and relatively short follow-up duration [10]. These limitations make them inappropriate to study rare, long-onset potentially severe or serious adverse events, as well as effects of possible interactions with other drugs particularly in patients with comorbidities, which may not be detected from phase I to phase III clinical trials. Therefore, data from real-life, provided by post-marketing safety surveillance studies, are necessary for deepening the knowledge about drug safety [11]. In OA, in particular, it has been reported that long-term safety data are limited. On the other hand, and to the best of the authors' knowledge, no systematic review of post-marketing surveillance studies of anti-OA drugs has been published so far. Such a review would be useful in providing an overview of characteristics and outcomes of post-marketing safety surveillance studies in OA.

The objective of this systematic literature review is therefore to identify all the published post-marketing safety surveillance studies on pharmacological treatments for OA and to describe the characteristics and the main findings of these studies. Thus, we sought to provide complementary evidence on the safety of anti-OA medications and insights into the state of post-marketing safety surveillance in OA.

2 Methods

2.1 Guidelines and Protocol Registration

This systematic literature review was conducted following the methodological guidance provided in the Cochrane Handbook [12]. The current report follows the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guideline [13].

The review protocol was pre-registered in the PROSPERO database (registration no. CRD42021227872).

2.2 Information Sources

The following four bibliographic databases were searched from inception to 4 November 2023, using detailed and highly sensitive search strategies: Medline (via Ovid), the Cochrane Central Register of Controlled Trials (Ovid CENTRAL), Scopus and TOXLINE (via ProQuest). An initial comprehensive search was first conducted on 30 December 2020, then the literature search was updated in 2023 (04/11/2023) to include additional studies published since the initial search date.

Post-marketing surveillance studies not published in scientific journals were not considered in this systematic review; therefore, grey literature (such as reports to drug regulatory agencies) was not searched. We conducted a manual search of any literature reviews identified through databases search and of references of included studies for

any additional individual study on post-marketing surveillance of anti-OA drugs.

2.3 Search Strategies

The search strategies were constructed following the Population/Problem, Intervention, Comparator, Outcome, and Study design (PICOS) framework. As this review does not address any specific anti-OA medications (Intervention) and does not consider any specific comparisons to other interventions (Comparator), the search strategy did not include these two components of the PICOS framework. Although safety is the outcome of interest in this review, the outcome component of the PICOS framework was also omitted. In fact, the review does not address any specific set of adverse events. Therefore, the search strategies included only the Population/Problem ("osteoarthritis") and the Study design ("post-marketing surveillance studies"/"phase IV studies"/real-life studies) components of the PICOS framework. Specific terms for individual phase IV study designs in pharmacoepidemiology (e.g. phase IV randomized clinical trials, cohort studies, case–control studies, analysis of secular trends) were not used, as this would generate substantial unnecessary records, given that these specific study designs are not used only for the purpose of post-marketing safety surveillance. To broaden the scope of the search, we added (as an exception to the principle announced before) the terms "case report" and "case series" to the words describing the study design. This is to avoid missing any case report or case series on real-life safety experiences with anti-OA drugs, which would not have been specifically reported/indexed as a post-marketing surveillance report. The detailed search strategies for the databases considered for this systematic review are reported in the Supplementary Information.

2.4 Eligibility Criteria

2.4.1 Inclusion Criteria

All individual post-marketing surveillance studies/publications addressing the safety of any pharmacological treatment for the management of OA were included in this systematic literature review. All types of study designs in pharmacoepidemiology were considered, including phase IV randomized clinical trials, cohort studies, case–control studies, analysis of secular trends, case series and case reports. Studies including both patients with OA and patients with other diseases for the assessment of drugs common to various conditions (e.g. NSAIDs, corticosteroids) were also included. Ultimately, post-marketing studies specifically designed to investigate interactions between anti-OA medications and other drugs in patients with OA were included.

2.4.2 Exclusion Criteria

Studies that are extensions of phase 3 RCTs, and usually reported as "long-term safety" studies, were not included in this systematic review. Likewise, randomized placebo-controlled trials performed after drug approval, but that are not typically designed for the purpose of pharmacovigilance, were excluded; these studies are those designed as phase 3 RCTs but performed after drug approval (sometimes referred to as "phase 5" trials). We also excluded controlled clinical trials designed as drug comparison studies or noninferiority studies, even if they included safety as outcome, unless they were formally described as post-marketing safety surveillance or real-life studies. For studies including both patients with OA and patients with diseases other than OA, those that did not report separate results for patients with OA only were excluded. Studies evaluating rofecoxib (Vioxx) were excluded from this systematic review, as this drug has already been withdrawn from the market [14]. In the case of studies reporting data on multiple drugs including rofecoxib, only those that have results separately reported for drugs other than rofecoxib were included. Ultimately, the following studies/papers were also excluded: evidence synthesis studies (narrative or systematic reviews), letters, comments, editorials or studies involving animals, plus published in languages other than English or French.

2.5 Study Selection Process

The Covidence online software (https://www.covidence.org/) was used to manage the whole study selection process. Two researchers (G.H. and L.L.) independently read the title and abstract of all the records from all the databases after duplicates removal, to exclude irrelevant studies. At this stage, all post-marketing studies on anti-OA drugs were included, whether safety was evoked or not in the title or abstract. Then, the same two investigators (G.H. and L.L.) independently reviewed the studies included for full-text review to include those that fully fitted the review selection criteria. Full-text exclusion reasons were documented. At both the title/abstract and full-text selection stages, disagreements between the two reviewers were solved by consensus or with the involvement of another member of the review team (O.B.).

2.6 Data Collection and Data Items

Two members of the review team (G.H. and L.L.) extracted relevant data from the included articles using a predefined standard data extraction form. Data were extracted from each article by one person, then systematically checked by one

of the review team members (G.H. or L.L.). The following data were extracted: (a) information for manuscript identification (Covidence identifier, first authors' name, publication year); (b) objective(s) of the study; (c) characteristics of the study (design, setting, duration, sample size, funding source, whether the study was reported as a post-marketing safety surveillance or mandated study); (d) characteristics of patients and disease (age, gender, location of OA); (e) treatment and characteristics (drug studied, dosage, formulation regimen, manufacturer, treatment duration, comparator); (f) main findings of the study (adverse events with frequencies or odds ratios/risk ratios); (g) conclusions of the study (authors' conclusion and/or perspectives).

Since the purpose of this review was to identify and describe the available post-marketing safety surveillance studies on pharmacological treatments for OA, and also to identify challenges in pharmacovigilance in OA, we did not contact authors for complementary information in case of incomplete or missing data in the manuscripts.

2.7 Outcomes of Interest

As a systematic review of post-marketing safety surveillance studies, the outcome of this research was any adverse events, or any safety issues reported in the included studies. Although failure in drug effectiveness has also been considered as harm to patient [15], this review did not cover effectiveness.

2.8 Methodological Quality Assessment

We assessed the methodological quality of the included studies using specific risk of bias (RoB) assessment tools, according to study design. Cohort and case–control studies were assessed using the Newcastle–Ottawa Scale (NOS). The NOS for cohort studies evaluates: (1) the selection of study participants, (2) the comparability of cohorts on the basis of the design or analysis and (3) the adequacy of outcome assessment. This tool is, indeed, the most commonly used RoB assessment tool for cohort and case–control studies [16], and was found to be better than the Risk Of Bias In Nonrandomized Studies-of Interventions (ROBINS-I) in terms of applicability, while showing similar reliability [17]. A high score indicates a low risk of bias. Case reports and case series were assessed using the Joanna Briggs Institute (JBI) critical appraisal checklist [18], the only tool currently available for the assessment of the methodological quality of case reports [16]. Risk of bias in randomized controlled trials was assessed using the Cochrane tool (RoB 1.0) [19].

2.9 Data Synthesis

We qualitatively synthetized the most relevant data extracted from the included studies. The specific data considered in the synthesis were those related to the study and interventions characteristics, the outcomes (adverse events) and the study authors' conclusions. We first synthetized the data in tables, then these were summarized in short text descriptions.

3 Results

3.1 Study Selection

The database search yielded a total of 16,990 records, from which 59 reports (58 individual studies) fulfilling the selection criteria were ultimately included in the systematic review. The study selection process is summarized in Fig. 1, including details on full-text exclusion reasons.

Of the 59 articles included, 44 were reports of cohort studies, 12 were case series or case reports, 2 articles were reports from a single RCT and 1 study was a nested case–control study. The drugs studied include non-steroidal anti-inflammatory drugs (NSAIDs) [20–47] (Table 1), intra-articular hyaluronic acid (IAHA) [48–63] (Table 2), symptomatic slow-acting drugs for osteoarthritis (SYSADOAs) [26, 64–69], corticosteroid injections [70–73], opioids [74–76] and herbal mixtures and other compound [77, 78] (Table 3).

3.2 Methodological Quality of Included Studies

The synthesis of the methodological quality assessment for the included studies is presented in the Supplementary Information. Cohort and case–control studies were assessed using the NOS scale, while case reports and cases series were evaluated with the JBI case reports critical appraisal tool.

The main methodological flaw of the included cohort studies is the absence of control groups. Supplementary Table 1 presents the synthesis of risk of bias in studies on NSAIDs, with only 6 cohort studies of 19 having a control group [20–23, 28, 29]. Two of them compared meloxicam with rofecoxib [28, 29], so only the meloxicam arm is reported herein; the remaining four cohort studies with a control group investigated the safety of celecoxib against meloxicam, naproxen or other NSAIDs [20–23]. Among 15 cohort studies investigating IAHA (Supplementary Table 2), only one had a control group [54]. Of the ten cohort studies on other drugs (including SYSADOAs, corticosteroid injections, opioids, and herbal mixtures and other compounds) (Supplementary Table 3), only two studies had a control group, including a study on corticosteroid injections [71] and another one on opioids [76].

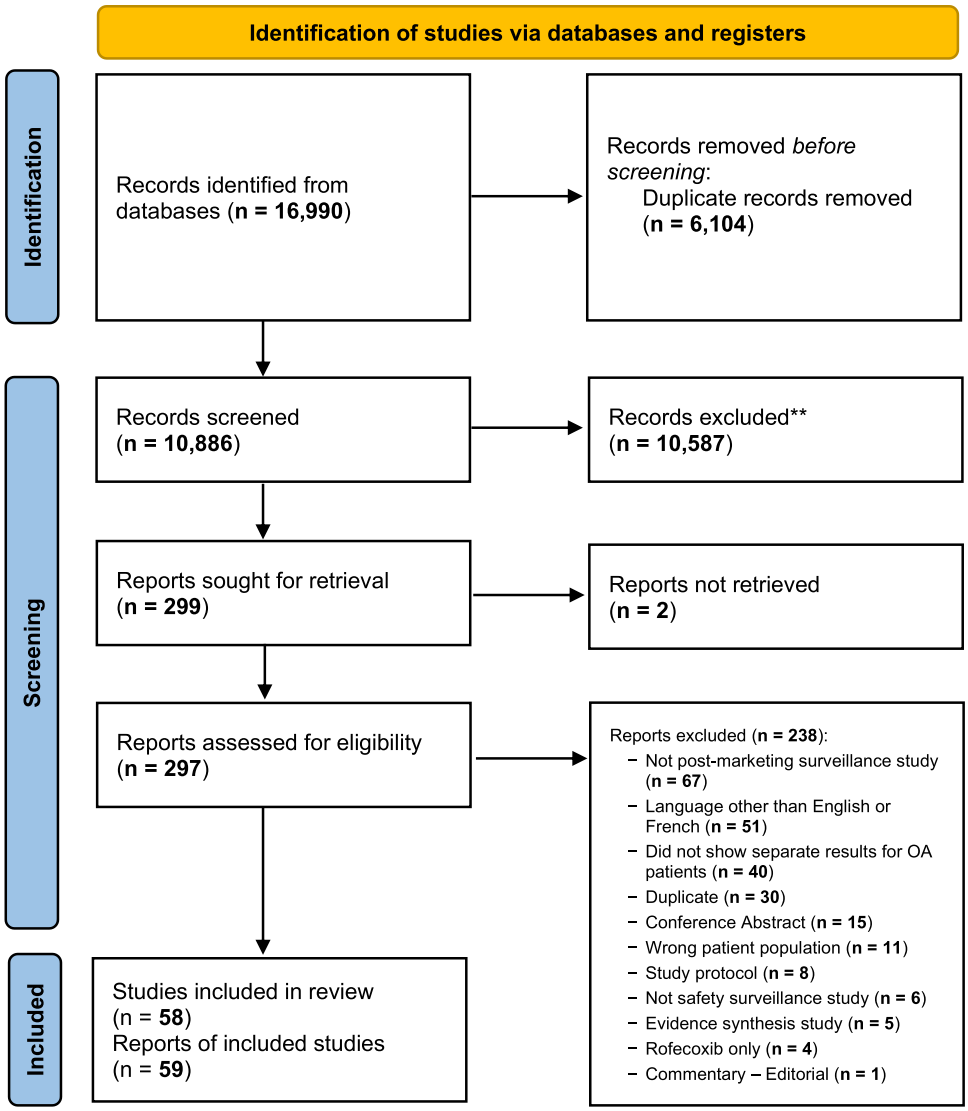

Fig. 1. PRISMA flow diagram of the systematic review

A total of 12 case reports or case series were included in this review. Almost all of them were quite well reported, having a 7–8 "yes" responses to the 8 questions of the JBI case reports critical appraisal tool; one case reports on SYSADOAs [68] and another one on corticosteroid injection [72] did not have a good reporting quality (Supplementary Tables 1–3). The only RCT (with two reports [24, 25]) included was assessed as a low risk of bias study (using the Cochrane RoB 1.0 tool), as was the sole case–control study included [26] (Supplementary Tables 4 and 5).

3.3 Characteristics of Included Studies and Overview of Outcomes by Drugs

3.3.1 Non-steroidal Anti-inflammatory Drugs (NSAIDs)

Among the included studies, NSAIDs were the most investigated anti-OA medications, with a total of 28 reports including 19 cohort studies (prospective or retrospective), 6 case reports or case series, 2 reports of a single RCT and 1 nested case–control study. The sample size of the cohort studies varied between 129 and 22,938 patients, while the follow-up duration varied between 4 weeks and 18 months. Most

Table 1 Summary of study and intervention characteristics, and main findings from individual studies on non-steroidal anti-inflammatory drugs (NSAIDs)

Study characteristics						Intervention characteristics		Main findings	
First author, year; (country)	Study design[(note)]/follow-up duration	Sample size	OA site	Age/% of female participants	Reported as PMSS?/source of funding	Intervention(s) (brand name)/dosage	Treatment duration	Outcomes: adverse events (frequency or HR/OR)	Authors' conclusion
Cunnington, 2008 [20] (USA)	Retrospective cohort study (M = 103 days for celecoxib and 56 days for naproxen, and 1016 days for the reference group)	Celecoxib (chronic): n = 16,580 Naproxen (chronic): n = 2907 Not exposed: n = 51,539	NR	No separate reports by drugs Chronic (total): < 65 years (48.3%); ≥ 65 years: (51.7%) Female (total): 64.5%	No, but study reported as being part of epidemiological studies requested by regulatory authorities to assess the safety of Cox-2 inhibitors. Funding: GlaxoSmithKline (GSK) UK	High and low doses studied. **Celecoxib** high > 200 mg; **Naproxen** high > 1000 mg Not exposed (comparator) Dosage: NR; "There was little accurate data on dose" (reported as a limitation of the study)	Chronic: at least 90 days continuous use Not exposed: subjects with no recorded exposure and short-term use of NSAIDs and Cox-2is	Cardiovascular event (hospitalization for an acute myocardial infarction or ischaemic stroke): Celecoxib: adjusted HR = 1.05, 95% CI 0.91–1.22 (versus non-chronic users) Naproxen: adjusted HR = 0.99, 95% CI 0.64–1.54 (versus non-chronic users)	In our analysis to ascertain whether differential risks exist between chronic use of Cox-2is and NSAIDs in the single largest disease indication of OA, we observed (…) no increased risks for celecoxib or naproxen compared with a non-chronic NSAID/Cox-2is
Laharie, 2010 [21] (France)	A population-based cohort study (between 8 and 12 weeks)	Patients with OA: celecoxib, n = 6150 (52.2%) Traditional NSAID (tNSAID), n = 4369 (19.1%); Other indications includerRheumatoid arthritis, Inflammatory rheumatism, Back pain, etc	NR	NR separately for patients with OA	No, but study reported as a real-life study. Funding: this study was funded by unconditional grants from Merck & Co. and Pfizer Inc	**Celecoxib** **tNSAIDs** (including ibuprofen, piroxicam, ketoprofen, diclofenac, naproxen, tiaprofenic acid) - (comparator) Dosage: NR	NR	Study outcomes: hospital admission rates for gastrointestinal (GI) or cardiovascular (CV) events **Results for patients with OA only** Celecoxib Serious CV event: n = 1 patient Severe GI event: n = NR tNSAIDs: Serious CV event: n = 3 patients Severe GI event: n = 3 patients	Hospitalization rates for GI bleeding were 10–20 times lower than expected from published randomized clinical trials, probably because of differences in drug usage and concomitant gastroprotection. CV event rates conformed to those expected from general population data. These results emphasize the necessity of developing population healthcare databases to explore such low event rates

Table 1 (continued)

Study characteristics						Intervention characteristics		Main findings	
First author, year; (country)	Study design[(note)]/follow-up duration	Sample size	OA site	Age/% of female participants	Reported as PMSS?/source of funding	Intervention(s) (brand name)/ dosage	Treatment duration	Outcomes: adverse events (frequency or HR/OR)	Authors' conclusion
Layton, 2003a [22] (England)	Non-interventional observational cohort technique (retrospective) (9 months)	Celecoxib [patients with OA, $n = 4905$ (28.1%); Others, $n = 12,553$ (71.9%)] Meloxicam [patients with OA, $n = 4434$ (23.2%); Others, $n = 14,653$ (76.8%)]	NR	NR separately for patients with OA Female (total sample): 68.3%	Yes, PEM Funding: Unconditional donations received from manufacturers of celecoxib and meloxicam (by the DSRU)	**Celecoxib (Celebrex®) Meloxicam (Mobic®)** (comparator) Dosage: NR "As the reporting of dose data was low, it was not adjusted for in the multivariate analysis.·	9 months	**Total sample (OA and Others) - Adjusted RR (95% CI) for celecoxib versus meloxicam** Cardiovascular: 1.72 (0.87, 3.40) Cerebrovascular: 1.66 (1.10, 2.51) Peripheral venous: 1.06 (0.51, 2.19) **Results in patients with OA only** (adjusted RRs not reported separately for patients with OA) Cardiovascular thromboembolic event: celecoxib ($n = 11$); meloxicam ($n = 3$) Cerebrovascular thromboembolic event: celecoxib ($n = 29$); meloxicam ($n = 13$) Peripheral venous thrombotic event: celecoxib ($n = 7$); meloxicam ($n = 8$)	This study reports a relative increase in the rate of cerebrovascular thromboembolic (TE) events in users of celecoxib compared with meloxicam. There was no difference in the rate of cardiovascular TE events or peripheral venous thrombotic events between users of these two drugs. The incidence of these three groups of events reported in each of these two drug cohorts was low (<0.5%), therefore the relevance of our findings needs to be taken into consideration with other clinical and pharmaco-epidemiological studies
Layton, 2003b [23] (England)	Non-interventional observational cohort technique (retrospective) (9 months)	Celecoxib [patients with OA, $n = 4905$ (28.1%); Others, $n = 12,553$ (71.9%)] Meloxicam [patients with OA, $n = 4433$ (23.2%); Others, $n = 14,654$ (76.8%)]	NR	NR separately for patients with OA	Yes, PEM Funding: Unconditional donations received from manufacturers of celecoxib and meloxicam (by the DSRU)	**Celecoxib (Celebrex®) Meloxicam (Mobic®)** (comparator) Dosage: NR "Limited information on starting dose and dose at event were recorded (…) for meloxicam, and reporting was incomplete for celecoxib	9 months	**Total sample (OA and Others) - Adjusted RR (95% CI) for celecoxib versus meloxicam** Symptomatic (acid/peptic) upper GI events: 0.77 (0.69, 0.85) Complicated upper GI conditions (perforations/ bleeding): 0.56 (0.32, 0.96) **Results in patients with OA only** (adjusted RRs not reported separately for patients with OA) Symptomatic (acid/peptic) upper GI events: celecoxib ($n = 285$); meloxicam ($n = 344$) Complicated upper GI conditions (perforations/bleeding): celecoxib ($n = 10$); meloxicam ($n = 21$)	This study reports a relative reduction (23%) in the incidence of symptomatic (acid/peptic) GI events, and a relative reduction (44%) in the incidence rate of complicated upper GI conditions (perforations/bleeding) for celecoxib compared with meloxicam

Table 1 (continued)

Study characteristics						Intervention characteristics		Main findings	
First author, year; (country)	Study design[(note)]/follow-up duration	Sample size	OA site	Age/% of female participants	Reported as PMSS?/source of funding	Intervention(s) (brand name)/ dosage	Treatment duration	Outcomes: adverse events (frequency or HR/OR)	Authors' conclusion
Solomon, 2017 [24] (Multinational: 923 centres in North America, Central America, South America, Asia, and Eastern Europe)	A double-blind, randomized, controlled, multicentre trial (phase IV study) - The PRECISION trial (Up to 42 months. Participants had a minimum follow-up of 18 months)	Total enrolled: $n = 24{,}081$ - including 21,645 patients with OA (89.9%) and 10.1% patients with RA. Celecoxib (AO): $n = 7259$ Naproxen (OA): $n = 7178$ Ibuprofen (OA): $n = 7208$	NR	For total sample ($n = 24{,}081$) Age, mean: 63.2 (±9.4) yrs. Female gender, n (%): 15,445 (64.1)	No, but PRECISION reported as a safety trial mandated by the US Food and Drug Administration (FDA). Funding: This PRECISION trial and these analyses were funded by Pfizer	**Celecoxib** 100 mg twice per day for OA. **Ibuprofen** 600 to 800 mg 3 times per day (comparator). **Naproxen** 375 to 500 mg twice per day (comparator) (administration of double dummy tablets so that all subjects received the study drug thrice daily)	Median follow-up on treatment was 20 months and was similar across the 3 treatment arms	**Primary analysis including all patients, HR (95% CI) – ITT analysis** Major NSAID toxicity* Naproxen versus celecoxib: 1.20 (1.04-1.39) Ibuprofen versus celecoxib: 1.38 (1.19-1.59) Expanded major NSAID toxicity† "Trends for the secondary outcome were similar" **Results for the subgroup of patients with OA, HR (95% CI) – ITT analysis** Major NSAID toxicity* Celecoxib versus naproxen: 1.18 (1.01–1.38) Celecoxib versus ibuprofen: 1.39 (1.19–1.62) Expanded major NSAID toxicity† Celecoxib versus naproxen: 1.25 (1.09–1.43) Celecoxib versus ibuprofen: 1.44 (1.26–1.65)	Among patients with symptomatic arthritis who had moderate to high risk of cardiovascular events, approximately 1 in 20 experienced a major toxicity over 1–2 years. Patients using naproxen or ibuprofen experienced significantly higher risk of major toxicity than those using celecoxib. (**Remark**: Conclusion based on analysis of total sample, including patients with rheumatoid arthritis). **Note from discussion**: "There was no subgroup interaction observed by age, gender, arthritis diagnosis, tobacco use, NSAID dose escalation, and history of gastrointestinal ulceration. These subgroup analyses were post hoc and should be considered hypothesis-generating."

Table 1 (continued)

Study characteristics						Intervention characteristics		Main findings	
First author, year; (country)	Study design[(note)]/follow-up duration	Sample size	OA site	Age/% of female participants	Reported as PMSS?/source of funding	Intervention(s) (brand name)/ dosage	Treatment duration	Outcomes: adverse events (frequency or HR/OR)	Authors' conclusion
Solomon, 2018 [25] (Multinational: 923 centres in the US, Canada, Australia, Brazil, Colombia, Costa Rica, Mexico, Panama, Peru, Philippines, Taiwan, Hong Kong, and Ukraine)	A double-blind, randomized, controlled, multicentre trial (phase IV study) - The PRECISION trial. Follow-up visits until month 42. Study patients were required to complete at least 18 months of follow-up visits	Total enrolled: $n = 24{,}081$ - including 21,645 patients with OA (89.9%) and 10.1% patients with RA. Celecoxib (OA): $n = 7259$ Ibuprofen (OA): $n = 7208$ Naproxen (OA): $n = 7178$	NR	For OA subgroup (Total, $n = 21{,}645$) Age, mean: 64 ± 9.3 yrs. Female sex: 13,661 (63.1%)	No, but PRECISION reported as a safety trial mandated by the US Food and Drug Administration (FDA). Funding: The PRECISION trial and these analyses were funded by Pfizer	**Celecoxib** at a dosage of 100 mg twice daily for OA. **Ibuprofen** at a dosage of 600–800 mg 3 times daily (comparator). **Naproxen** at a dosage of 375–500 mg twice daily (comparator)	Median follow-up on treatment was 20 months and was similar across the 3 treatment arms (reported from Solomon 2017)	**Results for the subgroup of patients with OA, HR (95% CI) - ITT analysis** Major adverse cardiovascular events Celecoxib versus ibuprofen: 0.84 (0.72–0.99) Celecoxib versus naproxen: 0.94 (0.80–1.10) Gastrointestinal events Celecoxib versus ibuprofen: 0.68 (0.51–0.91) Celecoxib versus naproxen: 0.73 (0.55–0.98) Renal events Celecoxib versus ibuprofen: 0.58 (0.40–0.82) Celecoxib versus naproxen: 0.77 (0.53–1.12) All-cause mortality Celecoxib versus ibuprofen: 0.93 (0.72–1.20) Celecoxib versus naproxen: 0.87 (0.68–1.12)	In conclusion, these subgroup analyses of the PRECISION trial, based on the underlying arthritis diagnosis, yield results that are similar but not identical to those of the overall trial. The OA subgroup randomized to receive celecoxib treatment experienced fewer CV events compared with the subgroup randomized to ibuprofen, but not the subgroup randomized to naproxen. The OA subgroup receiving celecoxib experienced fewer clinically significant adverse GI events than the subgroups receiving ibuprofen or naproxen, with similar trends observed in patients with RA. Renal events were less common in the OA subgroup receiving treatment with celecoxib compared with the subgroup randomized to ibuprofen but not in the subgroup randomized to naproxen, and in patients with RA, there were no differences between patients receiving the three drugs

Table 1 (continued)

Study characteristics						Intervention characteristics		Main findings	
First author, year; (country)	Study design[(note)]/follow-up duration	Sample size	OA site	Age/% of female participants	Reported as PMSS?/source of funding	Intervention(s) (brand name)/dosage	Treatment duration	Outcomes: adverse events (frequency or HR/OR)	Authors' conclusion
de Abajo, 2014 [26] (Spain)	A nested case-control study	Indication: Osteoarthritis (OA) Cases: $n = 174$ Controls: $n = 926$	NR	NR	No, but study performed using a primary care database validated for pharmaco-epidemiological research. Funding: This study was supported by a research grant from Fondo de Investigación Sanitaria—Ministerio de Ciencia e Innovación	**Traditional NSAIDs (tNSAIDs)**: aceclofenac, desoxibuprofen, dexketoprofen, diclofenac, ibuprofen, indometacin, ketorolac, lornoxicam, meloxicam, naproxen, piroxicam. Dosage: Dose range only reported for the three tNSAIDs more widely used (ibuprofen, diclofenac and aceclofenac)	'Current users': prescription lasted until index date or ended within 30 days prior to the index date. 'Past users': prescription ended between 31 and 365 days before the index date. 'Remote users': prescription ended before 365 days prior the index date. 'Non-users': no prescription before index date (reference category)	Risk of non-fatal acute myocardial infarction associated with NSAIDs (Indication: OA) - Among current users of tNSAIDs. Adjusted OR (95% CI): 1.04 (0.85–1.27) Note: Results not reported by indication (OA) for individual NSAIDs. Also, results not reported by indication (OA) for evaluation the effect of dose, duration, background cardiovascular (CV) risk, and concomitant low-dose aspirin use with current use of most widely used NSAIDs	The risk of nonfatal acute myocardial infarction varied with individual tNSAIDs, duration of treatment and background cardiovascular risk

Table 1 (continued)

Study characteristics						Intervention characteristics		Main findings	
First author, year; (country)	Study design[(note)]/follow-up duration	Sample size	OA site	Age/% of female participants	Reported as PMSS?/source of funding	Intervention(s) (brand name)/dosage	Treatment duration	Outcomes: adverse events (frequency or HR/OR)	Authors' conclusion
Khotib, 2019 [27] (Indonesia)	An observational retrospective study. (NR)	$n = 143$	Knee (bilateral, right unilateral, left unilateral)	Mean age: NR Female: $n = 115$ (80.42%)	No, but observational study using medical records of patients with OA. Funding: The Ministry of Research, Technology and Higher Education, Republic of Indonesia	**Different individual NSAIDs**; Combinations of NSAIDs with other NSAIDs or with other drugs (paracetamol and corticosteroids); *corticosteroid*; *glucosamine HCl*; *other drugs* (benzodiazepin, gabapentin, amitriptyline, lidocaine HCl 2%). Dosage: NR	NR	AEs with NSAID: heartburn, bloating, nausea, decreased appetite, dyspepsia (42 patients). AEs with NSAID+NSAID: heartburn, nausea, palpitations (4 patients). AEs with NSAID + corticosteroid: stomach ache, dyspepsia (4 patients). AEs with NSAID + paracetamol: hepatotoxic based on laboratory data (1) AEs with NSAID + ACE-I: reducing antihypertensive effect (1). AEs with NSAID + β-blocker: unspecified (7). AEs with NSAID + ARB: unspecified (7)	It can be concluded that OA therapy with a number of pain relievers shows an adequate therapeutic response with some side effects and interactions both pharmacokinetically and pharmacodynamically
Layton 2003c [28] (England)	Non-interventional observational cohort technique (retrospective) (9 months)	Meloxicam (patients with OA): $n = 4433$	NR	NR separately for patients with OA	Yes, PEM Funding: Unconditional donations received from manufacturers of rofecoxib and meloxicam (by the DSRU)	**Meloxicam (Mobic®)** (compared with rofecoxib) Dosage: NR « Limited information on starting dose and dose at event were provided (…) for meloxicam»	9 months	Cardiovascular thromboembolic event: meloxicam ($n = 3$) Cerebrovascular thromboembolic event: meloxicam ($n = 13$) Peripheral venous thrombotic event: meloxicam ($n = 8$)	(…). The incidence of these three groups of events reported in each of these two drug cohorts was low (less than 0.5%), therefore the relevance of our findings needs to be taken into consideration with other clinical and pharmacoepidemiological studies
Layton 2003d [29] (England)	Non-interventional observational cohort technique (retrospective) (9 months)	Meloxicam (patients with OA): $n = 4433$	NR	NR separately for patients with OA	Yes, PEM Funding: Unconditional donations received from manufacturers of rofecoxib and meloxicam (by the DSRU)	**Meloxicam (Mobic®)** (compared to rofecoxib)	9 months	Symptomatic (acid/peptic) upper GI events: meloxicam ($n = 344$) Complicated upper GI conditions (perforations/bleeding): meloxicam ($n = 21$)	This study reports a relative reduction (…) in the incidence rate of symptomatic (acid/peptic) GI events, and no difference in the incidence rate of complicated upper GI conditions (perforations/bleeding) for rofecoxib compared with meloxicam

Table 1 (continued)

Study characteristics						Intervention characteristics		Main findings	
First author, year; (country)	Study design[(note)]/follow-up duration	Sample size	OA site	Age/% of female participants	Reported as PMSS?/source of funding	Intervention(s) (brand name)/dosage	Treatment duration	Outcomes: adverse events (frequency or HR/OR)	Authors' conclusion
Varghese, 2022 [30] (India)	Case reports	1 case report about OA	NR	A female patient aged 39 years	Funding: Nil	Tablet of **meloxicam** 7.5 mg per day initially, later 15 mg per day for 1 month	1 month	Maculopapular rashes over the lips, cheeks, and upper extremities (rare case of meloxicam-induced Stevens-Johnson syndrome)	Causality assessment reported this case to be probable ADR as de-challenge and temporal relationship between the drug and the event was established
Dreiser, 1993 [31] (NR)	Non-blinded multicentre cohort trial (1 year)	$n = 133$	Lumbar spine: 78 (58.6%) Knee: 32 (24.1%) Hip: 20 (15%) Generalized OA: 3 (2.3%)	M = 62 years (range 41–82 years) Women: 88 (66.2%)	No, but tolerability was the primary outcome. Funding: NR, but co-author is employee of Helsinn Healthcare, producer of the study drug	**Nimesulide** 100 mg orally twice daily	1 year	No. of patients reporting AEs (indirect questioning): $n = 31$ AEs were responsible for 47.8% of discontinuations: $n = 11$ Severe AEs: $n = 9$ Laboratory parameters: no clinically significant changes. AEs by body system: no. of AEs reported, not frequencies (Gastro-intestinal tract, Central nervous system, and Skin AEs)	The results provide evidence that nimesulide (100 mg orally twice daily), is a safe drug for the therapeutic management of OA. Notably, the trial did not reveal any serious adverse event or contraindication with regard to the use of the drug in the geriatric population
Pochobradsky, 1991 [32] (Italy)	Open field investigation trial (cohort) (1–3 weeks)	$n = 22938$	Lumbar spine, cervical spine, knee, shoulder, hip, hand, dorsal spine, other, and not established	50.8 ± 16.1 years Female: 52.0%	Yes, "Spontaneous drug monitoring" Funding: NR, but co-author is employee of LBP Pharmaceutical Institute, producer of the study drug	**Nimesulide** (LBP Pharmaceutical Institute, Italy) Starting dose of 200 mg (tablets or granules), twice a day for four days, followed by a maintenance dose of 100 mg, twice a day	1–3 weeks, according to the clinical response	ADRs presumably related to therapy ($n = 1887$ patients): epigastralgia, pyrosis, nausea, diarrhoea, vomiting, skin rash, itch, dizziness, somnolentia, oedema, headache, aerophagia, sweating, flushing, xerostomia, constipation, other (reported frequencies not clear)	The results of this study suggest that nimesulide is effective and well tolerated in the short-term treatment of a large number of patients with osteoarthritis

Table 1 (continued)

Study characteristics						Intervention characteristics		Main findings	
First author, year; (country)	Study design[(note)]/follow-up duration	Sample size	OA site	Age/% of female participants	Reported as PMSS?/source of funding	Intervention(s) (brand name)/dosage	Treatment duration	Outcomes: adverse events (frequency or HR/OR)	Authors' conclusion
Busson, 1986 [33] (United Kingdom)	Open, multicentre study (18 months)	$n = 221$	NR	Mean age (min–max) Age, men: 56 years (30–81) Age, women: 60 years (28–85) Female: 133 (60.2%)	No, "Long-term, open evaluation of the efficacy and safety of flurbiprofen" Funding: NR	**Flurbiprofen** (Froben®) The majority of patients received 100-150 mg/day	3–6 months or more	Side effect (any) – principally gastro-intestinal, CNS, or dermatological: - Flurbiprofen total (incidence = 22.7%) - Flurbiprofen with concomitant NSAIDs ($n = 35/150$ patients) - Flurbiprofen without concomitant NSAIDs ($n = 15/70$ patients)	In this study, flurbiprofen was found to be effective in the relief of pain, and assessed by doctor and patient as producing significant progress over an 18-month period. It was particularly useful in that group in whom side-effects had caused them to stop taking a previously prescribed drug
Otsuka, 2017 [34] (Japan)	A multi-centre, open-label, uncontrolled prospective study (52 weeks)	$n = 201$ 40 mg (1 patch): $n = 101$ 80 mg (2 patches): $n = 100$	Knee, lumbar spine, cervical spine, and other sites	66.3±11.8 years Female: 151 (75.1%)	No, but SFPP is reported as "available for the treatment of OA". Funding: NR, but Taisho Pharmaceutical Co., Ltd. was involved in the design of the study, its conduct, and the data analysis. Three co-authors are employees of Taisho Pharmaceutical Co., Ltd	***S*-furbiprofen plaster (SFPP)** (Tokuhon Corporation, Tokyo Japan). 40 mg (1 patch) versus 80 mg (2 patches) dosages studied	52 weeks	No. of patients with abnormal changes in laboratory test for kidney function: *40 mg (1 patch)* Blood urea nitrogen (mg/dL) ↑: 1 Serum creatinine (mg/dL) ↑: 1 Hematuria (+): 1 Proteinuria (+): NR *80 mg (2 patches)* Blood urea nitrogen (mg/dL) ↑: 3 Serum creatinine (mg/dL) ↑: NR Hematuria (+): 2 Proteinuria (+): 1	Toward the end of 52-week application, a statistically significant increase in Serum creatinine (SCr) was observed in both 40 and 80 mg, but increment was small and subclinical. Attention should be paid to kidney function when applying SFPP to patients with multiple risk factors
Emanueli, 1981 [35] (Italy)	A phase IV multiclinic study (cohort) (4 weeks)	$n = 1629$	NR	Mean age: NR Women: $n = 1001$ (61.45%)	Not specially stated, but the trial is described as a phase IV study; and indoprofen is reported as a recently introduced NSAID Funding: NR	**Indoprofen** Most of the patients were given 3 tablets of Indoprofen daily (a total of 600 mg)	4 weeks	Any AEs: $n = 363$ (22.3%) GI tract AEs: represented 78% of all AEs Discontinuations due to AEs: 6.9%	In conclusion our multiclinic study has confirmed the usefulness of treating osteoarthritis with indoprofen because of the marked analgesic activity of the drug and the acceptable frequency of adverse reactions

Table 1 (continued)

Study characteristics						Intervention characteristics		Main findings	
First author, year; (country)	Study design[(note)]/follow-up duration	Sample size	OA site	Age/% of female participants	Reported as PMSS?/source of funding	Intervention(s) (brand name)/dosage	Treatment duration	Outcomes: adverse events (frequency or HR/OR)	Authors' conclusion
Ernst, 1997 [36] (USA)	Case report	$n = 1$	Hip OA	A 74-year-old white woman	Funding: NR	**Ibuprofen** (nonprescription tablets), **with concomitant warfarin** Ibuprofen 400 mg rid was prescribed for pain relief. The patient did not fill the prescription, but instead took nonprescription 200-mg tablets two to three times a day	NR	The patient developed significant elevation of the international normalized ratio (INR) after the addition of ibuprofen to her medication regimen. The patient experienced a decrease in haemoglobin concentration, asymptomatic hypotension, and increased blood urea nitrogen/creatinine ratio. Limited physical examination failed to locate a source of bleeding	Concomitant use of ibuprofen and warfarin should be avoided in elderly patients with complex medical problems treated with multiple medications
Gordon, 1980 [37] (Belgium, Finland, Germany, Italy and the Netherlands)	A non-comparative long-term follow-up study (cohort) (6 to 12 months)	$n = 154$	Knee; hip; spine; shoulder; finger; toe; other	Mean age(range): 63 (37-85 years) Female: 104 (68%)	No, but reported as a study in general practice. Funding: NR, but authors are all employees of Pfizer	**Piroxicam** The majority of patients (69%) completed their study treatment with the starting dose of 20 mg once daily. A few patients received 30 mg and fewer still 10mg; only four patients were on 40 mg/day	The average duration was 6 months with a range of 3–11 months	Treatment-related AEs: 16 patients (10.3%) Epigastric distress and other gastro-intestinal symptoms (nausea, abdominal discomfort, flatulence) were the most common AEs (most were mild or moderate in severity). The other side-effects included headache (1 case), insomnia (1), fatigue (2), and miscellaneous reactions (9). Dermatitis (1 case), numbness of extremities (1), and indigestion (1). Discontinuation due to AE (gastro-intestinal pain): 1 case. Ulceration or gastric bleeding: (0)	Toleration was excellent, with almost no drug-related side-effects reported during the long-term follow-up period. As with other drugs of its class, side-effects mostly involved upper gastro-intestinal discomfort but there were no reports of gastric bleeding or ulceration

Table 1 (continued)

Study characteristics						Intervention characteristics		Main findings	
First author, year; (country)	Study design[(note)]/follow-up duration	Sample size	OA site	Age/% of female participants	Reported as PMSS?/source of funding	Intervention(s) (brand name)/ dosage	Treatment duration	Outcomes: adverse events (frequency or HR/OR)	Authors' conclusion
Kameshwari, 2015 [38] (India)	Case report	$n = 1$	NR	A 59-year-old female patient	Source of Support: Adverse Drug Reaction Monitoring Center, Kakatiya Medical College, MGM Hospital, Telangna, India	**Etoricoxib** 60 mg orally	Only a single dose took by the patient	Toxic epidermal necrolysis (Patient presented with the symptoms of extensive rash all over the body with peeling of skin and fever)	Even though the chances of developing a serious unexpected reaction with etoricoxib is very rare, it cannot be completely neglected and requires a keen study of the history of the patient before prescribing this drug
Maestracci, 1979 [39] (France)	A cooperative, simple, and open trial (cohort) (12 months)	$n = 2040$	Hip or knee	Mean age: Male: 61,6 years; Female: 64,4 years Gender: Female (68,6%)	No, but study reported as a "Long-term trial of sulindac (in general practice)" Funding: NR, but acknowledgments to Laboratoires Merck-Sharp-Dohme-Chibret	**Sulindac** (Arthrocine) 200 to 400 mg of sulinidac per day in 2 doses. The average dosage used was 3.2 tablets per day	12 months	Any adverse event (at least one): $n = 277$ (half of the events were gastralgia); Withdrawals due to adverse events: $n = 12$ Gastrointestinal bleeding: $n = 2$ Neurosensory AEs (dizziness, headaches, insomnia, drowsiness): $n =$ NR Cutaneous AEs (pruritus, rash): n NR	This trial let us point out the non-impoverishment of effectiveness of sulindac and the keeping of its good tolerance for long term
Pillai, 2010 [40] (United States)	An observational multicentre, open-label, post-marketing study (cohort) (2 months)	$n = 1067$	Knee; Hand; Spine; Hip; Feet; Other	64 ± 12.3 years Of those who completed all study visits, 74% were females	Yes Funding: Primus Pharmaceuticals, Inc. was the financial sponsor of this study	**Flavocoxid** (Limbrel*) – Manufactured by Primus Pharmaceuticals, Inc. Dosage: 500 mg b.i.d	60 days	Dropped out to AEs: $n = 6$ Total AEs: 10.4% (Incidence) Body as a whole (Fever/chills, Fatigue): 0.4% Cardiovascular (Hypertension, Fluid retention): 0.3% Central nervous system: 1.0% Ear, nose, throat: 0.1% Eye (Blurred vision): 0.1% Hepatic (Increased liver function test): 0.1% Gastrointestinal: 7.4% Gynaecologic: 0.1% Musculoskeletal: 0.4% Respiratory system: 0.2% Skin: 0.4%	Within a 'real world' clinical rheumatology practice setting, flavocoxid demonstrated significant efficacy in the management of OA in multiple patient types and displayed significant potential for reducing the possibility of adverse GI side-effects and use of gastroprotective agents associated with more traditional OA medications

Table 1 (continued)

Study characteristics						Intervention characteristics		Main findings	
First author, year; (country)	Study design[(note)]/follow-up duration	Sample size	OA site	Age/% of female participants	Reported as PMSS?/source of funding	Intervention(s) (brand name)/ dosage	Treatment duration	Outcomes: adverse events (frequency or HR/OR)	Authors' conclusion
Banks, 1995 [41] (USA)	Retrospective analysis of cases reported to the Food and Drug Administration (FDA). (Case series)	$n = 180$ cases of diclofenac hepatic injury (including patients with and without OA)	NR	NR	No, but analysis of cases submitted to the voluntary reporting system of the FDA, between November 1988 and June 1991. Funding: Acknowledgment to Ciba-Geigy for financial support and provision of data	Diclofenac Dosage: NR	The duration of therapy before the detection of hepatic injury was under 6 months in 85% of all case. (including patients with and without OA)	Hepatotoxicity: $n = 139$ patients with OA (of the total of 180 cases analysed)	The data suggest that diclofenac-related liver injury is particularly likely to involve osteoarthritic females, presenting with jaundice 1–6 months after starting diclofenac, with injury that is predominantly hepatocellular and presumably caused by metabolic idiosyncrasy
Salemis, 2009 [42] (Greece)	Case Report	$n = 1$	Bilateral hip OA	A 60-year-old woman	Funding: NR	**Diclofenac sodium** 100 mg of diclofenac daily (for 2 to 3 severe painful episodes of the disease every month)	During the last paroxysm of pain, she had been taking 100 mg of diclofenac daily for 9 days	Spontaneous thigh hematoma (non-gastrointestinal bleeding): 1 case report	In conclusion, an extremely rare case of spontaneous thigh hematoma is described in a patient with severe bilateral hip osteoarthritis treated with diclofenac on a long-term basis
Scaricabarozzi, 1988 [43] (Italy)	A post-marketing survey (cohort) (up to 1 month)	$n = 467$ (patients with OA)	Neck, Back, Limbus or sacrum, Hand, Knee, Kip, Multiple	Age range: 7 to 87 years Female: $n = 257$ (patients with OA)	Yes Funding: NR	**Imidazole salicylate** One 750-mg tablets, 3 times a day	up to one month	Reported as "AEs related to treatment" – patients with OA Heartburn ($n = 21$) Epigastric pain ($n = 23$) Intestinal disorders ($n = 9$) Nausea or vomiting ($n = 5$) Dizziness ($n = 2$) Itching ($n = 1$) Flushing ($n = 0$)	The treatment was satisfactory in both patient groups, significantly reducing the intensity of pain and swelling and improving articular function. No adverse experiences that had not been reported previously were recorded; only some gastrointestinal side effects exceeded an incidence of 1%

Table 1 (continued)

Study characteristics						Intervention characteristics		Main findings	
First author, year; (country)	Study design[(note)]/follow-up duration	Sample size	OA site	Age/% of female participants	Reported as PMSS?/source of funding	Intervention(s) (brand name)/ dosage	Treatment duration	Outcomes: adverse events (frequency or HR/OR)	Authors' conclusion
Serni, 1990 [44] (Italy –Multiple countries study, but results for OA only not reported for others)	Post-marketing surveillance study (Cohort) (6 weeks)	$n = 776$ Italian study (only patients with OA included)	NR	Age range: 25-87 years Women: $n = 476$	Yes Funding: NR	**Etodolac** 200 to 600 mg/day of etodolac, as determined by the experimenter. "Most (87%) of the patients received 400mg/day of etodolac as their baseline dose."	6 weeks	Any AEs (124) Epigastric pain (30) Heartburn (15) Sickness (13) Abdominal pain (4) Diarrhoea (3) Malaise (12) Headache (4) Rash (4) Other (42) Confirmed ulcers (0) Withdrawals due to AEs (43; 5.5%) No clinically relevant changes in laboratory values	Gastrointestinal events were the most commonly reported among the study events that did occur, as expected for an NSAID. These results further support the safety of etodolac that was previously established in clinical trials
Thompson, 1979 [45] (Country not reported)	A long term, multicentre open study (Cohort) (1 year)	$n = 145$	Knee (85 patients), Hips (36 patients) and the Hands (35 patients)	97% were 50 years of age or over Females: $n = 120$ (82.8%)	NR, but study reported as a "long term, open study" "in patients who had previously reported intolerance to other NSAIDs" Funding: NR	**Naproxen** Therapy started at 250 mg b.d. for the first month after which it was increased, if necessary, up to a maximum of 500 mg b.d	12 months as maximum	Withdrawals due to AEs: 17 AEs reported as "drug related": Dyspepsia: $n = 13$ Constipation: $n = 13$ Nausea: $n = 9$ Dizziness: $n = 4$ Others: $n = 17$	Side-effects were troublesome enough to cause withdrawal from the trial in 17 patients. No drug-related changes in laboratory tests were noted. Naproxen has proved to be a safe and effective drug in a group of "difficult to treat patients" with osteoarthritis
Urdaneta, 1982 [46] (Brazil and Colombia) – OA cohort only	Long-term open non-comparative studies (Cohort) (Minimum 6 months)	$n = 129$	Knee, hip, neck (cervical region) and/or spine (dorsolumbar region)	Mean age of 59 years, range 35-78 Females: $n = 93$ (79%)	NR, but reported as a "Long-term clinical evaluation" study Funding: NR	**Fenbufen** Dosage: NR	At least 6 months	Heartburn ($n = 20$) Epigastric distress (23) Meteorism (4) Nausea (4) Melena (1) Pruritus (8) Dermatitis (7) Perspiration (2) Dizziness(3) Headache (6) Somnolence (1) One case of severe dermatitis required withdrawal from trial. Laboratory evaluations: Moderate elevation of alkaline phosphatase and SGOT (1); SGOT elevation to 160 units (1)	Fenbufen appears to be an active, safe and well-tolerated compound for the long-term treatment of patients with (…) osteoarthritis

Table 1 (continued)

Study characteristics						Intervention characteristics		Main findings	
First author, year; (country)	Study design[(note)]/follow-up duration	Sample size	OA site	Age/% of female participants	Reported as PMSS?/source of funding	Intervention(s) (brand name)/dosage	Treatment duration	Outcomes: adverse events (frequency or HR/OR)	Authors' conclusion
Day, 2021 [47] (South Africa)	Case-report	$n = 1$ (OA patient)	Lumbar (Chronic backpain related to underlying OA)	A 52-year-old woman	Funding: NR	The patient had eaten her regular biryani (a mixed rice dish originating on the Indian subcontinent) before taking **paracetamol and diclofenac**	NR	Anaphylaxis complicated by loss of consciousness	When reviewing the patient, it is important to educate them regarding which NSAIDs (if any) are safe to use – and to provide them with a list of safe and/or unsafe NSAIDs

NR not reported, *PMSS* post-marketing surveillance study, *M* median, *chronic* chronically exposed, *Not exposed* not chronically exposed, either non-chronic users [*n* 17,360] or non-users [*n* 34,179] (reference group); *GSK* GlaxoSmithKline UK, *Cox-2is* cyclo-oxygenase (Cox)-2 inhibitors, *PEM* prescription-event monitoring, *DSRU* Drug Safety Research Unit, *ADR* adverse drug reaction, *M* median, *AEs* adverse events, *CNS* central nervous system, *GI* gastro-intestinal, *ARB* angiotensin receptor blocker, *SGOT* serum glutamic-oxaloacetic transaminase, *RA* rheumatoid arthritis, *ITT* intent-to-treat

*Major toxicity includes major adverse cardiovascular events, serious gastrointestinal events (gastroduodenal haemorrhage, gastric outlet obstruction, gastroduodenal small or large bowel perforation, large or small bowel haemorrhage, acute gastrointestinal haemorrhage, symptomatic gastric or duodenal ulcer or anaemia defined as a decrease in haemoglobin ≥ 2 g/dL or haematocrit ≥ 10% with no clinical evidence of acute gastrointestinal bleed), renal events (development of renal insufficiency or renal failure, defined on the basis of development of any of the following: serum creatinine ≥2.0 mg/dL and increase of ≥0.7 mg/dL from baseline; hospitalization for acute renal failure with a doubling of the baseline serum creatinine or hyperkalaemia with ≥50% elevation in serum creatinine; or initiation of dialysis), and all-cause mortality.

[†]Expanded major toxicity includes major toxicity; plus heart failure exacerbations, such as incident heart failure or heart failure hospitalizations; hypertension hospitalizations; or iron-deficiency anaemia of gastrointestinal origin.

(note) Case reports and case series are reports of events observed in single patients or collections of patients. They are useful for raising hypotheses about drug effects, that can then be tested with more rigorous study designs. Despite their usefulness in pharmacoepidemiology, no statement about causation can be made based on reports by these studies.

Table 2 Summary of study and intervention characteristics, and main findings from individual studies on intra-articular hyaluronic acid (IAHA)

Study characteristics						Intervention characteristics		Main findings	
First author, year; (country)	Study design[(note)]/ follow-up duration	Sample size	OA site	Age/% of female	Reported as PMSS?/source of funding	Intervention(s) (brand name)/ dosage	Number of injections	Outcomes: adverse events (frequency or HR/OR)	Authors' conclusion
Baron, 2018 [48] (France)	A multi-centre, open, prospective, and observational (Cohort) (6 months for safety monitoring)	$n = 214$ patients (Per protocol sample: n=180)	Knee	62.9 ± 12.6 years Women: 123 (56.4%) (calculated on n=218 recruited patients)	Yes, routine post-market study Funding: LCA Pharmaceutical, Chartres, France	**Arthrum 2.5%** (3 mL, 75 mg hyaluronic acid) (LCA Pharmaceutical, Chartres, France)	Single-injection (1 single IA injection)	Minor local reaction (19); Post-injection pain on walking (7); Pruritus (1); Delayed pain (2) General or serious adverse event (0)	The present study suggests the clinical efficacy of a single IA injection of 3 mL viscoelastic solution containing 75 mg of high molecular weight (2.4 MDa) native HA
Bashaireh, 2015 [49] (Jordan)	A prospective, nonrandomized, unblinded, phase IV, multicentre, and post-marketing study (Cohort) (9 months)	$n = 84$ participants (full analysis)	Knee	55.83 ± 9.34 years Women: 36.36%	No, but reported as "a post-marketing phase IV study", with safety as outcome. Funding: Biopolymer GmbH & Co, KG (Germany)	**Crespine® Gel** (2 mL), a cross-linked HA product	Single injection	33 participants suffered from increased pain with limited mobility of the knee joint 72 hours post-injection, including: Only pain (17); pain and redness of the knee joint (7); pain and swelling (5); simultaneous pain, swelling, and redness (4) Limited mobility of the knee after injection, without experiencing pain, redness, or swelling (4) Serious side effects (0)	Hyaluronan should be encouraged as an alternative or adjunct treatment to oral analgesics to reduce their required doses, and delay potential future surgical intervention
Foti, 2011 [50] (Italy)	A prospective observational study (Cohort) (5 weeks)	$n = 1266$	Knee; Hip; Shoulder; Tibio-tarsal joint; Carpal joint	66 ± 12 years Women: $n = 840$ (66%)	No, but reported as observational study of normal medical practice Funding: Fidia Farmaceutici S.p.A. (Italy)	**Hyalubrix®**, (Fidia Farmaceutici SpA, Italy), containing sodium hyaluronate solution (1.5%; 2.0 mL) for IA injection, into one or more joints, as required	Once per week for 3 consecutive weeks	Patients with least one AE: $n = 10$ (0.8%); Discontinuation due to AE: ($n = 1$) Serious AEs: $n = 0$ Description of AEs (n NR): Pain at injection site; Swelling at injection site; Other	The study treatment was safe and well tolerated

Table 2 (continued)

Study characteristics						Intervention characteristics		Main findings	
First author, year; (country)	Study design[(note)]/ follow-up duration	Sample size	OA site	Age/% of female	Reported as PMSS?/source of funding	Intervention(s) (brand name)/ dosage	Number of injections	Outcomes: adverse events (frequency or HR/OR)	Authors' conclusion
Kim, 2023 [51] (South Korea)	A prospective, non-interventional, multicentre, post-marketing surveillance study (12 weeks after each injection – up to 36 weeks)	$n = 3.140$	Knee	64.03 ± 10.51 years Female: $n = 2.311$ (73.60%)	Yes, post-marketing surveillance study (**reported as *mandated PMS***) Funding: LG Chem, Ltd	**LBSA0103** (**Synovian™**; LGChem,Ltd., Iksan, Republic of Korea) is an HMW-HA (≥10 million dalton) cross-linked with 1,4-butanediol diglycidyl ether	Either one or two IA injections of LBSA0103 (follow up to 12 weeks after each injection) 2nd injections, if required, at 24 weeks after the 1st injection	Total AE: 250 (7.96%) AE–injection site reaction: 117 (3.73%) AE–other than injection site reaction: 143 (4.55%) Adverse drug reaction (ADR§): 100 (3.18%) Serious AEs: 17 (0.54%) Serious ADR: 0 (0.00%) Unexpected AE‡: 114 (3.63%) Unexpected ADR: 13 (0.41%)	Based on the findings of our study, we conclude that LBSA0103 has an acceptable benefit/risk profile when administered to patients aged ≥ 19 years for symptomatic relief of knee OA. Potential AEs noted after administration of LBSA0103 will be continued to be monitored through routine safety reporting channels
Long, 2021 [52] (Australia)	An open-labelled single arm trial - An analysis of prospectively collected outcome data (Cohort) (6 weeks follow up)	$n = 87$ (82 patients for final analysis)	Hip	54 ± 10.8 years Female: $n = 49$ (56.3%)	Not, but study of a commercially available HA in the clinical setting. Funding: No funding was received	**Durolane** (Bioventus Global LL, Netherlands), 3 ml preparation. A Non-animal derived, stabilized HA (NASHA) with molecular weight of >3000 kilodaltons	Single injection	Treatment-related significant AEs: $n = 0$ Minor pain: $n = 5$ patients Infection: $n = 0$ Other AEs: $n = 0$	A single injection of HA (NASHA) in the setting of hip joint OA was both safe and efficacious in this 87-patient cohort

Table 2 (continued)

Study characteristics						Intervention characteristics		Main findings	
First author, year; (country)	Study design[(note)]/ follow-up duration	Sample size	OA site	Age/% of female	Reported as PMSS?/source of funding	Intervention(s) (brand name)/ dosage	Number of injections	Outcomes: adverse events (frequency or HR/OR)	Authors' conclusion
Manfreda, 2017 [53] (Italy)	Case Report	$n = 1$	Knee (Bilateral)	A 59-year-old male	Funding: NR	**An intra-articular hyaluronate (Brand not specified)** injection A high molecular weight hyaluronic acid (about 1200 kDa)	Single injection	A severe septic arthritis and systemic sepsis, which lead to the death of the patient "Blood and knee synovial fluid cultures had clear and dramatic positive results for two different atypical microorganisms: multi-resistant Escherichia Coli and multi-resistant Klebsiella."	We recommend producing correct guidelines for a clean aseptic procedure of injection to obtain proper consensus from the patient and to pay attention to his clinical history and comorbidities before acting any kind of invasive treatment, including joint injection
Micu, 2022 [54] (Romania)	An open real-life setting study (retrospective cohort study) (6 months)	Case group: ($n = 15$) Control group ($n = 17$)	Hip	Cases: 67 years, IQR = 63 to 69 Controls: 61 years, IQR = 58 to 63 % of female: Cases: 80.0% Controls: 82.4%	No, but study in real-life setting Funding: None	Case group: **ultrasound-guided intraarticular injections (USGIAI) of HA (Brand not specified)** Control group: standard of care hip OA treatment with oral NSAIDs, pain killers, SYSADOA	Three consecutive weekly doses of HA-USGIAI (Case group)	No drug-related or injection dependent adverse effects were seen during follow-up	Our data suggest that HA-USGIAI may be an effective and safe treatment for moderate hip OA with short- and medium-term benefits

Table 2 (continued)

Study characteristics						Intervention characteristics		Main findings	
First author, year; (country)	Study design[(note)]/ follow-up duration	Sample size	OA site	Age/% of female	Reported as PMSS?/source of funding	Intervention(s) (brand name)/ dosage	Number of injections	Outcomes: adverse events (frequency or HR/OR)	Authors' conclusion
Migliore, 2011 [55] (Italy)	A prospective, observational, open, post-marketing study (Cohort). (18 months)	$n = 120$	Hip (Right, Left, Bilateral)	62 ± 11.8 years Women: $n = 63$ (52.5%)	Yes, post-marketing study (reported as a study in real life) Funding: Fidia Farmaceutici S.p.A	**HyalOne®** (Hyalubrix 60 Italian brand); 60 mg/4 mL; Ultrasound-guided intra-articular sodium hyaluronate (MW 1500–2000 kDa)	A single 4 ml (60 mg/4 mL) injection of HyalOne® every 6 months, with the possibility of an additional injection at the intervening 3-month intervals on clinical request	"No systemic AEs and septic complications were observed. Sixteen local pain adverse events were reported, out of 506 injections performed (3.19% per injection). All were mild and transient"	The study treatment reduced pain and improved mobility in osteoarthritis of the hip. These results in daily clinical practice demonstrate a beneficial effect and the safety of the study product and suggest adding intraarticular injections of HyalOne® to the armamentarium of conservative management of symptomatic hip osteoarthritis
Migliore, 2012 [56] (Italy)	A prospective, observational, open, post-marketing study (Cohort) (Up for 6 months)	$n = 114$	Hip	61.7 ± 10.04 years Female: $n = 59$	Yes (A prospective, observational, open, post-marketing study) Funding: NR	**Sinovial® Forte 1.6%** (IBSA Institut Biochimique SA, Lugano, Switzerland); 4 ml (2 vials) injection Sodium hyaluronate of an MW of 800-1200 KDa at a concentration of 32 mg/2 ml for one vial	Single injection (with optional, additional injections at the 3-month follow-up visit if symptomatically appropriate)	No systemic AEs were observed. Only 7 patients reported a local reaction at the injection site, consisting of mild pain and localized warmth, which resolved spontaneously No septic complications were observed	This study provides evidence of the efficacy and tolerability of Sinovial® Forte 1.6% in the treatment of patients affected by symptomatic hip OA

Table 2 (continued)

Study characteristics						Intervention characteristics		Main findings	
First author, year; (country)	Study design[(note)]/ follow-up duration	Sample size	OA site	Age/% of female	Reported as PMSS?/source of funding	Intervention(s) (brand name)/ dosage	Number of injections	Outcomes: adverse events (frequency or HR/OR)	Authors' conclusion
Migliore, 2017 [57] (Italy)	A prospective, observational, open, post-marketing study (cohort) (up to 7 years)	$n = 1022$	Hip	60 ± 18.4 years Females: $n = 527$ (51.6%)	Yes, post-marketing study Funding: NR	Ultrasound-guided **HyalOne®/ Hyalubrix®60** 4 ml (60 mg) intra-articular	Single injection into the affected hip every 6 months; if clinically needed, possible to administer up to 2 additional injections, with a maximum of 1 injection per 3-month period, in 1 year	Systemic or severe local side effects were not reported. In some cases there was a sensation of pain lasting from several hours to a few days	Our study supports the clinical efficacy and safety of HyalOne®/ Hyalubrix®60 in patients affected by OA. This is the first study, reporting on a large cohort of patients in different categories with a long follow-up on seven years. The data confirm the proper use of ultrasound-guided viscosupplementation (VS) as background therapy in the management of hip OA
Migliore, 2018 [58] (Italy)	Retrospective post-marketing cohort study (≥ 12 months of follow-up)	$n = 187$	Knee (unilateral, 89.6%)	62 ± 16.6 years Female: $n = 100$ (53.5%)	Yes, (retrospective post-marketing cohort study) Funding: NR	**HyalOne®** (second brand name Hyalubrix®60), a viscoelastic solution containing HA. 4 ml (60 mg) IA injection	A single 4 ml (60 mg) IA injection in the affected knee Additional injections were administered if clinically requested during follow-up	No systemic or severe local side effects were reported after the first or the second injection. In 8 cases, there was a sensation of pain lasting from several hours to a few days, regressing spontaneously	These results support the clinical effectiveness and safety of hyaluronic acid for up to 12 months for pain relief and function improvement in patients with knee OA, confirming previous data on intra-articular administration of hyaluronic acid as chronic therapy in the management of knee OA

Table 2 (continued)

Study characteristics						Intervention characteristics		Main findings	
First author, year; (country)	Study design[(note)]/ follow-up duration	Sample size	OA site	Age/% of female	Reported as PMSS?/source of funding	Intervention(s) (brand name)/ dosage	Number of injections	Outcomes: adverse events (frequency or HR/OR)	Authors' conclusion
Migliore, 2020 [59] (Italy)	Post-marketing cohort study (a multicentre, observational, retrospective analysis) (≥ 12 months follow-up)	$n = 198$	Hip	62 ± 14.2 years Women: $n = 84$ (42.5%)	Yes, (Post-marketing cohort study) Funding: NR	**HYMOVIS ONE (HYADD4-G)**, viscoelastic hyaluronan; 32 mg/4 mL (intra-articular injection)	Single injection	No systemic or severe local side effects were reported after the injection. In 5 out of 198 injections (2.5%), there was a sensation of pain lasting from several hours to a few days that spontaneously regressed	Our study supports the clinical efficacy and safety of a single HYMOVIS ONE injection for managing symptoms in patients with hip OA, confirming previous data on the use of HYMOVIS as a background therapy in the management of knee OA
Migliore, 2021 [60] (Italy)	A retrospective cohort post-marketing study (3-year follow-up)	$n = 43$	Hip	60 ± 18.5 years Females: $n = 23$ (53.5%)	Yes, reported as a cohort post-marketing study Funding: Mastelli S.r.l., Sanremo, Italy	PN-HPT™ Class-III CE-marked (0373) medical device (**Condrotide®**, Mastelli Srl, Sanremo, Italy), available as pre-filled, single-use, neutral glass 2-mL vial-syringes with a PN-HPT™ concentration of 40 mg in 2 mL	Two 2-mL vials of Condrotide® for a total of 4 mL and 80 mg PN-HPT™ every six months (ultrasound-guided intra-articular treatment)	Neither the patients nor the attending physicians reported systemic or severe local side effects. A few minor and transient local pains or burning sensations substantiated all reported side effects	The present study confirms the efficacy and safety shown by PN-HPT™ in previous studies, including a recent study on knee and ankle OA
Neustadt, 2003 [61] (USA)	Prospective cohort study (1 to 2 years	$n = 76$	Knee	64 ± 7.4 years Female: $n = 16$ (21%)	No, but uncontrolled study "in a clinical office setting". Funding: an educational grant from Sanofi-Synthelabo Inc	**Hyalgan®** (FIDIA S.p.A., Padua, Italy); 20 mg of sodium hyaluronate	Five intra-articular injections at weekly intervals	Injection-site pain: 20% of patients Injection-site bruising: 9% Headache, 24 hours after injection: 7.5% Nausea: 3% No systemic AEs, no "dropouts" due to AEs; No pseudoseptic reactions	Intra-articular sodium hyaluronate was an effective and safe treatment for pain in difficult-to-treat patients with moderate to severe OA of the knee

Table 2 (continued)

Study characteristics						Intervention characteristics		Main findings	
First author, year; (country)	Study design[(note)]/ follow-up duration	Sample size	OA site	Age/% of female	Reported as PMSS?/source of funding	Intervention(s) (brand name)/ dosage	Number of injections	Outcomes: adverse events (frequency or HR/OR)	Authors' conclusion
Pal, 2014 [62] (India)	An open-label, multicentre, phase 4 clinical trial (Cohort) (1 year - with follow up for another 4 weeks in case of repeat treatment)	$n = 394$	Knee	57.6 ± 9.8 years (based on $n = 392$ patients) Female: $n = 285$ (72.3%)	Yes, post-marketing study Funding: Study sponsored by Genzyme Biosurgery (now Sanofi)	**Hylan G-F 20**, 6-mL injection	A single 6-mL injection, with a repeat treatment phase (at weeks 26, 39, and 52), if needed	*Local target knee AEs* (any): $n = 23$ patients (6%) - Arthralgia: 16 patients [4%] - Synovitis: 4 patients [1%] - Other local target knee AEs (arthritis, bursitis, musculoskeletal stiffness, injection site pain, and injection site pruritus): 1 patient [0.3%] each None of the local target knee AEs were fatal; *Systemic AEs*: $n = 28$ patients (7%) Oedema peripheral, cellulitis, rash, or swelling of the face (considered to be related to the study treatment): 1 patient each; Serious AEs (SAEs): 6 patients (2%) - *all considered not related to the study treatment or procedure* None of the 11 retreated patients reported any AEs or SAEs during the 4-week retreatment phase	Among Indian patients within this study, a 6-mL Hylan G-F 20 injection was well tolerated and effective in treating symptomatic knee OA with significant long-term (1 year) improvement of outcomes. When needed, repeat treatment was safe and efficacious for 4 weeks
Yan, 2015 [63] (Hong Kong)	A prospective, multicentre, longitudinal study (Cohort) (1 year of follow-up)	$n = 95$ patients	Knee	62.0 ± 9.8 years Females: $n = 64$ (67.4%)	No, but uncontrolled study of a marketed treatment Funding: None	**Hylan G-F 20**, intra-articular preparation of 6 mL	Single injection	Pain (14 knees), swelling (2 knees), and warmth (2 knees). All of the AEs were mild and self-limiting. No patients required hospital admission or extra clinic visits for these self-reported events	Hylan G-F 20 is a safe and effective therapy to relieve pain and improve function for up to 1 year in Chinese patients with knee osteoarthritis

NR not reported, *PMSS* post-marketing surveillance study, *M* median, *MW* molecular weight

[§]ADR was defined as "adverse, unintended reactions from normal administration/use of the pharmaceutical, for which the causal relationship with the particular pharmaceutical cannot be excluded"

[‡]An unexpected AE was defined as "an AE whose nature, severity, specificity, or outcome is not consistent with the term or description used in the prescribing information (PI) in Korea"

(note) Case reports and case series are reports of events observed in single patients or collections of patients. They are useful for raising hypotheses about drug effects, which can then be tested with more rigorous study designs. Despite their usefulness in pharmacoepidemiology, no statement about causation can be made based on reports by these studies

Table 3 Summary of study and intervention characteristics, and main findings from individual studies on SYSADOAs, corticosteroid injections, opioids and herbal mixtures and other compound

Study characteristics						Intervention characteristics		Main findings	
First author, year; (country)	Study design[(note)]/follow-up duration	Sample size	OA site	Age/% of female	Reported as PMSS?/source of funding	Intervention(s) (brand name)/dosage	Treatment duration	Outcomes: adverse events (frequency or HR/OR)	Authors' conclusion
Symptomatic slow-acting drugs for osteoarthritis (SYSADOAs)									
Gluszko, 2016 [64] (Poland)	An open, prospective, observational study (Cohort) (6 months)	$n = 4822$ (recruited) (Note: $n = 4186$ patients attended all four visits and were included for efficacy analysis)	Knee	60.64 ± 11.59 years Women: $n = 3565$ (73.93%) (Sample: $n = 4822$)	No, but study described as real-life study. Funding: Angelini Pharma Poland	**Avocado/soybean unsaponifiables** (ASU) capsules (**Piascledine**); 300 mg ASU capsule/day	6 months	Diarrhoea: $n = 5$ Elevated blood pressure and headache: $n = 2$ Nausea, flatulence or abdominal pain: $n = 3$ Serious adverse reactions: $n = 0$ Only 56 patients provided reasons for ASU treatment discontinuation (on $n = 636$, 13.19% of all included patients who discontinued), of which 4 discontinued treatment because of AEs (diarrhoea, nausea, flatulence)	In summary, we conclude, that in our real-life study we were able to confirm, that the vast majority of patients adherent to the ASU treatment for 6 months showed gradual and substantial alleviation of joint pain, functional ability improvement and the reduction in NSAIDs intake. The results of our survey support recommendations indicating the usefulness of ASU in a routine symptomatic treatment of knee OA

Table 3 (continued)

Study characteristics						Intervention characteristics		Main findings	
First author, year; (country)	Study design[(note)]/follow-up duration	Sample size	OA site	Age/% of female	Reported as PMSS?/source of funding	Intervention(s) (brand name)/dosage	Treatment duration	Outcomes: adverse events (frequency or HR/OR)	Authors' conclusion
Renapurkar, 2010 [65] (India)	A post marketing survey (cohort) (4 months)	$n = 120$	Knee	Age range: 30–80 years Females: $n = 90$	Yes, reported as a post marketing survey Funding: "No Sponsors", but Drug Supplied By: REDDY LABS	**Diacerein** 50 mg tab 50 mg tab administered orally once daily	4 months	Reddish urine: $n = 2$ cases	We can conclude from the results that diacerein is very useful, disease modifying drug for patients with OA bringing about structural and functional changes in the joints of patients with OA with less adverse effects
Sharma, 2008 [66] (India)	Prospective open-label multicentre (314 centres) phase IV post-marketing surveillance study (cohort) (12 weeks)	$n = 7903$ patients included in the analysis	Knee	57.02 ± 9.46 years Female: 53,3% ("Approximately 46.7% of the patients were males")	Yes, Phase IV post-marketing surveillance study Funding: NR, but all 3 authors affiliated to a pharmaceutical company (Glenmark Pharmaceuticals Limited, Mumbai)	**Diacerein** 50 mg tablets administered twice daily	12 weeks	Any AEs: 5.44% Diarrhoea: 2.3% Gastritis: 0.99% Nausea: 0.61% Abdominal pain or discomfort: 0.44% Vomiting: 0.3% Severe or serious AEs: 0% Withdrawals due to AEs: 0% Significant change in vital parameters (temperature, pulse rate, and blood pressure): 0%	Thus, in conclusion, the results of the present study in a large population of Indian patients indicates that diacerein constitutes a novel approach to the treatment for the short- and long-term symptomatic management in Indian patients with osteo-arthritis of the knee

Table 3 (continued)

Study characteristics						Intervention characteristics		Main findings	
First author, year; (country)	Study design[(note)]/follow-up duration	Sample size	OA site	Age/% of female	Reported as PMSS?/source of funding	Intervention(s) (brand name)/dosage	Treatment duration	Outcomes: adverse events (frequency or HR/OR)	Authors' conclusion
de Abajo, 2014 [26] (Spain)	A nested case-control study	Cases (n): Non-use: 3675 Current: 34 Past: 61 Remote: 63 Controls (n): Non-use: 19070 Current: 282 Past: 283 Remote: 365	NR	NR	No, but study performed using a primary care database validated for pharmaco-epidemiological research. Funding: This study was supported by a research grant from Fondo de Investigación Sanitaria—Ministerio de Ciencia e Innovación	SYSADOAs (including **glucosamine and chondroitin sulphate**). Doses hardly differed and were not assessed. Note: "SYSADOAs (chondroitin sulphate and glucosamine) are prescription-only drugs widely used in Spain"	'Current users': prescription lasted until index date or ended within 30 days prior to the index date 'Past users': prescription ended between 31 and 365 days before the index date 'Remote users': prescription ended before 365 days prior the index date 'Non-users': no prescription before index date (reference category)	Risk of nonfatal acute myocardial infarction (AMI) associated with use of SYSADOAs: The (current) use of SYSADOAs was not associated with an increased risk of AMI overall (OR = 0.68; 0.47–0.99), after long-term treatment duration (OR = 0.72; 0.34–1.55) and in high cardiovascular (CV) risk patients (OR = 0.64; 0.36–1.14). Adjusted OR (95% CI) for: Past use: 1.19 (0.89–1.59) Remote use: 0.91 (0.69–1.21)	SYSADOAs did not increase the risk in any of the conditions examined
Chu, 2023 [67] (China)	Case report	$n = 1$	Lumbar (lumbar degenerative joint disease)	A 36-year-old woman	Funding: No financial support was received	**Glucosamine chondroitin** (1500 mg glucosamine sulphate and 1200 mg chondroitin sulphate daily) - dietary supplement	Less than 1 day ("within 3 hours of the first dose, she noticed the appearance of an itchy rash on her torso and legs)	Anaphylaxis (itchy rash on the entire body, and facial swelling). The patient also experienced nausea, dizziness, and vomiting	This case report demonstrates the need to recognize delayed allergic reactions as a potential side effect of widely used supplements, such as glucosamine chondroitin, which can produce hypersensitivity reactions in sensitive individuals

Table 3 (continued)

Study characteristics						Intervention characteristics		Main findings	
First author, year; (country)	Study design[(note)]/follow-up duration	Sample size	OA site	Age/% of female	Reported as PMSS?/source of funding	Intervention(s) (brand name)/dosage	Treatment duration	Outcomes: adverse events (frequency or HR/OR)	Authors' conclusion
Hoban, 2020 [68] (Australia)	Case reports	$n = 366$ adverse drug reactions (ADRs) cases	NR	61.81 ± 13.47 years Female: 64.2% (n=235)	No, but the study investigated ADRs spontaneously reported by patients to their General Practitioners. Funding: Work supported by The University of Adelaide Divisional Scholarship	**Glucosamine and chondroitin preparations** (Brand not specified) Note from Introduction: "Glucosamine is often sold in combination with chondroitin sulfate" Dosage: NR	NR	Hypersensitivity reactions: 71.85% of cases (n=263) Of these 263 cases, 92 cases were classified as mild (e.g., pruritus, urticaria and lip oedema), 128 cases classified as moderate (such as dyspnoea, nausea and abdominal pain), and 43 cases classified as severe (including amnesia, gait disturbance, somnolence and hypotension) Liver injury: 9 reports (2% of all ADRs) - (abnormal hepatic function, hepatotoxicity and hepatitis)	Results of this investigation support the need for clear labelling on glucosamine and chondroitin preparations to raise awareness of possible adverse events for those predisposed to allergy or atopy in response to shellfish

Table 3 (continued)

Study characteristics						Intervention characteristics		Main findings	
First author, year; (country)	Study design[(note)]/follow-up duration	Sample size	OA site	Age/% of female	Reported as PMSS?/source of funding	Intervention(s) (brand name)/dosage	Treatment duration	Outcomes: adverse events (frequency or HR/OR)	Authors' conclusion
Lila, 2023 [69] (Russia)	A multicentre prospective observational cohort study (64 weeks)	$n = 1102$	Knee; Hip	60.4 ± 7.0 years Female: $n = 968$ (87.8%)	No, but observational cohort study in routine clinical practice. Funding: NR	**Theraflex® (Capsules, glucosamine hydrochloride 500 mg and chondroitin sulphate 400 mg, [GA + CS]);** (Three times a day for the first 3 weeks, then twice daily)	64-week treatment (Minimal recommended treatment duration is 3-6 months)	Any AEs: $n = 190$ (17.2%) participants; AEs led to the cancellation of therapy: $n = 19$ (1.7%) patients Most common MedDRA system classes AEs: Musculoskeletal and connective tissue disorders: 5.3% Gastrointestinal disorders: 4.7% Infections and infestations: 4.4% Most common AEs by the Preferred Term: OA (worsening of the main diagnosis): 1.2% Upper abdominal pain: 1.3% Upper respiratory tract infections: 2.3% Headache: 1.3% AEs considered by the investigators as "related to the study product" were reported for 31 (2.8%) patients (a total of 33 AEs) and mainly included gastrointestinal disorders [25 AEs in 24 (2.2%) patients]. Serious AEs (SAEs): $n = 14$ (1.3%) patients. None of the SAEs were considered "related to the study product" by the investigator	Treatment with GA + CS combination showed low incidence of drug-related AEs, and high level of patients' satisfaction with the treatment along with high compliance with long duration of the treatment

Table 3 (continued)

Study characteristics						Intervention characteristics		Main findings	
First author, year; (country)	Study design[(note)]/follow-up duration	Sample size	OA site	Age/% of female	Reported as PMSS?/source of funding	Intervention(s) (brand name)/dosage	Treatment duration	Outcomes: adverse events (frequency or HR/OR)	Authors' conclusion
Corticosteroid injections									
Graf, 2022 [70] (Switzerland)	Reported as a "Retrospective single-centre case series" (In fact, a retrospective cohort study) (Between 1 and 12 months after injection)	$n = 1000$	Hip; Knee	57 ± 16 years Women: $n = 545$ (54%)	No, but retrospective cohort study assessing safety as outcome (data from hospital databases) Funding: NR	IACS injections with fluoroscopic guidance: Injection of 2 mL of 2% lidocaine and 1 mL of iopamidol 200 (200 mg of iodine per millilitre, Iopamiro; Bracco), and injection of 40 mg (1 mL) of **triamcinolone (Triamcort; Helvepharm)** and 3 mL more of lidocaine	Single injection	Severe complications: $n = 10$ patients (1%): Osteonecrosis: 4 Insufficiency fractures: 3 Rapid progressive OA: 3 All 10 complications occurred between 2 and 9 months after injection: six (60%) in the hip and four (40%) in the knee	Intraarticular steroid injection had a substantially lower complication rate than that reported in previous smaller studies. The rate of severe complications was disproportionally higher in women than in men

Table 3 (continued)

Study characteristics						Intervention characteristics		Main findings	
First author, year; (country)	Study design[(note)]/follow-up duration	Sample size	OA site	Age/% of female	Reported as PMSS?/source of funding	Intervention(s) (brand name)/dosage	Treatment duration	Outcomes: adverse events (frequency or HR/OR)	Authors' conclusion
Latourte, 2022 [71] (France)	A multicentre, population-based cohort study (5 years)	IA IACS: $n = 51$ (9.0%); IAHA injections: $n = 99$ (17.5%); No injections: $n = 414$ (63.1%)	Knee	IA IACS: 65.3 ± 8.4 yrs.; IAHA: 62.1 ± 7.7; No injections: 61.8 ± 8.6 yrs. Female (IA IACS): $n = 37$ (72.5%); Female (IAHA): 77 (77.8); Female (No injections): $n = 270$ (65.2%)	No, but study in a real-life setting (using data from a population based cohort of patients) Funding: Supported by the French Society of Rheumatology and ART-Viggo Association	***NR*** Reported limitations of the study: "… we do not have data on the type of glucocorticoids used or hyaluronan type and dosage"	NR "Participants were asked whether they received IA glucocorticoid or IAHA injections during the past 12 months."	Compared to untreated knees, those treated with IA glucocorticoid injections had a similar risk of incident TKR (hazard ratio [HR] 0.92; [95% CI 0.20, 4.14]) or K/L grade worsening (HR 1.33 [95%CI 0.64,2.79]). IAHA injections had no effect on the risk of TKR (HR 0.81 [95% CI 0.14, 4.63]) or K/L grade worsening (HR 1.36 [95% CI 0.85, 2.17]). Similar results were obtained for JSN, and when TKR and radiographic outcomes were combined Only 1 case of incident osteonecrosis occurred during the follow-up, in a knee that did not previously receive intraarticular injections	In this study, IA glucocorticoid injections for symptomatic knee OA did not significantly increase the 5-year risk of incident TKR or radiographic worsening. These findings should be interpreted cautiously and replicated in other cohorts

Table 3 (continued)

Study characteristics						Intervention characteristics		Main findings	
First author, year; (country)	Study design[(note)]/follow-up duration	Sample size	OA site	Age/% of female	Reported as PMSS?/source of funding	Intervention(s) (brand name)/dosage	Treatment duration	Outcomes: adverse events (frequency or HR/OR)	Authors' conclusion
Perolini, 2022 [72] (Switzerland)	Case report	$n = 1$	Knee	A 73-year-old woman	Funding: NR	**Intra-articular corticosteroids** injection	Single injection	This procedure was complicated by a septic arthritis requiring hospitalization, joint lavage, and intravenous antibiotic treatment	To date, there is no clear consensus regarding the use of intra-articular corticosteroid injection. Thus, the choice of treatment must be made according to patient's comorbidities and preferences. Patients should be informed about the potential complications and lack of proven long-term efficacy

Table 3 (continued)

Study characteristics						Intervention characteristics		Main findings	
First author, year; (country)	Study design[(note)]/follow-up duration	Sample size	OA site	Age/% of female	Reported as PMSS?/source of funding	Intervention(s) (brand name)/dosage	Treatment duration	Outcomes: adverse events (frequency or HR/OR)	Authors' conclusion
Smuin, 2016 [73] (USA)	Case Series	$n = 2$ cases (patients with OA)	Case 1: bilateral OA of the knee Case 3: OA of his knees bilaterally	Case 1: A 49-year-old woman Case 3: A 45-year-old white male	Funding: None	Case 1: bilateral **intraarticular triamcinolone** (80 mg) injections with 1% lidocaine. Case 3: intraarticular **triamcinolone** (80 mg) with 1% lidocaine (in the more symptomatic knee)	Case 1: Single injection (Also had a 6-year history IACS injections of the knees, excluding a 2-year period of HA injections). Case 3: Single injection	Case 1: Eleven days postinjection of triamcinolone, she complained of vision disturbances including black spots bilaterally and difficulty seeing out of her left eye. Other general complaints at this time included excruciating headaches and shortness of breath with accompanying left shoulder and arm pain Case 3: Seven days after the injection, he noted feelings of acute anxiety manifested by panic attacks (chest pain, diaphoresis, palpitations, nervousness, and tingling in his arms and legs). (…) He was diagnosed with substance-induced anxiety	Although all (…) uncommon adverse events are typically self limited, providers should be aware that they can occur and consider whether or not future corticosteroid injections should be offered

Table 3 (continued)

Study characteristics						Intervention characteristics		Main findings	
First author, year; (country)	Study design[(note)]/follow-up duration	Sample size	OA site	Age/% of female	Reported as PMSS?/source of funding	Intervention(s) (brand name)/dosage	Treatment duration	Outcomes: adverse events (frequency or HR/OR)	Authors' conclusion
Opioids									
Meyer-Junco, 2022 [74] (USA)	Case report (from a Case Series)	$n = 1$ (About an OA patient)	NR	A 79-year-old male	Funding: None	**Buprenorphine Transdermal Patch (BTP)**; 15 mcg/h transdermal applied once every 7 days. (…) A month after he was started on the patch his dose was increased to 20 mcg/h transdermal every 7 days	One and a half months	The patient developed a topical erythematous reaction directly under the site of application. He experienced itchiness and burning in this area (One and a half months after the increase of the dosage)	In patients experiencing a localized, non-diffuse skin reaction to BTP, transition to buccal buprenorphine may be a reasonable option

Table 3 (continued)

Study characteristics						Intervention characteristics		Main findings	
First author, year; (country)	Study design[(note)]/follow-up duration	Sample size	OA site	Age/% of female	Reported as PMSS?/source of funding	Intervention(s) (brand name)/dosage	Treatment duration	Outcomes: adverse events (frequency or HR/OR)	Authors' conclusion
Taber, 2017 [75] (USA)	A multicentre, open-label study (Cohort) (> 52 weeks)	$n = 307$	Knee (43.6%); Spine (40.7%); Hip; Shoulder; Ankle; Foot; and Hand	55.9 ± 10.8 years Female: n = 172 (56%)	No, but open-label single arm study of approved drug to evaluate safety and effectiveness. Funding: Purdue Pharma L.P	Single-entity, extended-release formulation of **hydrocodone (HYD); Hysingla® ER** (HYD; Purdue Pharma L.P., Stamford, CT, USA); Once-daily, 20–120 mg	> 52 weeks The study comprised a dose-titration period (≤45 days), a maintenance period (52 weeks), and an optional taper period (≤14 days)	Discontinuation due to AEs: $n = 68$ (22%) MedDRA system organ class TEAEs: Any TEAE: $n = 202$ (66%) Endocrine disorders: n = 3 (1%) Gastrointestinal disorders: $n = 144$ (47%) General disorders and administration-site conditions: $n = 40$ (13%) Injury, poisoning, and procedural complications: n = 11 (4%) Nervous system disorders: $n = 106$ (35%) Psychiatric disorders: n = 19 (6%) Skin and subcutaneous tissue disorders: $n = 28$ (9%). Serious TEAEs: Any: $n = 30$ (9.8%) Also reported by MedDRA system organ class and Preferred Term	In patients with OA, long-term HYD treatment was generally well tolerated and provided clinically important analgesia

Table 3 (continued)

Study characteristics						Intervention characteristics		Main findings	
First author, year; (country)	Study design[(note)]/follow-up duration	Sample size	OA site	Age/% of female	Reported as PMSS?/source of funding	Intervention(s) (brand name)/dosage	Treatment duration	Outcomes: adverse events (frequency or HR/OR)	Authors' conclusion
Wu, 2023 [76] (Taiwan)	A population-based retrospective cohort study Follow-up time(yr.): Tramadol: 3.79 ± 3.27; Control: 5.17 ± 3.99	Tramadol: n = 3093; Control: n = 3093	Post-traumatic OA of major joint of upper limbs or lower limbs	Age (Tramadol) 70.04 ± 7.62 yrs.; Age (Control): 70.04 ± 7.63 yrs. Female (Tramadol): n = 1313 (42.5%); Female (Control): n = 1297 (41.9%)	No, but study using a nationwide cohort database with safety as outcome. Funding: This research received no external funding	Tramadol cohort: ***Tramadol*** and the combinative drugs including tramadol; Control group: The patients who did not use tramadol but used any non-steroidal anti-inflammatory drugs, paracetamol, or muscle relaxants	A more-than-90-day within 1 year prescription	The primary outcome was any new diagnosis of a hip fracture requiring surgery. Tramadol use was identified as a risk factor for hip fracture (adjusted hazard ratio (aHR): 1.41; 95% confidence interval (CI): 1.09–1.82), especially among patients aged 60–70 years (aHR: 2.11; 95% CI 1.29–3.47) and among male patients (aHR: 1.83; 95% CI 1.24–2.70)	This is the first cohort study focusing on the association between long-term tramadol use and hip fracture among older adults with posttraumatic osteoarthritis. Tramadol, as a long-term pain control analgesic for older adults with posttraumatic osteoarthritis, may increase the risk of hip fracture, especially among male patients and those aged 60–70 years

Table 3 (continued)

Study characteristics						Intervention characteristics		Main findings	
First author, year; (country)	Study design[(note)]/follow-up duration	Sample size	OA site	Age/% of female	Reported as PMSS?/source of funding	Intervention(s) (brand name)/dosage	Treatment duration	Outcomes: adverse events (frequency or HR/OR)	Authors' conclusion
Herbal mixtures and other compound									
Berger, 1987 [77] (Germany)	A non-controlled clinical phase IV trial (Cohort) (8 weeks)	$n = 20{,}641$	Knee; Hip; Spine; Fingers	Min-max: 10 – 98 years (≈80% of participants were at least 50 years old) Female: 58%	No, but reported as a phase IV trial to meet the worldwide demand for further information about drug safety. Funding: Drug kindly supplied by BioResearch, Milan, Italy	**Ademetionine* (Gumbaral®)**, registered trademark of Homburg Degussa Pharma Gruppe, Frankfurt am Main, Germany 200 mg tablets, 3x2 tablets/day in first week, 2x2 tablets/day in second week, 2x1 tablet/day from third week onwards	8 weeks	Serious drug-related AEs: $n = 0$ Discontinuation due to AEs: 5.2%. Side effects (moderate or severe): 21% of the patients (most were related to the gastrointestinal tract). Fifteen deaths reported in the 20,641 patients during the study; above all due to myocardial infarctions and cerebrovascular accidents. "All deaths appeared to be explained by other factors and were not related to the administration of ademetionine	The tolerance was assessed as very good or good in 67 percent, as moderate in 8 percent, and as poor in 5 percent of cases. The trial therapy was discontinued prematurely because of symptoms of intolerance in 5 percent of the patients and because of a lack of efficacy in 2.3 percent of cases

Table 3 (continued)

Study characteristics						Intervention characteristics		Main findings	
First author, year; (country)	Study design[(note)]/follow-up duration	Sample size	OA site	Age/% of female	Reported as PMSS?/source of funding	Intervention(s) (brand name)/dosage	Treatment duration	Outcomes: adverse events (frequency or HR/OR)	Authors' conclusion
Ha, 2016 [78] (South Korea)	A multicentre single-arm phase IV clinical trial (Cohort) (24 weeks)	$n = 756$ (Safety analysis sample - all participants who took at least one dose)	Knee	(safety set) Mean (range): 59.7 (22–81) years Female: $n = 603$ (79.8%)	No, but study described as a phase IV study, specifically targeting safety. Funding: Greencross Corporation (South Korea)	**GCSB-5 (Shinbaros®, Green Cross Corporation, Yongin, Korea) – A mixture of six herbal extracts**.** GCSB-5 capsules (lot # 1518011, 300 mg each) twice per day (in the morning and evening)	24 weeks	Treatment emergent adverse events (TEAEs) – by MedDRA system organ classes: Gastrointestinal disorders: 179 (23.7%) subjects; Infections and infestations: 84 (11.1%); Musculoskeletal and connective tissue disorders: 66 (8.7%); Nervous system disorders: 59 (7.8%); Skin and subcutaneous tissue disorders: 40 (5.3%); General disorders and administration site conditions: 22 (2.9%); Miscellaneous: 74 (9.8%)	This 24-week open-label study demonstrated that the safety and efficacy profile of a new therapeutic agent, GCSB-5, for patients with osteoarthritis are comparable to a previously published study with celecoxib. The results of this study indicate that GCSB-5 can be used for a long-term treatment of patients with knee OA with a comparable gastrointestinal safety profile to celecoxib

NR not reported, *PMSS* post-marketing surveillance study, *M* median, *HA* hyaluronic acid, *MW* molecular weight, *MedDRA* Medical Dictionary for Regulatory Activities, *TEAEs* treatment-emergent adverse events, *IACS* intraarticular corticosteroid, *JSN* joint space narrowing, *TKR* total knee replacement

[*] Ademetionine is a synonym for *S*-adenosylmethionine

[**] 300 mg of dried extracts of the mixture of six herbs in a fixed ratio; *Saposhnikovia divaricate,* Schischk: *Glycine max,* Merrill: *Cibotium barometz,* J. Smith: *Eucommia ulmoides,* Oliver: *Achyranthes japonica,* Nakai: *Acanthopanax sessiliflorus,* Seem=4.444:2.778:2.778:1.389:4.444:4.444

[(note)] Case reports and case series are reports of events observed in single patients or collections of patients. They are useful for raising hypotheses about drug effects, that can then be tested with more rigorous study designs. Despite their usefulness in pharmacoepidemiology, no statement about causation can be made based on reports by these studies.

studies included more female than male subjects. Specific NSAIDs investigated and outcomes are summarized below (further details in Table 1):

- Celecoxib or naproxen versus no exposure (one study) [20]: Celecoxib was taken by 16,580 patients and naproxen by 2907 patients for at least 90 days of continuous use, compared with 51,539 subjects with no recorded exposure or short-term use of NSAIDs. Cardiovascular event (hospitalization for an acute myocardial infarction or ischaemic stroke) was the outcome of that study. The results showed no increased risks for celecoxib (adjusted HR = 1.05, 95% CI 0.91–1.22) or naproxen (adjusted HR = 0.99, 95% CI 0.64–1.54), compared with non-chronic NSAID/Cox-2 inhibitor use.
- Celecoxib versus traditional NSAID (tNSAID): Hospital admission rates for gastrointestinal (GI) or cardiovascular (CV) events in real-life use of celecoxib ($n = 6150$ patients with OA) and tNSAID ($n = 4369$ patients with OA) were investigated in a population-based cohort study conducted in France [21]. Only one OA patient experienced a CV event in the celecoxib group, against three patients with OA in the tNSAID cohort (Table 1). In this study, which included various patient populations, the authors reported that GI or CV event rates were not different between products, even for patients aged over 60 years old [21].
- Celecoxib versus meloxicam: Two retrospective cohort studies with 9-month follow-up duration each involved celecoxib (Celebrex®) and meloxicam (Mobic®). One study included 9339 patients with OA [22] and the other 9338 patients with OA [23], with celecoxib taken by 4905 patients in each study. The outcomes of interest in these studies were incidence rates of thromboembolic events (cardiovascular event; cerebrovascular events; peripheral venous thrombotic event) [22] and incidence rates of selected gastrointestinal events [23]. In the first study [22], authors concluded that the incidence of these three groups of events reported in each of these two drug cohorts was low, stressing however that the relevance of their findings needs to be considered together with other clinical and pharmaco-epidemiological studies. In the study investigating incidence rates of selected gastrointestinal events [23], the authors reported a relative reduction in the incidence of symptomatic (acid/peptic) GI events, and in the incidence rate of complicated upper GI conditions (perforations/bleeding) for celecoxib compared with meloxicam.
- Celecoxib versus ibuprofen, or naproxen (two reports from the PRECISION trial): PRECISION was a randomized, multicentre, double-blind, noninferiority trial involving patients with rheumatoid arthritis (RA) or osteoarthritis who were at increased cardiovascular risk. A total of 24,081 patients were enrolled in this trial, including 21,645 patients with OA (89.9%) and 2436 (10.1%) patients with rheumatoid arthritis (RA), followed up for up to 42 months, with a minimum follow-up duration of 18 months. The two reports from of this trial included in this review are those that presented separate results for patients with OA [24, 25]. The first report examined the risk of two composite outcomes, namely "major NSAID toxicity" and "expanded major NSAID toxicity" (as defined by authors; see notes of Table 1), for celecoxib compared with ibuprofen or naproxen [24]. The primary analyses based on the total sample (patients with OA and RA combined) showed that patients using naproxen or ibuprofen experienced significantly higher risks of major toxicity than those using celecoxib. Conversely, hypothesis-generating subgroup analysis for patients with OA showed increased risks for celecoxib, compared with ibuprofen or naproxen, although there was no subgroup interaction observed by arthritis diagnosis (OA versus RA) [24]. While the subgroup analyses were reported as "post hoc" in this first report, the second report from the PRECISION trial investigated the relative risks of cardiovascular (CV), gastrointestinal (GI) and renal adverse events during treatment with the same NSAIDs, this time separately in patients with OA and patients with RA [25]. Results of analyses showed similar or lower risks of CV, GI and renal adverse events for celecoxib, compared with treatment with ibuprofen or naproxen in patients with OA [25].
- Meloxicam was further investigated in three studies, two of which were retrospective cohort studies with 9-month follow-up duration each (compared with rofecoxib; results for rofecoxib not reported in this manuscript) [28, 29], and one case report [30]. AEs reported in the two cohort studies ($n = 4433$ patients with OA in each study) were cardiovascular and cerebrovascular thromboembolic event, peripheral venous thrombotic event, symptomatic (acid/peptic) upper GI events and complicated upper GI conditions (perforations/bleeding) (details in Table 1). It is worth noting that the focus of these studies were thromboembolic events [28] and selected gastrointestinal events [29]. The case report was about a female patient of 39 years old who experienced maculopapular rashes over the lips, cheeks and upper extremities (a rare case of meloxicam-induced Stevens–Johnson syndrome) [30].
- Nimesulide: Two cohort studies investigated nimesulide. One was a 1-year follow-up duration study (long-term treatment) of 133 patients [31], while the second study included 22,938 patients for 1–3-week follow-up duration (short-term treatment) [32]. In the long-term study,

authors failed to report numbers of patients with specific AEs (frequencies). Severe AEs (not specified) were reported by nine patients, while AEs related to the following body systems were reported: gastro-intestinal tract, central nervous system and skin [31]. In the short-term duration study, AEs reported in selected number of patients ($n = 1887$) as presumably related to therapy were: epigastralgia, pyrosis, nausea, diarrhoea, vomiting, skin rash, itch, dizziness, somnolentia, oedema, headache, aerophagia, sweating, flushing, xerostomia, constipation and other [32].

- Flurbiprofen (Froben®) treatment was investigated in an 18-month cohort study ($n = 221$), with or without concomitant NSAIDs, and was found to be principally associated with gastro-intestinal, CNS or dermatological AEs [33].
- *S*-furbiprofen plaster (a topical NSAID) was investigated in a 52-week cohort study ($n = 201$ patients) in which authors observed a statistically significant increase in serum creatinine at both 40 and 80 mg doses, but increment was small and subclinical [34].
- Indoprofen was found to be associated with mainly GI tract AEs (78% of all AEs) in a 4-week duration cohort study including 1629 patients [35].
- Ibuprofen, with concomitant warfarin: There was a case report of a 74-year-old white woman with hip OA who developed significant elevation of the international normalized ratio (INR) after the addition of ibuprofen to her medication regimen. The patient experienced a decrease in haemoglobin concentration, asymptomatic hypotension and increased blood urea nitrogen/creatinine ratio [36].
- Piroxicam was investigated in a cohort study of 6–12-month follow-up duration ($n = 154$) in which epigastric distress and other gastrointestinal symptoms (nausea, abdominal discomfort and flatulence) were found to be the most common AEs (most being mild or moderate in severity) [37].
- Etoricoxib: A case of toxic epidermal necrolysis with etoricoxib was reported with a 59-year-old female patient who took only a single dose of 60 mg orally [38].
- Sulindac (Arthrocine®): One cohort study with 2040 participants with hip or knee OA who were followed up for 12 months reported mainly gastralgia, but also gastrointestinal bleeding, neurosensory AEs (dizziness, headaches, insomnia and drowsiness) and cutaneous AEs (pruritus and rash) [39].
- Flavocoxid (Limbrel®): A cohort study of 2-month duration investigated flavocoxid in 1067 patients. The most commonly reported AEs were gastrointestinal AEs (7.4% of participants). Other AEs included those related to the central nervous system (1.0% of patients) and the musculoskeletal system (0.4% of patients) [40].
- Diclofenac: Two of the included studies, a case series [41] and a case report [42], were about diclofenac alone in patients with OA. The case series study reported an analysis of 180 cases of diclofenac hepatic injury (involving 139 patients with OA) submitted to the Food and Drug Administration (FDA), suggesting that diclofenac-related liver injury is particularly likely to involve osteoarthritic females, presenting with jaundice 1–6 months after starting diclofenac, with injury that is predominantly hepatocellular and presumably caused by metabolic idiosyncrasy [41]. The case report was about an extremely rare case of spontaneous thigh haematoma described in a 60-year-old woman with severe bilateral hip OA treated with diclofenac sodium on a long-term basis [42].
- Paracetamol and diclofenac: A case of anaphylaxis complicated by loss of consciousness was reported in a 52-year-old OA woman who had eaten her regular biryani (a mixed rice dish originating on the Indian Subcontinent) before taking paracetamol and diclofenac for chronic back pain related to underlying OA [47].
- Imidazole salicylate: A post-marketing survey (cohort study) of up to 1 month duration ($n = 467$ patients with OA) found that one 750-mg tablet, three times a day of imidazole salicylate was associated with the following "treatment-related AEs": Heartburh, epigastric pain, intestinal disorders, nausea or vomiting, dizziness, and itching [43].
- Etodolac was investigated in a post-marketing surveillance study on a cohort of 776 patients with OA with a 6-week follow-up duration. Gastrointestinal events (including epigastric pain, heartburn, abdominal pain and diarrhoea) were the most commonly reported AEs [44].
- Naproxen: One cohort study (1-year duration) including 145 patients with OA and intolerance to other NSAIDs reported the following "drug-related" AEs: dyspepsia, constipation, nausea, dizziness and other AEs (not specified). Authors reported that side-effects were troublesome enough to cause withdrawal from the trial in 17 patients. Nevertheless, they concluded that naproxen has proved to be a safe and effective drug in a group of "difficult to treat patients" with OA [45].
- Fenbufen: In a cohort study ($n = 129$ patients, minimum 6-month follow-up duration) reporting mainly GI AEs, authors concluded that fenbufen appeared to be a safe and well-tolerated compound for long-term treatment of patients with OA. One case of severe dermatitis required withdrawal from trial [46].
- Traditional NSAIDs (see list in Table 1): A nested case–control study estimated the risk of non-fatal acute myocardial infarction (AMI) associated with traditional

NSAIDs (tNSAIDs) in different subgroups of patients. When all tNSAIDs were considered together as a group, no increased risk of AMI was observed among OA patient current users compared with non-users (adjusted OR = 1.04; 95% CI 0.85–1.27). Results by individual NSAIDs were not reported separately for patients with OA [79].

– Various individual NSAIDs or combinations of NSAIDs with other NSAIDs or with other drugs were investigated in a single retrospective cohort study including 143 patients with knee OA. AEs with NSAIDs were heartburn, bloating, nausea, decreased appetite and dyspepsia. AEs with NSAID + corticosteroid were stomach ache and dyspepsia [27].

3.3.2 Intra-articular Hyaluronic Acid (IAHA)

Sixteen observational studies investigated various IAHA preparations under specific brand names, including Arthrum 2.5%, Crespine® Gel, Hyalubrix®, LBSA0103 - Synovian™, Durolane, HyalOne®, Sinovial® Forte 1.6%, HYMOVIS ONE (HYADD4-G), Condrotide®, Hyalgan® and Hylan G-F 20. Fifteen of these studies were cohort studies, with follow-up duration ranging from 5 weeks to 7 years. These studies largely included patients with OA of the knee or hip. The mean age of participants in most of these studies (n = 12/16) was ≥ 60 years old, and most of them (n = 12) included more female (> 50%) than male participants (details in Table 2).

– HyalOne® (Hyalubrix® 60 Italian brand) was investigated in three cohort studies. One prospective cohort study included 120 patients with hip OA followed up for 18 months after receiving a single 4-mL (60 mg/4 mL) injection of HyalOne® every 6 months, with the possibility of an additional injection at the intervening 3-month intervals on clinical request [55]. Another prospective cohort study of up to 7-year follow-up duration included 1022 patients with hip OA who received a single injection (60 mg/4 mL) into the affected hip every 6 months, with additional injections if clinically needed [57]. The third study was a retrospective cohort study with ≥ 12 months of follow-up of 187 patients with knee OA receiving a single IA injection (60 mg/4 mL) in the affected knee, also with additional injections if clinically needed [58]. In all three studies, no systemic or severe local side effects, or septic complications, were reported; transient local pain was the only side effect reported in some patients.
– Hyalubrix® (Fidia Farmaceutici SpA, Italy): This hyaluronic acid preparation (sodium hyaluronate solution 1.5%, 2.0 mL for IA injection) was investigated in a 5-week follow-up duration prospective cohort study in 1266 patients with OA in various locations, including the hip and the knee, who received one injection per week for three consecutive weeks. Specific AEs reported were pain at the injection site, swelling at the injection site, and other (not specified). No serious AEs occurred [50].
– Hylan G-F 20*:* Two cohort studies of at least 1 year follow-up investigated the effects of a single 6-mL injection of Hylan G-F 20 in patients with knee OA [62, 63], with a repeat treatment phase as needed in one of these studies [62]. Local AEs reported in the first study (n = 394 patients included) were arthralgia, synovitis, arthritis, bursitis, musculoskeletal stiffness, injection site pain and injection site pruritus [62]. Systemic AEs were, oedema peripheral, cellulitis, rash or swelling of the face (considered to be related to the study treatment); six patients (2%) experienced serious AEs, all considered not related to the study treatment or procedure [62]. In the second study (n = 95 patients), AEs reported were pain, swelling and warmth, which were all of mild severity [63].
– Arthrum 2.5% (LCA Pharmaceutical, Chartres, France): In a prospective cohort study of 6-month follow-up duration for safety monitoring, 214 patients with knee OA received a single IA injection of Arthrum 2.5% (3 mL, 75 mg hyaluronic acid). The AEs reported were minor local reaction, post-injection pain on walking, pruritus and delayed pain. There were no general or serious AEs reported [48].
– Crespine® Gel was investigated in a prospective cohort study including 84 participants with knee OA, followed up for 9 months after a single injection of Crespine® Gel (2 mL), a cross-linked HA product. Increased pain with limited mobility of the knee joint 72 h post-injection was reported in most of the participants, including pain only, pain and redness of the knee joint, pain and swelling, simultaneous pain, swelling and redness. Limited mobility of the knee after injection, without experiencing pain, redness or swelling, was also reported in a few participants. No serious side effects were reported [49].
– LBSA0103 Synovian™ (LGChem,Ltd., Iksan, Republic of Korea): This hyaluronic acid preparation was investigated in a prospective cohort study including 3140 participants with knee OA who received either one or two IA injections of LBSA0103 and were followed-up for 12 weeks after each injection and up to 36 weeks (with the second injection, if required, at 24 weeks after the first injection). Injection site reaction and AEs other than injection site reaction were reported; notably, no serious adverse drug reactions (ADR) were reported, while serious AEs deemed not related to intervention were reported in 17 patients. Authors concluded that LBSA0103 had an acceptable benefit–risk profile, suggesting that AEs noted after administration of LBSA0103 would continue to be monitored through routine safety reporting channels. It is

worth noting that this study was reported as a mandated post-marketing surveillance study [51].

- Durolane (Bioventus Global LL, the Netherlands): Prospectively collected outcome data were analysed for 82 patients with hip OA, followed up for 6 weeks after a single injection of this non-animal-derived, stabilized HA (NASHA) with molecular weight > 3000 kilodaltons, 3 ml preparation. Only minor pain was reported by five patients; there were no treatment-related significant AEs, infection or other AEs [52].
- Sinovial® Forte 1.6% (IBSA Institut Biochimique SA, Lugano, Switzerland): One prospective cohort study including 114 patients with hip OA investigated Sinovial® Forte 1.6%. Patients received a single injection (4 mL, two vials) of this sodium hyaluronate with MW of 800–1200 KDa at a concentration of 32 mg/2 mL for one vial, with optional additional injections at the 3-month follow-up visit if symptomatically appropriate and were followed up for up to 6 months. No systemic AEs were observed. Only seven patients reported a local reaction at the injection site, consisting of mild pain and localized warmth, which resolved spontaneously. No septic complications were observed [56].
- HYMOVIS ONE (HYADD4-G): 198 patients with hip OA received a single intra-articular injection of this viscoelastic hyaluronan (32 mg/4 mL) and were followed-up for at least 12 months, in a post-marketing cohort study (retrospective analysis). No systemic or severe local side effects were reported. In 2.5% of cases, there was a sensation of pain lasting from several hours to a few days that spontaneously regressed [59].
- Condrotide® (Mastelli Srl, Sanremo, Italy) was investigated in a 3-year follow-up duration retrospective cohort post-marketing study involving 43 patients with hip OA. These patients received ultrasound-guided intra-articular treatment of two 2-mL vials of Condrotide® for a total of 4 mL and 80 mg PN-HPT™ every 6 months. Neither the patients nor the attending physicians reported systemic or severe local side effects. A few cases of minor and transient local pain or burning sensation were all the reported side effects [60].
- Hyalgan® (FIDIA S.p.A., Padua, Italy): In a prospective cohort study of 1–2 years follow-up of 76 patients with knee OA who received five intra-articular injections of Hyalgan® (20 mg of sodium hyaluronate) at weekly intervals, the following AEs were reported: injection-site pain, injection-site bruising, headache and nausea. No systemic AEs, no dropouts due to AEs and no pseudo-septic reactions were reported [61].
- An ultrasound-guided intra-articular injection (USGIAI) of HA (brand not specified) was compared with standard-of-care hip OA treatment with oral NSAIDs, pain killers, SYSADOA in an open real-life setting study (a retrospective cohort study). Patients were treated with three consecutive weekly doses of HA-USGIAI and followed up for 6 months. No drug-related or injection-dependent adverse effects were seen during follow-up [54].
- There was a case report of severe septic arthritis and systemic sepsis that led to the death of the patient, a 59-year-old male who received a single injection of an intra-articular hyaluronate (brand not specified) for knee OA. Authors reporting this case recommended producing correct guidelines for a clean aseptic injection procedure, to obtain proper consensus from the patient, and to pay attention to his clinical history and comorbidities before implementing any kind of invasive treatment, including joint injection [53].

3.3.3 *Symptomatic Slow-Acting Drugs for Osteoarthritis (SYSADOAs) (*Table 3*)*

- Avocado/soybean unsaponifiables (Piascledine®) at a dosage of 300 mg capsule/day was investigated in a prospective cohort study of 6-month follow-up duration including 4822 patients with knee OA. The following AEs were experienced by a few numbers of patients: diarrhoea, elevated blood pressure and headache, and nausea, flatulence or abdominal pain. No serious adverse reactions were experienced [64].
- Diacerein: Two post-marketing surveillance cohort studies, both conducted in India, investigated diacerein in patients with knee OA, with different dosages, sample sizes and follow-up durations [65, 66]. The first study included 120 patients who received 50 mg tablet administered orally once daily and were followed up for 4 months, the only AEs reported being reddish urine (2 cases) [65]. The second study was a 12-week duration study including 7903 patients who were treated with 50 mg tablets administered twice daily. The AEs reported were diarrhoea, gastritis, nausea, abdominal pain or discomfort and vomiting; there were no severe or serious AEs reported, and none of the study participants withdrew owing to AEs [66].
- SYSADOAs (including glucosamine and chondroitin sulphate): The risk of nonfatal acute myocardial infarction (AMI) associated with various drugs used in OA was investigated in a nested case–control study in Spain. The authors reported that SYSADOAs (chondroitin sulphate and glucosamine) are prescription-only drugs that are widely used in Spain. This study found that SYSADOAs did not increase the risk of AMI in any of the conditions examined [26].
- Glucosamine and chondroitin preparations (non-prescription grade) were investigated in three studies: two case reports [67, 68] and a prospective cohort study [69]. The first case report is about a 36-year-old woman who devel-

oped a skin rash with delayed onset after taking 1500 mg glucosamine sulphate and 1200 mg chondroitin sulphate pills for lumbar degenerative joint disease. Within 3 h of the first dose, she noticed the appearance of an itchy rash on her torso and legs. This was suspected to be an allergic reaction to the supplement. The brand of the supplement used was not specified [67]. The second study investigated cases of adverse drug reactions (ADRs) to glucosamine and chondroitin in the Australian population between 2000 and 2011, with a primary focus on hypersensitivity reactions. In this study of 366 ADRs to glucosamine and chondroitin preparations, 71.85% of cases ($n = 263$) were found to have hypersensitivity reactions [68]. In the prospective cohort study, 1102 patients with knee or hip OA were treated with Theraflex® (capsules of glucosamine hydrochloride 500 mg and chondroitin sulphate 400 mg), three times a day for the first three weeks, then twice daily, for a total of 64 weeks of treatment and follow-up duration. Most common Medical Dictionary for Regulatory Activities (MedDRA) system classes AEs were musculoskeletal and connective tissue disorders, gastrointestinal disorders, infections and infestations. AEs considered by the investigators as "related to the study product" were reported for 31 (2.8%) patients and mainly included gastrointestinal disorders (in 24 patients) [69].

3.3.4 Corticosteroid Injections

The safety of corticosteroid injections was investigated in two cohort studies [70, 71]. In addition, specific safety concerns were reported by a case report [72] and a case series [73] (Table 3).

- The first cohort study included 1000 patients with knee or hip OA who received a single injection of triamcinolone (Triamcort, Helvepharm) and where followed up for 1–12 months after injection to determine the number of patients with complications. The following severe complications were reported in 1% of patients: osteonecrosis, insufficiency fractures and rapid OA progression, all of which occurred between 2 and 9 months after injection [70].
- In the second cohort study with 5-year follow-up duration and self-reported treatment with glucocorticoid or IAHA injections, the authors reported that they did not have data on the type of glucocorticoids used and dosage, which was outlined as a limitation of the study. The objective of the study was to determine whether glucocorticoid injections increase the risk of knee OA progression over 5 years. Despite the limitation outlined, the authors concluded that IA glucocorticoid injections for symptomatic knee OA did not significantly increase the 5-year risk of incident TKR or radiographic worsening, though stressing that these findings should be interpreted cautiously [71].
- The case report was about a 73-year-old woman who received a single intra-articular corticosteroid injection for knee OA. The procedure was then complicated by septic arthritis requiring hospitalization, joint lavage and intravenous antibiotic treatment [72].
- The case series included two patients with knee OA (49 and 45 years old) who experienced rare AEs associated with corticosteroid injections (intra-articular triamcinolone 80 mg with 1% lidocaine, single injection). The first patient complained of vision disturbances including black spots bilaterally and difficulty seeing out of her left eye, 11 days post-injection. The second patient noted feelings of acute anxiety manifested by panic attacks, 7 days after the injection, and was diagnosed with substance-induced anxiety [73].

3.3.5 Opioids

Three [74–76] of all the studies included in this review investigated various opioids (Table 3).

- The first study is a case series including a 79-year-old male who was treated with a buprenorphine transdermal patch for OA. One and a half months after the increase of the dosage (from 15 mcg/h transdermal applied once every 7 days to 20 mcg/h transdermal every 7 days), the patient developed a topical erythematous reaction directly under the site of application. He experienced itchiness and burning in this area [74].
- The second study is a cohort study including 307 patients with OA who were treated with an extended-release formulation of hydrocodone (Hysingla® ER, Purdue Pharma L.P.) and were followed up for more than 52 weeks. Twenty-two percent of the patients discontinued the study owing to AEs, while serious treatment-emergent AEs (TEAEs) occurred in 9.8% of patients. MedDRA system organ class TEAEs reported include gastrointestinal disorders (47% of patients) and nervous system disorders (35% of patients) [75] (details in Table 3).
- In the third study, in which the primary outcome was any new diagnosis of a hip fracture requiring surgery following treatment with tramadol and the combinative drugs including tramadol, tramadol use was identified as a risk factor for hip fracture, especially among patients aged 60–70 years and among male patients (Table 3), when compared with patients who did not

use tramadol but used any NSAID drugs, paracetamol or muscle relaxants [76].

3.3.6 Herbal Mixtures and Other Compounds

- Ademetionine* (Gumbaral®): A large phase IV cohort study (n = 20,641) was conducted to obtain further information about the safety of ademetionine in patients with OA. Over 8 weeks treatment duration, no serious drug-related AEs were reported. Twenty-one percent of patients reported moderate or severe AEs, most of which were related to the gastrointestinal tract. Some deaths occurred, all reported as appearing to be explained by other factors and not related to the treatment [77].
- GCSB-5 (Shinbaros®, Green Cross Corporation, Yongin, Korea) – a mixture of six herbal extracts was assessed in a 24-week duration cohort study including 756 patients with knee OA. Several AEs were reported, including mainly gastrointestinal disorders (23.7% of subjects). Authors concluded that GCSB-5 had a comparable gastrointestinal safety profile to celecoxib [78].

4 Discussion

This study intended to describe the characteristics and the main findings of published post-marketing safety surveillance studies of anti-OA medications. In terms of study characteristics, most were cohort studies without control groups, thus making them high risk of bias studies. Sample sizes varied substantially from a hundred to several thousand for a few studies, follow-up durations mainly from several months to 1 year, while only a very few studies were explicitly reported as post-marketing safety surveillance or mandated studies (Tables 1–3). Regarding findings, globally, the results reported in this manuscript confirm previous evidence from our meta-analyses of placebo-controlled trials on the safety of cyclooxygenase-2 inhibitors [8], topical non-steroidal anti-inflammatory drugs (NSAIDs) [5], symptomatic slow-acting drugs for osteoarthritis (SYSADOAs) [6], intra-articular hyaluronic acid (IAHA) [7] and opioids [9]. A few additional safety concerns were reported, mainly from case reports or case series on specific drugs, all of which require further investigations with more rigorous study designs before any definitive conclusions can be reached. Studies were also retrieved on other compounds such as herbal mixtures [78] and ademetionine (Gumbaral) [77], with mainly gastrointestinal tract AEs reported for both compounds.

Regarding topical NSAIDs, only *S*-furbiprofen plaster (SFPP), which was included in our meta-analysis of phase 3 RCTs [5], was investigated in a study included in this review [34]. That study focussed on the impact on kidney function of long-term application of SFPP [34] and therefore did not report on other AEs commonly assessed with topical NSAIDs [5].

Our previous meta-analysis comparing cox-2 inhibitors with placebo treatment in patients with OA found that these drugs were associated with increased risks of both upper gastrointestinal and cardiovascular AEs [8]. Among the studies included in this systematic review, four large cohort studies and a non-inferiority RCT (with two reports) [20–25] investigated the post-marketing safety of chronic use of celecoxib against no recorded exposure or non-chronic NSAIDs use [20], traditional NSAID [21] meloxicam [22, 23], and ibuprofen or naproxen [24, 25]. Overall, the results of these studies show a better or similar cardiovascular, gastrointestinal and renal safety profile for celecoxib (at a daily dose of 200 mg, where dosage was reported), compared with other NSAIDs. These results are consistent with findings of the original publication from the PRECISION trial, which showed that, at moderate doses, celecoxib was noninferior to ibuprofen or naproxen with regard to cardiovascular safety (analysis based on the total sample including both patients with OA and with RA) [80]. However, this better safety profile of celecoxib, at the daily dose recommended by regulatory agencies, should be weighed against efficacy when compared with other NSAIDs [81]. One of the reports from the PRECISION trial, which examined whether various patient subgroups had differential risks of "NSAIDs toxicity", showed mixed results for patients with OA and RA, compared with the results of the primary analyses including all patients, for the same outcomes. Although obvious differences may exist in drug safety profiles between patients with OA and with RA owing to relevant patient and disease characteristics, as well as to differences in drug dosage, a more plausible explanation for these results may be the "artificial" composite nature of the outcomes assessed (see notes of Table 1). This kind of "personalized" outcome definition should therefore be avoided when analysing drug safety results, and classifications by System Organ Classes (SOCs) should rather be used [82, 83].

IAHA was investigated in 15 cohort studies, which assessed various hyaluronic acid (HA) preparations. Only minor injection site reactions were reported with most HA preparations. Although such evidence may be reassuring, given the limited number of studies available on each of these preparations and their relatively small sample size, further post-marketing surveillance studies including more patients are warranted to allow definitive conclusions on the safety of HA preparations. In fact, the results reported in this manuscript are consistent with findings of our previous meta-analysis of placebo-controlled trials, which concluded that IAHA seemed not to be associated with any safety issue in the management of OA, on the basis of data from studies not allowing concomitant anti-OA medications

[7]. However, the same meta-analysis found a possible association of IAHA with increased risk of serious AEs when used with concomitant OA medications, a finding that we reported as requiring further investigations [7]. In the current systematic review, serious AEs (not specified) were reported in two cohort studies, which were deemed by the authors not related to treatment [51, 62]. Although these events may rather be procedure related or even related to factors other than the HA itself (such as comorbidities or concomitant drugs), further high-quality research is warranted to rule out any doubts about the safety of IAHA injections in patients with OA.

SYSADOAs have been part of the treatment armamentarium of OA, including different agents such as glucosamine sulphate (GS), chondroitin sulphate (CS), avocado−soybean unsaponifiables (ASU) and diacerein [84], although not all clinical guidelines recommend their use. Two cohort studies investigating diacerein [65, 66] and one assessing ASU (Piascledine®) [64] were included in this review. The results reported with these compounds are consistent with the findings of our previous meta-analysis of placebo-controlled trials [6], with gastrointestinal AEs and reddish urine being the most frequent AEs reported with diacerein [65, 66]. Regarding ASU, mainly gastrointestinal AEs were reported in the single cohort study retrieved [64]. In the current review, the only study on prescription-grade GS and CS concluded that these compounds did not increase the risk of any of the conditions examined [26], a result that is consistent with the findings of our previous meta-analysis [6]. It is worth noting that only pharmaceutical-grade compounds are recommended for the management of OA [84].

Corticosteroid injections were not assessed in our previous safety meta-analyses. Of the two cohort studies investigating intra-articular corticosteroids (IACS) among the studies included in this systematic review, one reported osteonecrosis, insufficiency fractures and rapid progressive OA as severe complications in patients [70]. These findings are consistent with the conclusions of a recent meta-analysis that found that the use of IACS may contribute to imaging features of knee cartilage loss [85]. In contrast, in the second cohort study included in this review, the authors found that IACS injections for symptomatic knee OA did not significantly increase the 5-year risk of incident total knee replacement or radiographic worsening; however, given the limitations of that study, the authors stressed that these findings should be interpreted cautiously and replicated in other cohorts [71].

Lastly, among the opioid drugs that were included in our previous safety-focussed meta-analysis [9], hydrocodone (extended-release formulation) [75] and tramadol [76] were investigated each in a post-marketing safety surveillance cohort study in patients with OA. The AEs associated with the use of hydrocodone [75] (Table 3) were similar to those reported in the single study on hydrocodone included in our previous meta-analysis, although reporting was far more exhaustive in the study included in this review [9]. The study on tramadol reported a positive association between long-term use and hip fractures, especially among male patients and those aged 60–70 years [76]. This finding adds to the numerous AEs associated with tramadol use, as previously reported [9]. Although opioids have been part of the treatment armamentarium of osteoarthritis, current recommendations for their use vary across international guidelines [84, 86, 87].

We acknowledge several limitations of this systematic review. First, we restricted our literature search to studies published in English or French language. Therefore, 51 studies were excluded because their full-text manuscript was reported in other languages only. Even if evidence showed that restricting systematic reviews to English-language publications has little impact on their conclusions [88], we acknowledge that this number of excluded studies is substantial when compared with the number of studies ultimately included in this review. Nevertheless, it is worth keeping in mind that not all these studies would have necessarily been included in the review if they were reported in English, as some could finally be excluded for other reasons. Second, we also excluded a number of studies because they did not report separate results for patients with OA. Though such exclusions could indeed be seen as a limitation, we rather consider this option as a strength of this systematic review, as it allows direct evidence on anti-OA medications for patients with OA. Third, we may have inadvertently excluded some studies as not post-marketing surveillance studies, particularly those designed as RCTs and comparing various drugs, mainly because reporting was not clear for many studies. Finally, despite being highly sensitive, our search strategies may have missed some cohort studied or RCTs that did not include specific terms denoting post-marketing surveillance in their title, abstract or keywords.

The purpose of this research was to provide insights into the state of post-marketing safety surveillance of drugs used in OA and to identify potential challenges in this setting. In this sense, the limitations of the review, as outlined above, offer the opportunity to highlight some areas of improvement in the field of post-marketing safety surveillance in OA, particularly regarding the reporting of manuscripts. The same way our previous meta-analyses and other research have outlined issues in the reporting of safety results in manuscripts on RCTs, this review shows that the quality of reporting is a burning issue in the field of post-marketing

safety research in OA. This highlights the urgent need for a reporting guideline, in the form of a "preferred reporting items", which could also suggest a framework for reporting of AEs, such as the one recently published [83]. In particular, many studies in this systematic review were not explicitly reported as post-marketing safety surveillance studies, which made the selection of studies not straightforward. Future research and reports should also consider providing results per disease if including several patient populations, particularly when investigating drugs common to several conditions. The risk of bias assessment of included studies has shown that the major methodological flaw of the cohort studies included in this review is the absence of control groups. It is therefore important that future post-marketing safety surveillance studies of drugs used in OA consider including patients under other treatment options, to facilitate causality assessment. Lastly and importantly, this systematic review also showed that only a few phase IV studies had a real goal of safety surveillance. More emphasis should therefore be placed on post-marketing safety surveillance of anti-OA medications, with more rigorous and adequately powered studies that have safety as primary outcome. Despite the importance of these studies, they are hardly feasible owing to the costs and are therefore generally conducted or sponsored by pharmaceutical companies. Authors of a survey investigating the practice of post-marketing studies in Germany reported that these studies are not improving drug safety surveillance, stressing that high remuneration and strict confidentiality clauses could influence the physicians' reporting behaviours of adverse drug reactions [89]. Therefore, to improve the credibility and usefulness of post-marketing safety surveillance, these studies should be conducted by academic institutions or public health agencies.

5 Conclusions

The results of this research confirm previous evidence on the safety of anti-OA medications from meta-analyses of randomized placebo-controlled trials. Given the limited number of studies retrieved on most anti-OA drugs and the relative short duration of these studies, real-life safety surveillance of anti-OA medications should be strengthened with large cohort studies of longer durations and complemented by publications of consolidated data from adverse drug reaction report registries. Beyond the evidence reported in this manuscript on the safety of the various anti-OA medications, this systematic review importantly highlights the urgent need for a guideline to improve the reporting of post-marketing safety surveillance studies. In particular, future studies should be explicitly reported as post-marketing safety surveillance studies, and where applicable, results should be desegregated to provide evidence on drug safety per disease or patient populations.

Supplementary Information The online version contains supplementary material available at https://doi.org/10.1007/s40265-025-02162-4.

Acknowledgments The authors thank Fabienne Damblon for helping with the full-text search and Anton Geerinck for contributing to part of the data extraction.

Declarations

Funding This work was supported by the *Distinguished Scientist Fellowship Program (DSFP) of the King Saud University* (Riyadh, Kingdom of Saudi Arabia), and by an *Unrestricted Educational Grant* provided by *Interface Science et Recherche ASBL*, a Belgian non-for-profit organization aiming at supporting high-quality scientific research conducted at the University of Liège (Belgium). The authors of this research are grateful to ReumaNL and to Doctor Corné Baatenburg de Jong for their support to their scientific activities. However, the conception of the study and development of the protocol, the collection and synthesis of the data and their interpretation, the drafting of this manuscript and the decision to submit it for publication were the sole responsibility of the authors, without any influence of any third party.

Conflict of Interest G. Honvo, L. Lengelé, M. Alokail, and N. Al-Daghri have nothing to declare. O. Bruyère reports consulting or lecture fees from Amgen, Aptissen, Biophytis, IBSA, Mylan, Novartis, Nutricia, Orifarm, Sanofi, UCB and Viatris, outside the submitted work. J.Y.R. (1) has received consultancy fees from IBSA, Promedius, Viatris, Rejuvenate Biomed, Celltrion, Agnovos, Theramex, Versanis Bio and Chugai; (2) has been a member of the Speakers Bureau for IBSA, RADIUS HEALTH, VIATRIS, AGNOVOS and TRB CHEMEDICA; (3) has received research grants (through institutions) from IBSA, Radius Health, Echolight, Viatris, Theramex and TRB Chemedica. Jean-Yves Reginster is an Editorial Board member of *Drugs*. Professor Reginster was not involved in the selection of peer reviewers for the manuscript nor any of the subsequent editorial decisions.

Ethics Approval As a systematic literature review, ethical approval was not required to conduct this research.

Consent to Participate Not applicable.

Consent for Publication Not applicable.

Data Availability All relevant data that support the findings of this study have been reported in the manuscript and in the supplementary information.

Code Availability Not applicable.

Author Contributions G.H., O.B. and J.Y.R. conceived the study and design. G.H. and O.B. drafted the review protocol. G.H. conducted the literature search. G.H. and L.L. contributed to the study selection, data extraction and risk of bias assessment. G.H., O.B., L.L., J.Y.R., M.A. and N.A.-D. contributed to the interpretation of the data. G.H. and O.B. drafted the manuscript. All authors critically reviewed the manuscript and gave their approval for this version to be published.

References

1. Litwic A, Edwards MH, Dennison EM, Cooper C. Epidemiology and burden of osteoarthritis. Br Med Bull. 2013;105:185–99. https://doi.org/10.1093/bmb/lds038. (**Epub 2013/01/23. PubMed PMID: 23337796; PubMed Central PMCID: PMCPMC3690438**).
2. Palazzo C, Ravaud JF, Papelard A, Ravaud P, Poiraudeau S. The burden of musculoskeletal conditions. PLoS ONE. 2014;9(3):e90633. https://doi.org/10.1371/journal.pone.0090633. (**Epub 2014/03/07. PubMed PMID: 24595187; PubMed Central PMCID: PMCPMC3942474**).
3. Cross M, Smith E, Hoy D, Nolte S, Ackerman I, Fransen M, et al. The global burden of hip and knee osteoarthritis: estimates from the global burden of disease 2010 study. Ann Rheum Dis. 2014;73(7):1323–30. https://doi.org/10.1136/annrheumdis-2013-204763. (**Epub 2014/02/21. PubMed PMID: 24553908**).
4. Hermann W, Lambova S, Muller-Ladner U. Current treatment options for osteoarthritis. Curr Rheumatol Rev. 2018;14(2):108–16. https://doi.org/10.2174/1573397113666170829155149.
5. Honvo G, Leclercq V, Geerinck A, Thomas T, Veronese N, Charles A, et al. Safety of topical non-steroidal anti-inflammatory drugs in osteoarthritis: outcomes of a systematic review and meta-analysis. Drugs Aging. 2019;36(Suppl 1):45–64. https://doi.org/10.1007/s40266-019-00661-0. (**Epub 2019/05/11. PubMed PMID: 31073923; PubMed Central PMCID: PMCPMC6509095**).
6. Honvo G, Reginster JY, Rabenda V, Geerinck A, Mkinsi O, Charles A, et al. Safety of symptomatic slow-acting drugs for osteoarthritis: outcomes of a systematic review and meta-analysis. Drugs Aging. 2019;36:65–99. https://doi.org/10.1007/s40266-019-00662-z. (**Epub 2019/05/11. PubMed PMID: 31073924; PubMed Central PMCID: PMCPMC6509099**).
7. Honvo G, Reginster JY, Rannou F, Rygaert X, Geerinck A, Rabenda V, et al. Safety of intra-articular hyaluronic acid injections in osteoarthritis: outcomes of a systematic review and meta-analysis. Drugs Aging. 2019;36(Suppl 1):101–27. https://doi.org/10.1007/s40266-019-00657-w. (**Epub 2019/05/11. PubMed PMID: 31073925**).
8. Curtis E, Fuggle N, Shaw S, Spooner L, Ntani G, Parsons C, et al. Safety of cyclooxygenase-2 inhibitors in osteoarthritis: outcomes of a systematic review and meta-analysis. Drugs Aging. 2019;36(Suppl 1):25–44. https://doi.org/10.1007/s40266-019-00664-x. (**Epub 2019/05/11. PubMed PMID: 31073922; PubMed Central PMCID: PMCPMC6509094**).
9. Fuggle N, Curtis E, Shaw S, Spooner L, Bruyere O, Ntani G, et al. Safety of opioids in osteoarthritis: outcomes of a systematic review and meta-analysis. Drugs Aging. 2019;36(Suppl 1):129–43. https://doi.org/10.1007/s40266-019-00666-9. (**Epub 2019/05/11. PubMed PMID: 31073926; PubMed Central PMCID: PMCPMC6509215**).
10. Glasser SP, Salas M, Delzell E. Importance and challenges of studying marketed drugs: what is a phase IV study? Common clinical research designs, registries, and self-reporting systems. J Clin Pharmacol. 2007;47(9):1074–86. https://doi.org/10.1177/0091270007304776. (**Epub 2007/09/04. PubMed PMID: 17766697**).
11. WHO. The Importance of Pharmacovigilance - Safety Monitoring of Medicinal Products: World Health Organization; 2002. Available from: http://apps.who.int/medicinedocs/fr/d/Js4893e/. Accessed 01 Mar 2022.
12. Higgins JPT, Green S. Cochrane handbook for systematic reviews of interventions. Version 5.1.0 (updated March 2011). Available from: www.handbook.cochrane.org The Cochrane Collaboration; 2011 Updated March 2011. Accessed 15 July 2019.
13. Moher D, Liberati A, Tetzlaff J, Altman DG, Group P. Preferred reporting items for systematic reviews and meta-analyses: the PRISMA statement. J Clin Epidemiol. 2009;62(10):1006–12. https://doi.org/10.1016/j.jclinepi.2009.06.005. (**Epub 2009/07/23. PubMed PMID: 19631508**).
14. Krumholz HM, Ross JS, Presler AH, Egilman DS. What have we learnt from Vioxx? BMJ. 2007;334:120–3. https://doi.org/10.1136/bmj.39024.487720.68.
15. Thomas D, Klika C. Pharmacovigilance systems. Clinical Pharmacy Education, Practice and Research2019. p. 215-25.
16. Ma LL, Wang YY, Yang ZH, Huang D, Weng H, Zeng XT. Methodological quality (risk of bias) assessment tools for primary and secondary medical studies: what are they and which is better? Mil Med Res. 2020;7(1):7. https://doi.org/10.1186/s40779-020-00238-8. (**Epub 2020/03/01. PubMed PMID: 32111253; PubMed Central PMCID: PMCPMC7049186**).
17. Zhang Y, Huang L, Wang D, Ren P, Hong Q, Kang D. The ROBINS-I and the NOS had similar reliability but differed in applicability: A random sampling observational studies of systematic reviews/meta-analysis. J Evid Based Med. 2021;14(2):112–22. https://doi.org/10.1111/jebm.12427. (**Epub 2021/05/19. PubMed PMID: 34002466**).
18. Moola S, Munn Z, Tufanaru C, Aromataris E, Sears K, Sfetcu R, et al. Chapter 7: Systematic reviews of etiology and risk. In: Aromataris E, Munn Z (Editors). JBI Manual for Evidence Synthesis: JBI; 2020. Available from: https://synthesismanual.jbi.global. Accessed 26 June 2024.
19. Higgins JPT, Green S. Cochrane handbook for systematic reviews of interventions. Version 5.1.0 (updated March 2011). Available from: www.handbook.cochrane.org: The Cochrane Collaboration; 2011 Updated March 2011.
20. Cunnington M, Webb D, Qizilbash N, Blum D, Mander A, Jonsson Funk M, et al. Risk of ischaemic cardiovascular events from selective cyclooxygenase-2 inhibitors in osteoarthritis. Pharmacoepidemiol Drug Saf. 2008;17(6):601–8. https://doi.org/10.1002/pds.1590.
21. Laharie D, Droz-Perroteau C, Benichou J, Amouretti M, Blin P, Begaud B, et al. Hospitalizations for gastrointestinal and cardiovascular events in the CADEUS cohort of traditional or Coxib NSAID users. Br J Clin Pharmacol. 2010;69(3):295–302. https://doi.org/10.1111/j.1365-2125.2009.03588.x. (**Epub 2010/03/18. PubMed PMID: 20233201; PubMed Central PMCID: PMCPMC2829700**).
22. Layton D, Hughes K, Harris S, Shakir SAW. Comparison of the incidence rates of thromboembolic events reported for patients prescribed celecoxib and meloxicam in general practice in England using Prescription-Event Monitoring (PEM) data. Rheumatology (Oxford). 2003;42(11):1354–64.
23. Layton D, Hughes K, Harris S, Shakir SAW. Comparison of the incidence rates of selected gastrointestinal events reported for patients prescribed celecoxib and meloxicam in general practice in England using prescription-event monitoring (PEM) data. Rheumatology (Oxford). 2003;42(11):1332–41.
24. Solomon DH, Husni ME, Libby PA, Yeomans ND, Lincoff AM, Lupsilonscher TF, et al. The risk of major NSAID toxicity with celecoxib, ibuprofen, or naproxen: a secondary analysis of the PRECISION trial. Am J Med. 2017;130(12):1415–22. https://doi.org/10.1016/j.amjmed.2017.06.028. (**PubMed PMID: 28756267**).
25. Solomon DH, Husni ME, Wolski KE, Wisniewski LM, Borer JS, Graham DY, et al. Differences in safety of nonsteroidal antiinflammatory drugs in patients with osteoarthritis and patients with rheumatoid arthritis: a randomized clinical trial. Arthritis Rheumatol. 2018;70(4):537–46. https://doi.org/10.1002/art.40400. (**Epub 2017/12/22. PubMed PMID: 29266879**).

26. de Abajo FJ, Gil MJ, Garcia Poza P, Bryant V, Oliva B, Timoner J, et al. Risk of nonfatal acute myocardial infarction associated with non-steroidal antiinflammatory drugs, non-narcotic analgesics and other drugs used in osteoarthritis: a nested case-control study. Pharmacoepidemiol Drug Saf. 2014;23(11):1128–38. https://doi.org/10.1002/pds.3617. (**Epub 2014/04/03. PubMed PMID: 24692325**).
27. Khotib J, Setiawan HU, Nurhan AD, Rahadiansyah E, Ardianto C, Rahmadi M. Analysis of effectiveness and drug related problems of pain reliever for knee osteoarthritis: Weighing clinical risk and benefit. J Basic Clin Physiol Pharmacol. 2019. https://doi.org/10.1515/jbcpp-2019-0338.
28. Layton D, Heeley E, Hughes K, Shakir SAW. Comparison of the incidence rates of thromboembolic events reported for patients prescribed rofecoxib and meloxicam in general practice in England using prescription-event monitoring (PEM) data. Rheumatology (Oxford). 2003;42(11):1342–53.
29. Layton D, Heeley E, Hughes K, Shakir SAW. Comparison of the incidence rates of selected gastrointestinal events reported for patients prescribed refocoxib and meloxicam in general practice in England using prescription-event monitoring data. Rheumatology. 2003;42(5):622–31. https://doi.org/10.1093/rheumatology/keg141.
30. Varghese AM, Kandra NV, Vangoori Y, Uppala PK, Uttaravelli U, Saibaba SV, et al. Theophylline and meloxicam-induced Stevens-Johnson syndrome (SJS): rare case reports. Egypt Pharm J. 2022;21(4):531–5. https://doi.org/10.4103/epj.epj_69_22.
31. Dreiser RL, Benevelli DC. Long term tolerability profile of nimesulide in the treatment of osteoarthritis. Drugs. 1993;46 Suppl 1(ec2, 7600076):270–4.
32. Pochobradsky MG, Mele G, Beretta A, Montagnani G. Post-marketing survey of nimesulide in the short-term treatment of osteoarthritis. Drugs Exp Clin Res. 1991;17(3):197–204.
33. Busson M. A long-term study of flurbiprofen in rheumatological disorders: II. Osteoarthrosis. J Int Med Res. 1986;14(1):7–12.
34. Otsuka N, Yataba I, Matsushita I, Matsumoto H, Hoshino Y, Terada Y. A minimal impact of long-term S-flurbiprofen plaster application on kidney function in osteoarthritis patients. Clin Exp Nephrol. 2017;21(6):1060–7. https://doi.org/10.1007/s10157-017-1406-9.
35. Emanueli A, Sacchetti G. Indoprofen in the treatment of osteoarthritis. Results of a phase IV multiclinic study in 1629 patients. Eur J Rheumatol Inflamm. 1981;4(1):113–7.
36. Ernst ME, Buys LM. Reevaluating the safety of concurrent warfarin and ibuprofen therapy: a case report. J Pharm Technol. 1997;13(6):244–7. https://doi.org/10.1177/875512259701300610.
37. Gordon AJ, Estabrooks TF, Dessain P. Treatment of osteoarthrosis with piroxicam in general practice: long-term follow-up in a multicentre study. J Int Med Res. 1980;8(6):375–81.
38. Kameshwari JS, Devde R. A case report on toxic epidermal necrolysis with etoricoxib. Indian J Pharmacol. 2015;47(2):221–3. https://doi.org/10.4103/0253-7613.153436. (**Epub 2015/04/17. PubMed PMID: 25878388; PubMed Central PMCID: PMCPMC4386137**).
39. Maestracci D, Sarre J. Long-term therapy of osteoarthritis of the hip and the knee by sulindac (a cooperative trial in general practice). Semaine des Hopitaux. 1979;55(7–8):379–83.
40. Pillai L, Burnett BP, Levy RM, Group GSC. GOAL: multicenter, open-label, post-marketing study of flavocoxid, a novel dual pathway inhibitor anti-inflammatory agent of botanical origin. Curr Med Res Opin. 2010;26(5):1055–63. https://doi.org/10.1185/03007991003694522.
41. Banks AT, Zimmerman HJ, Ishak KG, Harter JG. Diclofenac-associated hepatotoxicity: analysis of 180 cases reported to the food and drug administration as adverse reactions. Hepatology. 1995;22(3):820–7. https://doi.org/10.1002/hep.1840220320.
42. Salemis NS. Spontaneous thigh hematoma associated with diclofenac. Am J Emerg Med. 2009;27(1):129.e1-e2. https://doi.org/10.1016/j.ajem.2008.04.014.
43. Scaricabarozzi I, Chinea B, Scotti A. Imidazole salicylate in the treatment of osteoarthrosis and musculoskeletal trauma: a post-marketing survey. Clin Ther. 1988;10(2):229–36.
44. Serni U. Global safety of etodolac: reports from worldwide post-marketing surveillance studies. Rheumatol Int. 1990;10(1 Supplement):23–7. https://doi.org/10.1007/BF02274752.
45. Thompson M, Akyol MS, Cosh J. Naproxen in patients with osteoarthritis and intolerance to other non-steroidal anti-inflammatory drugs. Eur J Rheumatol Inflamm. 1979;2(1):25–8.
46. Urdaneta E, Bonnelli J, Curiel HE, Soria G. Long-term clinical evaluation of fenbufen in the treatment of rheumatoid arthritis and osteoarthritis: Latin-American experience. Pharmacology. 1982;25(Suppl. 1):79–87. https://doi.org/10.1159/000137782.
47. Day C, Peter J. The many faces of NSAID reactions. Curr Allergy Clin Immunol. 2021;34(3):128–31.
48. Baron D, Flin C, Porterie J, Despaux J, Vincent P. Hyaluronic Acid Single Intra-Articular Injection in Knee Osteoarthritis: A Multicenter Open Prospective Study (ART-ONE 75) with placebo post hoc comparison. Curr Ther Res Clin Exp. 2018;88:35–46. https://doi.org/10.1016/j.curtheres.2018.04.001. (**Epub 2018/08/03. PubMed PMID: 30069277; PubMed Central PMCID: PMCPMC6066596**).
49. Bashaireh K, Naser Z, Hawadya KA, Sorour S, Al-Khateeb RN. Efficacy and safety of cross-linked hyaluronic acid single injection on osteoarthritis of the knee: a post-marketing Phase IV study. Drug Des Devel Ther. 2015;9:2063–72. https://doi.org/10.2147/DDDT.S81524. (**Epub 2015/04/22. PubMed PMID: 25897212; PubMed Central PMCID: PMCPMC4396588**).
50. Foti C, Cisari C, Carda S, Giordan N, Rocco A, Frizziero A, et al. A prospective observational study of the clinical efficacy and safety of intra-articular sodium hyaluronate in synovial joints with osteoarthritis. Eur J Phys Rehabil Med. 2011;47(3):407–15.
51. Kim JG, Kim K-I, Park K-B, Park Y-G, Bae JH, Seo Y-J, et al. Safety and effectiveness of intra-articular injection of a highly cross-linked hyaluronic acid, LBSA0103 (Synovian): Results from a post-marketing surveillance study in South Korea. PLoS ONE. 2023;18(6):e0287222. https://doi.org/10.1371/journal.pone.0287222.
52. Long DM, Fitzpatrick J. Safety and efficacy of a single intra-articular injection of hyaluronic acid in osteoarthritis of the hip: a case series of 87 patients. BMC Musculoskelet Disord. 2021;22(1):797. https://doi.org/10.1186/s12891-021-04672-0.
53. Manfreda F, Rinonapoli G, Nardi A, Antinolfi P, Caraffa A. A fatal sepsis caused by hyaluronate knee injection: how much the medical history and the informed consent might be important? Case Rep Orthop. 2017;2017(101591806):1518401. https://doi.org/10.1155/2017/1518401.
54. Micu MC, Micu A, Bolboaca SD. Ultrasound-guided injection with hyaluronic acid in hip osteoarthritis: efficacy and safety in a real-life setting. Clin Rheumatol. 2022;41(8):2491–8. https://doi.org/10.1007/s10067-022-06154-7.
55. Migliore A, Massafra U, Bizzi E, Lagana B, Germano V, Piscitelli P, et al. Intra-articular injection of hyaluronic acid (MW 1500–2000 kDa; HyalOne) in symptomatic osteoarthritis of the hip: a prospective cohort study. Arch Orthop Trauma Surg. 2011;131(12):1677–85. https://doi.org/10.1007/s00402-011-1353-y. (**Epub 2011/08/05. PubMed PMID: 21814776**).
56. Migliore A, Massafra U, Bizzi E, Giovannangeli F, Tormenta S. Intraarticular ultrasound-guided injection of sinovial® forte 1.6% in patients affected by symptomatic hip osteoarthritis:

Effectiveness and safety in a large cohort of patients. Eur J Inflamm. 2012;10(1):71–9. https://doi.org/10.1177/1721727X1201000108.
57. Migliore A, Massafra U, Frediani B, Bizzi E, Sinelnikov Yzchaki E, Gigliucci G, et al. HyalOne R in the treatment of symptomatic hip OA - data from the ANTIAGE register: seven years of observation. Eur Rev Med Pharmacol Sci. 2017;21(7):1635–44.
58. Migliore A, Frediani B, Gigliucci G, Anichini SE, Cassol M, Crimaldi S, et al. One-year follow-up showing effects of single intra-articular injection of hyaluronic acid (1,500–2,000 kDa) in symptomatic knee osteoarthritis. J Biol Regul Homeost Agents. 2018;32(6):1433–41.
59. Migliore A, Frediani B, Gigliucci G, Foti C, Crimaldi S, De Lucia O, et al. Efficacy of a Single intra-articular HYMOVIS ONE injection for managing symptomatic hip osteoarthritis: a 12-month follow-up retrospective analysis of the ANTIAGE register data. Orthop Res Rev. 2020;12(101531415):19–26. https://doi.org/10.2147/ORR.S239355.
60. Migliore A, Graziano E, Martin LSM, Sorbino A, Raichi M, Boni G. Three-year management of hip osteoarthritis with intra-articular polynucleotides: a real-life cohort retrospective study. J Biol Regul Homeost Agents. 2021;35(3):1189–94. https://doi.org/10.23812/21-178-L.
61. Neustadt DH. Long-term efficacy and safety of intra-articular sodium hyaluronate (Hyalgan) in patients with osteoarthritis of the knee. Clin Exp Rheumatol. 2003;21(3):307–11.
62. Pal S, Thuppal S, Reddy KJ, Avasthi S, Aggarwal A, Bansal H, et al. Long-term (1-year) safety and efficacy of a single 6-ml injection of Hylan g-f 20 in Indian patients with symptomatic knee osteoarthritis. Open Rheumatol J. 2014;8(101480507):54–68. https://doi.org/10.2174/1874312901408010054.
63. Yan CH, Chan WL, Yuen WH, Yung PSH, Ip KY, Fan JCH, et al. Efficacy and safety of hylan G-F 20 injection in treatment of knee osteoarthritis in Chinese patients: results of a prospective, multicentre, longitudinal study. Hong Kong Med J Xianggang yi xue za zhi. 2015;21(4):327–32. https://doi.org/10.12809/hkmj144329.
64. Gluszko P, Stasiek M. Symptom-modifying effects of oral avocado/soybean unsaponifiables in routine treatment of knee osteoarthritis in Poland. An open, prospective observational study of patients adherent to a 6-month treatment. Reumatologia. 2016;54(5):217–26. https://doi.org/10.5114/reum.2016.63661. (**Epub 2016/12/21. PubMed PMID: 27994265; PubMed Central PMCID: PMCPMC5149568**).
65. Renapurkar DK, Mathur S, Jagdishwer Rao KL. Evaluation of efficacy and safety of diacerein in osteoarthritis of knee joint. Int J Pharma Bio Sci. 2010;1(3):1–12.
66. Sharma A, Rathod R, Baliga VP. An open prospective study on postmarketing evaluation of the efficacy and tolerability of diacerein in osteo-arthritis of the knee (DOK). J Indian Med Assoc. 2008;106(1):54–68 (**Epub 2008/08/19. PubMed PMID: 18705272; PubMed Central PMCID: PMCPMID: 18705272**).
67. Chu EC-P, Huang KHK, Cheung G, Ng G, Lin A. Delayed skin allergy to glucosamine chondroitin supplement. Cureus. 2023;15(3): e36310. https://doi.org/10.7759/cureus.36310.
68. Hoban C, Byard R, Musgrave I. Hypersensitive adverse drug reactions to glucosamine and chondroitin preparations in Australia between 2000 and 2011. Postgrad Med J. 2020;96(1134):190–3. https://doi.org/10.1136/postgradmedj-2019-136957. (**Epub 2019/10/11. PubMed PMID: 31597786**).
69. Lila AM, Alekseeva LI, Baranov AA, Taskina EA, Kashevarova NG, Lapkina NA, et al. Chondroitin sulfate and glucosamine combination in patients with knee and hip osteoarthritis: a long-term observational study in Russia. World J Orthop. 2023;14(6):443–57. https://doi.org/10.5312/wjo.v14.i6.443.
70. Graf DN, Thallinger A, Zubler V, Sutter R. Intraarticular steroid injection in hip and knee with fluoroscopic guidance: reassessing safety. Radiology. 2022;304(2):363–9. https://doi.org/10.1148/radiol.210668.
71. Latourte A, Rat A-C, Omorou A, Ngueyon-Sime W, Eymard F, Sellam J, et al. Do glucocorticoid injections increase the risk of knee osteoarthritis progression over 5 years? Arthritis Rheumatol (Hoboken, NJ). 2022;74(8):1343–51. https://doi.org/10.1002/art.42118.
72. Perolini S, Paschoud C, Venkatachalam A. Complication of an intra-articular injection with corticosteroids. Revue Medicale Suisse. 2022;18(804):2181–3. https://doi.org/10.53738/REVMED.2022.18.804.2181.
73. Smuin DM, Seidenberg PH, Sirlin EA, Phillips SF, Silvis ML. Rare adverse events associated with corticosteroid injections: a case series and literature review. Curr Sports Med Rep. 2016;15(3):171–6. https://doi.org/10.1249/JSR.0000000000000259.
74. Meyer-Junco L, Rea B, Mendoza K, Fudin J. Application site reactions from the buprenorphine transdermal patch: a case series. J Pain Palliat Care Pharmacother. 2022;36(1):49–54. https://doi.org/10.1080/15360288.2022.2051676.
75. Taber L, Baldridge S, He E, Ripa SR. Hysingla® ER, a once-daily, single-entity hydrocodone with abuse-deterrent properties in treating chronic nonmalignant and nonneuropathic pain in patients with osteoarthritis. Postgrad Med. 2017;129(1):133–9. https://doi.org/10.1080/00325481.2017.1274224.
76. Wu TY, Wu WT, Lee RP, Chen IH, Yu TC, Wang JH, et al. Tramadol may increase risk of hip fracture in older adults with post-traumatic osteoarthritis. J Perso Med. 2023. https://doi.org/10.3390/jpm13040580.
77. Berger R, Nowak H. A new medical approach to the treatment of osteoarthritis. Report of an open phase IV study with ademetionine (Gumbaral). Am J Med. 1987;83(5A):84–8.
78. Ha C-W, Park Y-B, Kyung H-S, Han C-S, Bae K-C, Lim H-C, et al. Gastrointestinal safety and efficacy of long-term GCSB-5 use in patients with osteoarthritis: A 24-week, multicenter study. J Ethnopharmacol. 2016;189(7903310, k8t):310–8. https://doi.org/10.1016/j.jep.2016.05.031.
79. !!! INVALID CITATION !!! [27].
80. Nissen SE, Yeomans ND, Solomon DH, Luscher TF, Libby P, Husni ME, et al. Cardiovascular safety of celecoxib, naproxen, or ibuprofen for arthritis. N Engl J Med. 2016;375(26):2519–29. https://doi.org/10.1056/NEJMoa1611593. (**Epub 2016/12/14. PubMed PMID: 27959716**).
81. da Costa BR, Pereira TV, Saadat P, Rudnicki M, Iskander SM, Bodmer NS, et al. Effectiveness and safety of non-steroidal anti-inflammatory drugs and opioid treatment for knee and hip osteoarthritis: network meta-analysis. BMJ. 2021;375:n2321. Epub 2021/10/14. https://doi.org/10.1136/bmj.n2321. PubMed PMID: 34642179; PubMed Central PMCID: PMCPMC8506236 at www.icmje.org/disclosure-of-interest/ and declare: support from the Arthritis Society, Canada Research Chairs Programme, National Institute for Health Research, Chevening Scholarship Program for the submitted work. P.J. serves as unpaid member of the steering group of trials funded by Appili Therapeutics, Abbot Vascular, and Terumo; he has received research grants to the institution from Appili Therapeutics, and honorariums to the institution for participation in advisory boards or consulting from Amgen, Ava and Fresenius, but has not received personal payments by any pharmaceutical company or device manufacturer. A.J.S. has been a paid consultant by Janssen-Cilag and GlaxoSmithKline. P.T. has received royalty payments as contributing author and editor for journals, textbooks and articles published by Elsevier, Little Brown, Wolters Kluwer, and John Wiley and Sons; PT has been an independent paid consultant to CHEOR Solutions (Canada), Innovative Science Solutions LLC and Reformulary Group; he serves as unpaid chair of the management subcommittee, of the executive

committee of OMERACT; OMERACT receives unrestricted educational grants from the American College of Rheumatology, European League of Rheumatology, Amgen, Astra Zeneca, Bristol Myers Squibb, Celgene, Eli Lilly, Genentech/Roche, Genzyme/Sanofi, Horizon Pharma, Merck, Novartis, Pfizer, PPD, Quintiles, Regeneron, Savient, Takeda Pharmaceutical, UCB Group, Vertex, Forest and Bioiberica; P.T. serves as an independent committee member in Data Safety Monitoring Boards of FDA approved trials being conducted by UCB Biopharma GmbH and SPRL, Parexel International and Prahealth Sciences. All other authors report no financial relationships with any organizations that might have an interest in the submitted work in the previous three years. All authors report no other relationships or activities that could appear to have influenced the submitted work.

82. Brown EG, Wood L, Wood S. The medical dictionary for regulatory activities (MedDRA). Drug Saf. 1999;20(2):109–17. https://doi.org/10.2165/00002018-199920020-00002. (**Epub 1999/03/19. PubMed PMID: 10082069**).
83. Honvo G, Bannuru RR, Bruyere O, Rannou F, Herrero-Beaumont G, Uebelhart D, et al. Recommendations for the reporting of harms in manuscripts on clinical trials assessing osteoarthritis drugs: a consensus statement from the European Society for Clinical and Economic Aspects of Osteoporosis, Osteoarthritis and Musculoskeletal Diseases (ESCEO). Drugs Aging. 2019;36(Suppl 1):145–59. https://doi.org/10.1007/s40266-019-00667-8. (**Epub 2019/05/11. PubMed PMID: 31073927; PubMed Central PMCID: PMCPMC6509216**).
84. Bruyère O, Honvo G, Veronese N, Arden NK, Branco J, Curtis EM, 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). Semin Arthritis Rheum. 2019;49(3):337–50. https://doi.org/10.1016/j.semarthrit.2019.04.008. (**Epub 2019/05/28. PubMed PMID: 31126594**).
85. Ibad HA, Kasaeian A, Ghotbi E, Roemer F, Jarraya M, Ghazi-Sherbaf F, et al. Longitudinal MRI-defined cartilage loss and radiographic joint space narrowing following intra-articular corticosteroid injection for knee osteoarthritis: a systematic review and meta-analysis. Osteoarthr Imaging. 2023. https://doi.org/10.1016/j.ostima.2023.100157. (**Epub 2024/03/08. PubMed PMID: 38455990; PubMed Central PMCID: PMCPMC10919225**).
86. Bannuru RR, Osani MC, Vaysbrot EE, Arden NK, Bennell K, Bierma-Zeinstra SMA, et al. OARSI guidelines for the non-surgical management of knee, hip, and polyarticular osteoarthritis. Osteoarthr Cartil. 2019;27(11):1578–89. https://doi.org/10.1016/j.joca.2019.06.011. (**Epub 2019/07/07. PubMed PMID: 31278997**).
87. Kolasinski SL, Neogi T, Hochberg MC, Oatis C, Guyatt G, Block J, et al. 2019 American College of Rheumatology/Arthritis Foundation guideline for the management of osteoarthritis of the hand, hip, and knee. Arthritis Rheumatol. 2020;72(2):220–33. https://doi.org/10.1002/art.41142.
88. Dobrescu AI, Nussbaumer-Streit B, Klerings I, Wagner G, Persad E, Sommer I, et al. Restricting evidence syntheses of interventions to English-language publications is a viable methodological shortcut for most medical topics: a systematic review. J Clin Epidemiol. 2021;137:209–17. https://doi.org/10.1016/j.jclinepi.2021.04.012. (**Epub 2021/05/03. PubMed PMID: 33933579**).
89. Spelsberg A, Prugger C, Doshi P, Ostrowski K, Witte T, Husgen D, et al. Contribution of industry funded post-marketing studies to drug safety: survey of notifications submitted to regulatory agencies. BMJ. 2017;356:j337. Epub 2017/02/09. https://doi.org/10.1136/bmj.j337. PubMed PMID: 28174182; PubMed Central PMCID: PMCPMC5477378 at www.icmje.org/coi_disclosure.pdf and declare: no support from any organisation for the submitted work other than Transparency International Germany; no financial relationships with any organisations that might have an interest in the submitted work in the previous three years; no other relationships or activities that could appear to have influenced the submitted work. PD is an unpaid member of the IMEDS steering committee at the Reagan-Udall Foundation for the FDA, which focuses on drug safety research. PD is also an associate editor at The BMJ.