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Review

Does sex affect the efficacy of systemic pharmacological treatments of pain in knee osteoarthritis? A systematic review

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ABSTRACT

Objective: To determine whether sex influences the analgesic efficacy of systemic pharmacological treatment in patients with knee osteoarthritis.
Design: A systematic review, guided by Cochrane methods, sourced studies from Medline, Cochrane Library, Embase, and CINAHL Plus with Full Text as of October 10, 2022. Eligible studies were double-blind RCTs evaluating systemic pharmacological treatments for knee osteoarthritis in adults, with minimum 30-day treatment duration, reporting sex-specific results or mentioning sex subgroup analysis for analgesic efficacy. The risk of bias was assessed using the Cochrane Risk of Bias tool version 2 (RoB 2).
Results: 9 studies (5201 participants) met inclusion criteria, analyzing drugs including duloxetine, etoricoxib, tapentadol, naproxcinod, lutikizumab, and rofecoxib. Only one study reported sex-specific results. Review findings suggested no significant sex-based differences in treatment efficacy, however, data were limited due to a lack of sex-specific reporting or inclusion of sex in subgroup analyses.
Conclusions: Current evidence does not support the existence of sex differences in the analgesic efficacy of systemic knee osteoarthritis treatments. However, this conclusion is substantially limited by the paucity of sex-specific reporting of results or subgroup analyses in most primary studies, emphasizing the need for future research to report on sex-stratified data to allow for comprehensive, personalized treatment strategies.

1. Introduction

Osteoarthritis (OA) is the most common degenerative joint condition worldwide. OA causes significant pain and disability and greatly impairs the quality of life of more than 302 million people around the world and over 32 million people in the United States alone [1,2]. OA affects different joints at different rates, with the hands, knees, hips, and spine (particularly lower cervical and lower lumbar regions) most commonly affected. However, because of the large impact of lower extremity OA, a significant amount of research has focused primarily on knee and hip osteoarthritis.

Currently, available treatments for symptomatic knee OA include pharmacologic therapies (NSAIDs, duloxetine, topical capsaicin, etc.) and non-pharmacologic interventions (weight loss, physical therapy, exercise, or surgery) [1]. Each of the aforementioned treatments comes with varying levels of efficacy as well as different safety profiles, making individualized and holistic treatment of the utmost importance. These OA treatments are usually prescribed in the same standardized fashion to adults from different backgrounds, and current treatment guidelines do not consider patient sex (referring to biological sex [biological attribute, typically binary], not to be confused with gender [a person's self-identity within a spectrum of cultural, social and behavioral factors]) as a relevant factor during the decision-making process, despite evidence showing important differences in how OA affects people of each sex [3]. Studies have shown that women with OA report higher levels of pain, greater serum CRP levels, and higher levels of functional impairment compared to their male counterparts [3].

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Additionally, there is a growing body of research that points to differences in the perception and level of pain between the sexes, with females usually reporting higher levels of pain than males in the clinical setting [4]. While this has been studied mostly in the setting of acute post-procedural pain, a similar trend has been seen in studies on allodynic perception and chronic pain [5], with females showing greater pain sensitivity [6].

Aside from the multiple sex differences that have been described for various aspects of osteoarthritis, sex has been shown to influence many aspects of pharmacology, including pharmacokinetics (drug absorption, distribution, metabolism, and excretion) and pharmacodynamics (the biochemical, physiologic, and molecular effects of a drug). In general, women tend to have lower body weight and height, which is associated with higher drug levels for any given dose [7]. Sex has also been shown to influence the activity of drug-metabolizing enzymes, meaning that pharmacokinetic and pharmacodynamic differences cannot be eliminated by simply adjusting by height, weight, and body composition. These simple, yet relevant factors can lead to important differences in the efficacy and safety of common pharmacological treatments and further support the importance of having sex-specific considerations when designing and reporting the results of clinical trials not only for osteoarthritis but also for other medical conditions.

Despite recommendations for equal enrollment and sex-specific data analysis, many clinical trials continue to fail to comply with FDA recommendations for the Evaluation of Gender Differences in Clinical Investigations [8]. Such failures include the lack of female representation in clinical trials and the mixed reporting of results in clinical trials, instead of the recommended reporting of data for each independent sex group [9]. Such problems make it impossible to determine the presence or absence of sex-specific differences in treatment response and interferes with the development of more personalized pharmacological treatments and potentially better outcomes.

A study evaluating the reporting of sex effects by systematic reviews on interventions in chronic pain found that the percentage of systematic reviews that included sex effects ranged from 31% for low back pain to 68% for fibromyalgia [10]. Moreover, many of the primary randomized controlled trials in these reviews did not include details on sex distribution, and only 16% reported sex effects in their efficacy analyses [10].

To the best of our knowledge, no study has specifically addressed the existence of sex-specific differences in the efficacy of systemic pharmacological treatments for symptomatic knee OA. The objective of this systematic review is therefore to assess available evidence from clinical trials to evaluate the role of sex as a potential effect modifier in the response to systemic pharmacological treatment (analgesic efficacy) in patients with knee osteoarthritis. If there indeed exists influence of such factor, further research could be focused on developing more personalized treatment regimens with potentially better safety and efficacy profiles, which could lead to better treatment outcomes. If current studies do not allow for a comprehensive sex-specific analysis, this further emphasizes the need for the reporting of sex-specific data in clinical trials to enable the evaluation of potential sex-differences in treatment efficacy.

2. Methods

This systematic review is reported in accordance to the PRISMA 2020 guidelines [11]. The protocol for this systematic review can be found on PROSPERO (registration; CRD42022365387). The research question for the present review was formulated using the PICO model; Population: Studies with adult male and female participants with painful knee osteoarthritis; Interventions: Randomized controlled trials evaluating the pain efficacy of pharmacological treatments in the treatment of knee osteoarthritis; Comparisons: Sex/gender subgroups within interventions (treatment vs placebo/control groups); Outcomes: Response to treatment as reflected by pain reduction (primary outcome).

2.1. Eligibility criteria

To be included in the systematic review, studies needed to report results from double-blind, randomized controlled trials assessing the efficacy of pharmacological treatments for painful knee osteoarthritis in adult male and female participants. Eligible studies were required to feature radiographic or clinical diagnosis of knee OA, interventions with a minimum of 30 days of duration, and either 1) report results independently for each sex, or 2) report subgroup analyses that included sex-by-treatment interactions.

Exclusions included pediatric studies, those involving patients with joint pain from non-OA conditions or autoimmune inflammatory arthritic conditions, in vitro or animal studies, surgical or rehabilitation interventions, alternative medicine studies, and those that did not meet the intervention duration requirement.

2.2. Information sources and search strategy

We collaborated with a research librarian (QEW) to develop a comprehensive search strategy with keywords and controlled vocabulary describing selected pharmacologic treatments, pain, and knee osteoarthritis. We applied a modified filter to identify clinical trials [12]. We performed the search on Medline (Ovid), the Cochrane Library (Wiley), Embase (Elsevier), and CINAHL Plus with Full Text (Ebsco). All searches were performed on October 10, 2022. Searches were limited to human studies published in English. Conference abstracts, editorials, and non-published studies were excluded. We did not restrict based on geography or publication date. The reference lists of included studies were reviewed for relevant citations. Full database searches are available in Appendix 1.

2.3. Study selection

Two reviewers (SE and GW) screened studies for eligibility using Rayyan [13]. Automation tools were not used. Studies qualified for inclusion in this systematic review if they met the following criteria:

- Study subjects included adult male and female patients with symptomatic knee OA, diagnosed either radiographically or clinically.
- The study was a double-blind, randomized controlled trial that assessed the efficacy of systemic pharmacological treatments for painful knee osteoarthritis.
- The interventions involved lasted for a minimum of 30 days.
- The articles reported results independently for each sex or mentioned a subgroup analysis that included sex as an independent factor.
- The articles reported pain relief for knee osteoarthritis separate from other joints (e.g., spine, hand, or hip).

The first step in the selection process involved screening all search results based on title and abstract. If a citation was considered potentially eligible and relevant, the full-text article was retrieved for further assessment. In the second phase, each full-text article was evaluated to determine whether it fulfilled all the eligibility criteria. If any of the criteria were not met, the article was excluded. Any disagreements about inclusion were resolved through discussion, making the need for a final decision from a third reviewer (TJS) unnecessary.

2.4. Data items

Data extraction was performed by SES and GW using a standardized template. Each paper was independently assessed by reviewers for data collection and extraction. Items for data extraction included publication details (author, journal, year of publication), study details (drug studied, comparators [placebo or active comparators], study location, and

treatment duration), participant characteristics (sex, age, BMI), and pain outcomes (analgesic response to treatment) in relation to sex.

2.5. Risk of bias in individual studies

The Cochrane Risk of Bias Version 2 (RoB 2) tool for Randomized Controlled Trials was used to assess the risk of bias in each study by SES and GW, both at the study and outcome levels. Risk of bias was assessed independently by SES and GW, blinded from each other's assessments. Results of both reviewers were compared, and conflicts were reviewed. In case of disagreement, the reviewers were able to achieve consensus by discussion.

3. Results

3.1. Study selection

Of 4574 citations screened, only 9 studies met the inclusion criteria (Fig. 1.). No additional citations were identified through reference lists. Most studies were excluded due to mixed reporting of analgesic efficacy for multiple osteoarthritis joints (spine, hip, knee, hand, etc.), not explicitly mentioning any type of subgroup analysis, not being relevant to the aims of this study (sex-by-treatment interactions in analgesic efficacy), or not mentioning sex as a factor in subgroup analyses.

Some studies initially appeared to meet inclusion criteria, but were later removed for not reporting results for separate OA joints (or not mentioning joint as a factor in their subgroup analyses) [14–17] or for not having performed subgroup analyses [18].

3.2. Study characteristics

In this systematic review, nine articles were included in the final review. All included studies were reports of double-blind, randomized controlled trials studying the analgesic efficacy of pharmacological treatments for osteoarthritis pain with a treatment duration ranging from 6 weeks to 52 weeks. Articles were published between 2000 and 2019, and involved different systemic pharmacological treatments for OA pain, such as NSAIDs [19–22], SNRIs [23–25], opioids [26], and biologics [27]. Most studies were performed in North America and/or Europe, with two studies including participants from more than 25 countries [19,21], and one performed in Asia alone. Study populations ranged between 231 and 987 participants, with all trials including male and female adults, mostly between 60 and 65 years of age, with a majority of White participants, with some including participants of Hispanic, Asian, and Black/African American ethnicities.

Primary efficacy endpoints included the Brief Pain Inventory scale [23,24], Western Ontario and McMaster Universities Osteoarthritis Index (WOMAC) pain subscale [19–21,27], Numerical rating scale [25,26], and pain (100 mm VAS) when walking [22].

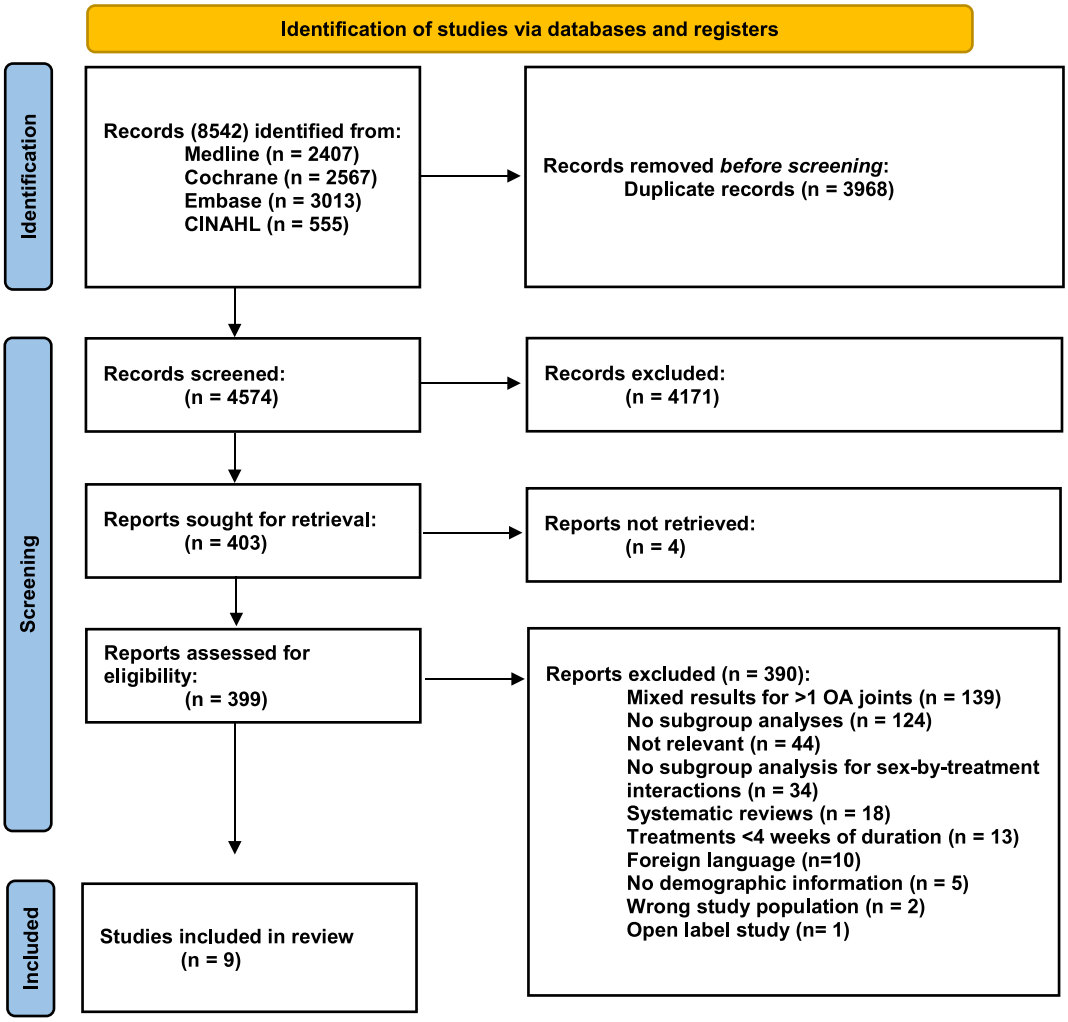

Fig. 1. Study selection flowchart.

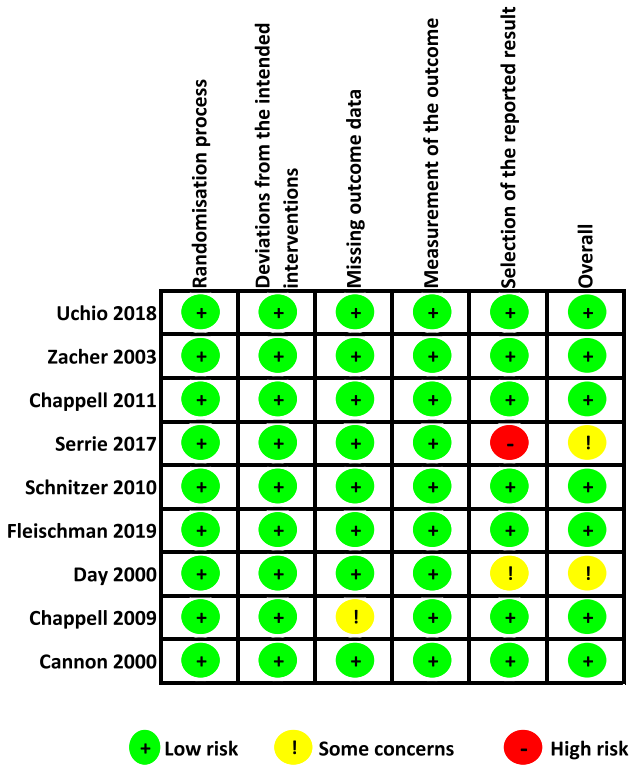

Fig. 2. Risk of bias assessments.

3.3. Risk of bias assessments

Because the review was focused on the effects of being assigned to an intervention (rather than adhering to said intervention), risk of bias assessments were performed for the intention-to-treat population rather than the per-protocol population. Results of the risk of bias assessment are presented in Fig. 2.

There was 85.2% agreement (46 of 54 items) between both reviewers. After a second review and comparison of the 8 differences, reviewers reached consensus for all items, and involvement of a third reviewer was not necessary.

3.4. Findings of included studies

Included studies encompassed four different OA-pain medication categories, including non-steroidal anti-inflammatory drugs [19–22], serotonin–norepinephrine reuptake inhibitors [23–25], opioids (Serrie et al., 2017), and biologics (Fleischmann et al., 2019). Relevant characteristics of included studies are summarized in Table 1.

3.5. Non-steroidal anti-inflammatory drugs

Zacher et al., 2003 examined the efficacy of etoricoxib versus diclofenac or placebo for a total of 6 weeks [19]. This study enrolled a total of 516 participants with OA diagnosis based on ACR criteria. The primary efficacy endpoint was the WOMAC Pain subscale (VAS) which showed a 31.3 mm reduction (from ~63 mm) in the etoricoxib group and 30.9 mm reduction (from ~62 mm) in patients treated with diclofenac. Additional pre-specified subgroup interactions were calculated, including sex; however, no significant qualitative treatment-by-subgroup interactions were discovered.

Schnitzer et al., 2010 examined varying doses (750 mg/BID vs 375 mg/BID) of oral naproxcinod efficacy versus active comparator (naproxen) and matching placebo for a total of 13 weeks [20]. Screening 1350 subjects of both genders (approximately 67% and 74% females respectively), ≥40 years of age (average 61.6 ± 9.4 years and 61.9 ± 9.2 years respectively), with ACR diagnosis of knee OA, a total of 918 (68%) were randomized, with matching baseline characteristics. Using three co-primary efficacy endpoints (WOMAC pain, WOMAC function, and PGA scale), both doses of naproxcinod were found to have statistically significant superiority to placebo ($P \leq 0.0003$), and both doses of naproxcinod were demonstrated statistically non-inferiority to naproxen (500 mg/BID/PO). Additionally, subgroup analyses were conducted, including sex. No significant treatment-by-subgroup interactions were discovered.

Day, 2000 examined the efficacy of varying doses (12.5 mg/QD vs 25 mg/QD) of oral rofecoxib, active comparator (Ibuprofen) and matching placebo for a total of 6 weeks [21]. Screening 1023 subjects of both genders (approximately 79% and 78% females respectively), ≥40 years of age (average 64.9 ± 8.4 years and 62.9 ± 8.3 years respectively), with ARA diagnosis of knee or hip OA, a total of 809 (79%) subjects were randomized, with matching baseline characteristics. Using three co-primary efficacy endpoints (pain walking on a flat surface, patient's global assessment, and investigator's global assessment), statistically significantly greater results were seen with rofecoxib compared to placebo and rofecoxib efficacy was similar to Ibuprofen (2400 mg/TID). Additionally, subgroup analyses were performed, including sex; no statistically significant interactions were discovered.

Cannon et al., 2000 examined the efficacy of varying doses (12.5 mg/QD vs. 25 mg/QD) of oral rofecoxib versus active comparator (diclofenac) for a total of 52 weeks [22]. Enrollment for the study included individuals of both genders (approximately 65% and 68% females respectively), ≥40 years of age (average 62.8 ± 10.2 years and 62.8 ± 10.3 years respectively), with ACR diagnosis of knee or hip OA. A total of 784 subjects were randomized, with matching baseline characteristics. Using three co-primary for efficacy endpoints (WOMAC pain on walking, patient's global assessment, and physician's global assessment), treatment responses were seen within 2 weeks and were sustained throughout the treatment phase. Both doses were also found to have comparable clinical efficacy to diclofenac 50 mg/TID. Additional subgroup analyses were conducted, including sex. No statistically significant interactions were observed.

3.6. Serotonin–norepinephrine reuptake inhibitors

Uchio et al. examined duloxetine efficacy versus matching placebo for a total of 14 weeks [23]. Screening 395 subjects of both genders (approximately 80% females), ≥40 years of age (average 65.5 ± 8.0 years), with ACR diagnosis of knee OA, a total of 354 (89%) were randomized, with matching baseline characteristics, except for prior pharmacologic therapeutic use. Using the BPI-Severity scale as the primary efficacy endpoint, an average change of −2.57 at Week 14 was seen for duloxetine compared with an average change of −1.80 for placebo, demonstrating statistical superiority ($P < 0.0001$). Additional subgroup analyses were conducted based on treatment-by-sex interactions, but no statistically significant differences were observed, with males exhibiting similar treatment responses to females.

Chappell et al., 2011 examined the efficacy of escalating doses (60 mg/QD vs 120 mg/QD) of oral duloxetine versus matching placebo for a total of 15 weeks [24]. Enrollment for the study included individuals of both sexes (approximately 83% females), ≥40 years of age (average 61.9 ± 9.2 years), with ACR diagnosis of knee OA. A total of 256 subjects were randomized, with approximately matching baseline characteristics, except for proportion of females in the duloxetine group ($P = 0.012$). Using the BPI-Severity scale as the primary efficacy endpoint, a statistically significantly higher percentage of participants had a ≥30% response in the duloxetine group (65.3%) compared to placebo (44.1%; $P \leq 0.001$). No statistical superiority in the ≥50% responder group was seen between duloxetine and placebo ($P = 0.068$). Overall, a statistically significant reduction in average pain was observed in the duloxetine group versus placebo from week 2 and maintained through all study time

Table 1
Relevant characteristics and findings of included studies.

ID	Author/Year	Study Drug	Treatment duration	Total (n)	Outcome
1	Uchio et al., 2018	Duloxetine	14 weeks	353	*"The response to duloxetine was similar in men (adjusted mean difference from placebo [95% CI]: −0.79 [−1.50 to −0.09]; P=0.0276) and women (−0.75 [−1.14 to −0.36]; P=0.0002)."*
2	Zacher et al., 2003	Etoricoxib	6 weeks	516	*"Consistency of treatment effect was measured across pre-specified subgroups of gender, age, race, joint, ACR functional class and tertiles of patient global assessment of disease status."*
3	Chappell et al., 2011	Duloxetine	13 weeks	256	*"No significant treatment-by-subgroup interactions of clinical relevance were observed with respect to baseline demographics (age, gender, and origin)."*
4	Serrie et al., 2017	Tapentadol PR	15 weeks	987	*"Pre-specified exploratory analyses also showed no significant differences between active treatments and placebo in reductions of pain intensity when groups were stratified by baseline pain intensity category, gender, or age."*
5	Schnitzer et al., 2010	Naproxcinod	13 weeks	918	*"The results of subgroup analyses by center, age, gender, race, ethnicity, aspirin use, diabetic status, hypertensive status and baseline WOMAC pain category were consistent with the results of the primary efficacy analysis."*
6	Fleischmann et al., 2019	Lutikizumab	50 weeks	347	*"There were no meaningful differences in WOMAC pain scores at weeks 16, 26, and 52 based on age, gender, race, or body weight."*
7	Day et al., 2000	Rofecoxib	6 weeks	809	*"Separate analyses were performed to evaluate effects on treatment differences of subgroup factors, including race, age, sex, study joint (knee vs hip), and prior OA medication use (NSAID vs acetaminophen)."*
8	Chappell et al., 2009	Duloxetine	13 weeks	231	*"No significant treatment-by-subgroup interactions were seen in analyses of the other subgroups; baseline severity of OA pain, duration of OA pain, NSAID use (yes/no), gender, and origin (Caucasian versus other)."*
9	Cannon et al., 2000	Rofecoxib	52 weeks	784	*"Treatment-by-factor analysis for the 3 primary end points showed that there was no statistically significant interaction with treatment for various subgroups, including location of the study joint (knee or hip), previous OA medication (NSAID or acetaminophen), age, and sex."*

points. Additionally, pre-specified subgroup analyses were conducted, including treatment-by-sex interactions; no statistically significant differences were observed.

Chappell et al., 2009 examined the efficacy of two different doses (60 mg/QD vs 120 mg/QD) of oral duloxetine versus matching placebo for a total of 13 weeks [25]. Screening 343 subjects of both genders (approximately 63% females), ≥40 years of age (average 62.1 ± 9.6 years), with ACR diagnosis of knee OA, a total of 231 (67%) were randomized, with matching baseline characteristics. Using the weekly mean of the 11-point NRS pain scale as the primary efficacy endpoint, a statistically significant reduction was observed in the duloxetine group compared to placebo for each week (P = 0.006). This statistically significant reduction was also seen for both 30% and 50% responder rates (59.3% vs 44.5%, P = 0.033; and 47.2% vs. 29.4%, P = 0.006, respectively). Additional subgroup analyses were conducted to determine if treatment-by-subgroup interactions existed; no statistically significant interactions were seen.

3.6.1. Opioids

Serrie et al., 2017 examined prolonged-release (PR) tapentadol efficacy versus active comparator (controlled-release (CR) oxycodone) and matching placebo for a total of 15 weeks [26]. Screening 1301 subjects of both genders (approximately 72% females), ≥40 years of age (average 62.4 ± 9.4 years), with ACR diagnosis of knee OA, a total of 990 (76%) [987 ITT population] were randomized, with comparable baseline characteristics. Using the average change in pain from baseline (10-point VAS pain scale) as the primary efficacy endpoint, numerically larger reductions in pain for tapentadol PR versus placebo were observed but did not reach statistical significance (P = 0.152). The proportion of subjects with ≥30% reduction in pain were comparable between tapentadol PR and placebo groups (41.1% vs 40.9% respectively, P = 0.976), but were smaller in the oxycodone CR and placebo group (26% vs 40.9% respectively, P < 0.001). Additional pre-specified subgroup analyses were performed to determine potential treatment-by-subgroup interactions; however, no statistically significant differences were observed.

3.6.2. Biologics

Fleischmann et al., 2019 examined the efficacy of varying doses (25 mg/Q2wk/SC vs 100 mg/Q2wk/SC vs 200 mg/Q2wk/SC) of the anti-Interleukin 1α/β dual variable domain Immunoglobin, lutikizumab, versus matching placebo in a Phase II double-blind trial for a total of 50 weeks [27]. Having screened 1571 subjects of both genders (approximately 71%, 62%, and 65% females respectively) between the ages of 35 and 74 years of age (average 61.6 ± 7.5, 50.2 ± 8.2, and 59.1 ± 10.3 years respectively), with ACR diagnosis of knee OA, a total of 350 (22%) (347 LOCF population) subjects were randomized, with well-matched baseline characteristics. Focusing on the co-primary endpoint of change in WOMAC pain score at Week 16, a statistically significant reduction was observed for the 100 mg dose group (P = 0.050), but not for the 25 mg and 200 mg dose groups (P = 0.834 and P = 0.415 respectively). While WOMAC pain reduction was observed in all treatment groups and the placebo group from Week 16–52, these results did not reach statistical significance. Additional pre-specified subgroup analyses were conducted to determine potential treatment-by-subgroup interactions; however, no statistically significant differences in treatment efficacy by sex were observed in initial or post-hoc analyses.

4. Discussion

The objective of this systematic review was to evaluate if there is an influence of sex on the efficacy of analgesic treatments for knee osteoarthritis. In our review, we identified nine eligible studies that reported the results of subgroup analyses exploring sex-by-treatment interactions of various drug classes such as non-steroidal anti-inflammatory drugs, serotonin–norepinephrine reuptake inhibitors, opioids, and biologic agents. All nine studies included a statement that no significant sex -by -treatment interaction was found; however, it is likely that the studies in the present review lacked the statistical power required to detect such interactions even if they did exist. Only one of the nine studies reported actual efficacy data by sex in the text or supplementary materials.

The results of our systematic review demonstrate how rare it is for studies of knee OA efficacy to report results by sex or incorporate sex as a variable in efficacy subgroup analyses, despite guidelines and federal regulations for data collection and analysis which have been present for almost 30 years [8,28]. Indeed, this point is clearly made in regard to NIH-funded clinical trials, where the federal register states that such trials should be "designed and carried out in a manner sufficient to provide for a valid analysis of whether the variables being studied in the trial affect women or members of minority groups, as the case may be, differently than other subjects in the trial [28]." The same should apply to reporting such results. This omission creates a considerable gap in the literature and limits the study of potential sex-specific responses to pharmacological treatments for knee osteoarthritis pain, which could obscure potentially valuable information that could help guide individual patient management. Our review demonstrates the need, at the very least, of reporting results by sex across osteoarthritis trials, even if individual studies are not powered to demonstrate such differences, as this would allow future meta-analyses to address differences in response to

treatment in this population.

Sex is known to influence numerous aspects of physiology and health. In the setting of pain, sex has been seen to influence an individual's pain experience, analgesic response to medications, and drug metabolism [29,30]. Differences in pain, both clinically and experimentally, have been observed between sexes, with females reporting, and exhibiting higher levels of pain than their male counterparts [31]. Despite the awareness of these trends, the mechanisms responsible for these differences are yet to be elucidated. Furthermore, most of the studies evaluating sex differences in pain have focused in acute/post-procedural pain and rarely on chronic pain, which are known to be distinct clinical entities. Significant sex differences have been observed in the pharmacodynamic and pharmacokinetic profiles of common analgesic medications. For example, plasma concentrations of duloxetine have been found to be higher in females than in males due to lower CYP1A2 activity in females [32,33] and greater morphine-induced analgesia among women [30]. Additionally, analgesic drug use differs between men and women, with women showing higher rates of analgesic prescriptions and higher over-the-counter analgesic use.

In the setting of osteoarthritis, sex has been known to influence multiple aspects, such as pain severity, functional impairment, rate of cartilage loss, and inflammatory markers [3,34]. Considering the significant amount of reported sex differences in osteoarthritis and other facets of health, it is imperative to explore these differences further and determine if current analgesic regimens are equally effective in men and women, or if sex-based adjustments may be warranted. Moreover, it is imperative to improve the reporting of sex results in the manuscripts of clinical trials and allow for more robust systematic reviews and meta-analyses in the future, especially considering that recommendations for sex-specific reporting of results have existed for decades [8].

The results of this review are limited by the small quantity of eligible randomized controlled trials reporting sex-by-treatment interactions or results by sex in the final publication. Additionally, results may have been limited by focusing on only one location of osteoarthritis (knee) and it is possible that more studies would have been eligible if other locations or joints were considered. Moreover, it is likely that included studies were underpowered to detect interaction effects as compared to main effects, further limiting the possibility of exploring differences in treatment response by sex [35]. Further research in this topic is thus warranted to better understand the underpinnings and mechanisms that may give rise to sex differences in chronic pain conditions such as osteoarthritis and also determine if the analgesic response to pharmacological treatments is modified by sex and if so, the extent to which these differences occur. This could potentially provide insight for the future development of more personalized treatments for chronic pain in osteoarthritis patients. Thus, while our results are not sufficient to evaluate sex differences in the analgesic response, they emphasize the need for more rigorous and detailed reporting in future research, particularly in relation to sex-specific outcomes. Prospective studies explicitly designed to investigate the influence of sex on the efficacy of pharmacological treatments for knee osteoarthritis are necessary to truly elucidate whether sex plays a role in the response to treatment.

5. Conclusions

Available evidence is insufficient to evaluate differences in the analgesic response to pharmacological treatments of knee osteoarthritis between males and females. Current studies are limited by small sample sizes and insufficient statistical power, further aggravated by a generalized lack of sex-specific reporting in published studies. Our findings emphasize the need for more comprehensive research incorporating sex-stratified reporting and analysis which would allow for future meta-analyses to determine whether sex-based differences exist. Results of such meta-analyses could potentially aid in the development of more personalized treatment strategies for pain in knee osteoarthritis patients.

Registration

The protocol for this systematic review was registered on PROSPERO (CRD42022365387).

Author contributions

SES and TJS were responsible for the conception of the study. QEW designed and conducted database searches. SES and GW screened abstracts and full texts, and performed article selection, data extraction, and risk of bias assessments. SES, TJS, GW, and LB contributed to the interpretation of the data. All authors contributed to the writing and reviewing of the final manuscript. All authors revised and approved the final version of the article. SES, TJS, and GW take responsibility for the integrity of the work as a whole.

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Authorship

All authors should have made substantial contributions to all of the following [1]: the conception and design of the study, or acquisition of data, or analysis and interpretation of data [2], drafting the article or revising it critically for important intellectual content [3], final approval of the version to be submitted. By signing below each author also verifies that he (she) confirms that neither this manuscript, nor one with substantially similar content, has been submitted, accepted or published elsewhere (except as an abstract). Each manuscript must be accompanied by a declaration of contributions relating to sections [1,2] and [3] above. This declaration should also name one or more authors who take responsibility for the integrity of the work as a whole, from inception to finished article. These declarations will be included in the published manuscript.

Studies involving humans or animals

Clinical trials or other experimentation on humans must be in accordance with the ethical standards of the responsible committee on human experimentation (institutional and national) *and* with the Helsinki Declaration of 1975, as revised in 2000. Randomized controlled trials should follow the Consolidated Standards of.

Conflicts of interest

The authors have no conflicts of interest to declare.

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All contributors who do not meet the criteria for authorship as defined above should be listed in an acknowledgements section. Examples of those who might be acknowledged include a person who provided purely technical help, writing assistance, or a department chair who provided only general support. Such contributors must give their consent to being named. Authors should disclose whether they had any writing assistance and identify the entity that paid for this assistance.

Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.ocarto.2024.100438.

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