Title

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Authors

Jones, Ian A
Talehakimi, Arad
Murphy, Linda S
et al.

Publication Date

2023-04-01

DOI

10.1016/j.artd.2023.101097

Peer reviewed

Arthroplasty Today 20 (2023) 101097

Contents lists available at ScienceDirect

Arthroplasty Today

journal homepage: http://www.arthroplastytoday.org/

Original Research

Duloxetine for Postoperative Pain Control Following Knee or Hip Replacement: A Systematic Review and Meta-Analysis

Ian A. Jones, MD [a], Arad Talehakimi, MS [b], Linda S. Murphy, MS [c], Jennifer C. Wang, BS [d], Amit S. Piple, MD [d], Alexander B. Christ, MD [d], Nathanael D. Heckmann, MD [d,*]

[a] Department of Anesthesiology and Pain Medicine, University of Washington, Seattle, WA, USA
[b] Kansas City University College of Osteopathic Medicine, Kansas City, MO, USA
[c] Irvine Libraries Reference Department, University of California, Irvine, CA, USA
[d] Department of Orthopaedic Surgery, Keck School of Medicine of USC, Los Angeles, CA, USA

ARTICLE INFO

Article history:
Received 9 November 2022
Received in revised form
8 December 2022
Accepted 2 January 2023
Available online xxx

Keywords:
Arthroplasty
Duloxetine
TKA
THA
Pain catastrophizing

ABSTRACT

Background: Duloxetine is a Food and Drug Administration–approved selective norepinephrine reuptake inhibitor for treating depression, anxiety, fibromyalgia, and neuropathic and chronic musculoskeletal pain. This meta-analysis aims to evaluate the efficacy of duloxetine in reducing pain and postoperative opioid use following lower extremity total joint arthroplasty.

Methods: A literature search was performed, identifying randomized controlled trials investigating duloxetine for pain management after total hip and total knee arthroplasty. Data from the visual analog scale (VAS) for pain during movement and at rest were extracted for postoperative days (PODs) 1, 3, 7, and 14, as well as postoperative week 6 and postoperative month 3. Opioid use data were obtained at 24, 48 and 72 hours. All data were analyzed using inverse variance with random effects and presented as weighted mean difference.

Results: Eight unique studies were identified and included, 7 of which were analyzed quantitatively. Duloxetine decreased postoperative opioid consumption at 48 and 72 hours. For VAS for pain at rest, significantly reduced pain was reported by duloxetine-treated patients at POD 3, POD 7, and postoperative week 6. For VAS for pain at movement, significantly reduced pain was reported by duloxetine-treated patients at POD1, POD 3, POD 7, POD 14, postoperative week 6, and postoperative month 3.

Conclusions: Duloxetine appears to decrease postoperative pain and opioid consumption following total joint arthroplasty. However, definitive conclusions are limited by small sample size and study heterogeneity. While there is a need for follow-up studies to determine the optimal dose, duration, and patient population, strong preliminary data provide robust support for future large-scale efficacy studies.

Introduction

Postoperative pain control is a critical component of comprehensive postsurgical patient care, as it affects patient satisfaction and operative outcomes and can result in pathophysiologic neural alterations that evolve into chronic pain syndromes [1,2]. Tissue trauma resulting from surgery is thought to lead to both central and peripheral nerve sensitization, resulting in an activity-dependent increase in spinal neurons excitation and a decreased threshold of nociceptive afferents, respectively [3,4].

Historically, opioids have been the preferred drug of choice for the management of postoperative pain following joint arthroplasty [2]. However, when used in excess, opioids can lead to deleterious side effects and have the potential for both addiction and abuse [1,5,6]. These risks are particularly important in orthopaedics given that orthopaedic surgeons are highest prescribers amongst all surgeons [7].

In light of the concerns surrounding excessive opioid use, multimodal analgesic regimens utilizing a combination of opioid

* Corresponding author. Department of Orthopaedic Surgery, Keck School of Medicine of USC, 1520 San Pablo Street, Ste 2000, Los Angeles, CA 90333. Tel.: +1 323 704 6363.
E-mail address: nate.heckmann@gmail.com

https://doi.org/10.1016/j.artd.2023.101097

and nonopioid analgesic drugs targeting different sites within the central and peripheral nervous system have emerged as the new standard in managing postoperative pain [2,8]. Among commonly used interventions, such as acetaminophen and nonsteroidal anti-inflammatory drugs, there is a growing body of evidence suggesting duloxetine may have utility in the management of postoperative pain [9,10].

Duloxetine is a relatively balanced serotonin and norepinephrine reuptake inhibitor shown to be effective in managing neuropathic pain [11,12]. Several reviews have evaluated the effect of duloxetine on postoperative pain and opioid consumption [9,13]. Most notably, Branton et al. [10] recently published a review assessing whether duloxetine reduced pain and opioid consumption following elective orthopaedic surgery. While their review was a catalyst for continued inquiry into the use of duloxetine in the postoperative setting, it only included 2 studies that evaluated duloxetine in total joint arthroplasty (TJA). Given the rising interest in duloxetine use during total knee (TKA) and total hip arthroplasty (THA), this systematic literature review and meta-analysis aims to examine the current evidence regarding duloxetine use in patients undergoing lower extremity TJA. The primary aim is to assess whether perioperative administration of duloxetine is effective in reducing postoperative opioid consumption and pain. The secondary aim is to aggregate data on the methodology, safety, and primary outcomes.

Methods

This systematic review was conducted in accordance with the Joanna Briggs Institute (JBI) System for the Unified Management, Assessment and Review of Information methodology for systematic reviews of effectiveness evidence [14], which allows for exports and analysis consistent with the Preferred Reporting Items and Systematic Reviews and Meta-Analyses guidelines and the Preferred Reporting Items and Systematic Reviews and Meta-Analyses Statement [15,16]. The review was prospectively registered on PROSPERO (registration ID#: CRD42022309539).

Search strategy

The search strategy aimed to identify both published and unpublished studies. Full details for the search methods for study selection can be found in Figure 1 and Appendix 1.

Assessment of methodological quality and inclusion

Eligible studies were screened by 2 independent reviewers (I.A.J. and A.T.) at the study level for methodological quality using standardized critical appraisal instruments from JBI for experimental studies. Domains assessed included JBI standard questions for the assessment of clinical trials. (Appendix 2) When necessary, authors were contacted to request missing or additional data for clarification. Any disagreements were resolved through discussion. A third reviewer (N.H.) served as a tiebreaker to discuss and resolve any discrepancies.

Following critical appraisal, outcomes from studies that were found to have both clinically and statistically significant differences between treatment and comparator groups at baseline were excluded from the meta-analysis portion of this review. Clinically significant differences were considered to be those that were highly likely to influence the validity of clinical outcomes, such as differences in baseline pain score for an unblinded study. Otherwise, all studies, regardless of their methodological quality, underwent data extraction and synthesis when possible.

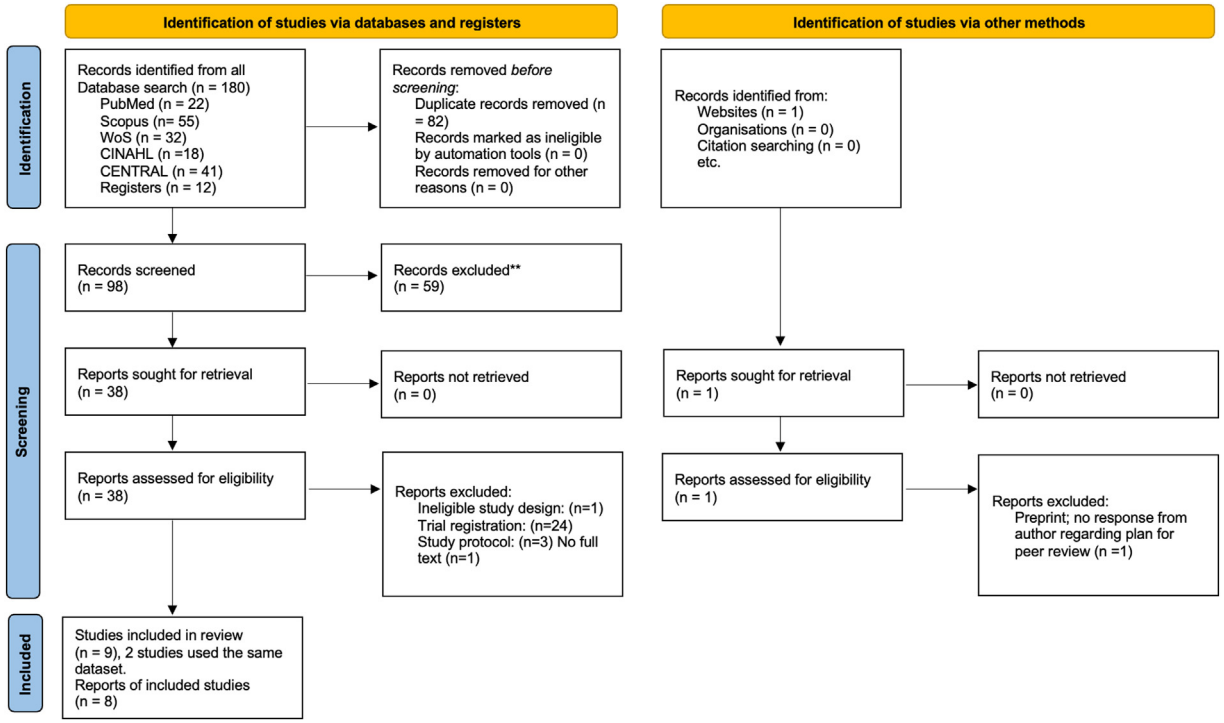

Figure 1. Flow diagram of literature search, screening, full-text review, and study inclusion based on Preferred Reporting Items for Systematic Review and Meta-Analyses (PRISMA) guidelines. *Specific timepoints not specified on Chinese Clinical Trial Registry.

Data extraction

Data was extracted from by 2 independent reviewers (I.A.J. and A.T.) using the standardized JBI data extraction tool. In addition to extracting quantitative values necessary to perform the meta-analysis, information pertaining to trial registration, type of surgery performed, number of patients per study arm, screening questionnaire(s) used, and dosing schedule were obtained. Registered primary outcomes were compared to reported primary outcomes to evaluate overall study success. Additionally, secondary outcomes were extracted from all studies, regardless of whether they contributed to the qualitative synthesis.

Data synthesis

Studies were pooled in statistical meta-analysis using JBI System for the Unified Management, Assessment and Review of Information. Effect sizes were expressed as weighted final postintervention mean differences and 95% confidence intervals (CIs) were calculated for analysis. Meta-analysis was only performed for outcomes that were comparable at a specific time point across ≥3 included studies. For the outcome of postoperative opioid use, only 24-hour, 48-hour, and 72-hour opioid use analyzed as long-term data were reported in <3 of the included studies. Values were converted to morphine milligram equivalents as needed. The outcome of VAS pain with movement (VAS-M) and VAS pain at rest (VAS-R) were obtained baseline, postoperative day (POD) 1, POD 3, POD 7, POD 14, postoperative week 6, and postoperative month 3, as these were reported in ≥3 studies. VAS scores reported on a 0-100 scale were converted to a 0-10 scale to maintain consistency across studies. Additionally, for 2of the included studies, reported average pain severity was used for pain at rest and reported pain with general activity was used for pain with movement [17,18]. When studies did not report the standard deviation (SD), they were calculated from the standard error or 95% CI using the Cochrane method. The SD was calculated from the 95% CI using critical values from the t-distribution because studies tended to have small sample sizes. In cases where the SD was not reported or could not be calculated, the corresponding author was contacted via email. The mean was calculated from the median and interquartile range as suggested by Wan et al. [19].

Statistical analyses were performed using inverse variance with random effects [20]. Heterogeneity was assessed statistically using the standard chi-squared and I-squared tests. A funnel plot was not utilized to assess for publication bias as there were fewer than 10 studies included in the meta-analysis.

Results

Nine randomized controlled studies qualified for inclusion. However, 2 of these studies used the same dataset, leaving 8 unique study populations for final analysis (Table 1). Seven authors were contacted to solicit missing information. Three authors responded with data, 2 of which could be included in the meta-analysis. The remaining were excluded because values lacked information needed to perform meta-analysis (eg, no SD or 95% CI reported). All but 1 study at least partially registered the study trial and prespecified the primary outcome. Six studies investigated duloxetine for TKA, 1 study investigated duloxetine for THA, and 1 study investigated both TKA and THA. Three studies failed to use a true placebo. There was also variable use of screening questionnaires, with the Central Sensitization Inventory and Hamilton Depression Scale most frequently used.

Qualitative review of outcome data demonstrated a high degree of heterogeneity, variable success, and robust safety profile. Most notably, among the studies that specified their primary outcome (ie, trial registration or published protocol), only 3 studies fully achieved their primary aim [17,25,26]. A fourth study was partially successful [18]. Of the 307 unique patients treated with duloxetine, no significant adverse events were reported.

Quantitative analysis of studies reporting postoperative opioid consumption

Seven of the 8 included studies reported data on opioid consumption. After contacting authors, 5 of these studies provided potentially analyzable data and therefore were included in the final analysis on opioid consumption (Fig. 2). The only time points that were reported in at least 3 studies were 24, 48, and 72 hours. In studies where duloxetine was compared to placebo or no treatment, there was no significant difference in opioid consumption at 24 hours (weighted mean difference [WMD]: −2.64; 95% CI: −11.81, 6.53; $P = .573$). However, patients receiving duloxetine required less opioids at 48 (WMD: −11.98; 95% CI -21.32, −2.65; $P = .012$) and 72 (WMD: −10.73; 95% CI -21.37, −0.09; $P = .048$) hours.

Quantitative analysis of studies reporting pain scores

All of the included studies had potentially analyzable data for VAS. However, data from Rienstra et al. [23] were excluded from the meta-analysis as baseline VAS scores between duloxetine and control groups showed statistical significance. As such, 7 studies were included overall in the final analysis of VAS scores between duloxetine and comparator treatments. (Figs. 3 and 4) There was no significant difference in baseline VAS-R or VAS-M scores among the included studies. For VAS-R, significantly reduced pain was reported by duloxetine-treated patients at POD 3 (WMD: −0.52; 95% CI: −0.83, −0.22; $P = .001$), POD 7 (WMD: −0.80; 95% CI: −1.38, −0.22; $P = .007$), and postoperative week 6 (WMD: −2.01; 95% CI: −2.41, −1.61; $P < .001$). For VAS-M, significantly reduced pain was reported by duloxetine-treated patients at POD 1 (WMD: −0.72; 95% CI: −1.31, −0.13; $P = .016$), POD 3 (WMD: −0.56; 95% CI: −0.99, −0.12; $P = .012$), POD 7 (WMD: −0.96; 95% CI: −1.41, −0.50; $P < .001$), POD 14 (WMD: −1.02; 95% CI: −1.72, −0.33; $P = .004$), postoperative week 6 (WMD: −1.41; 95% CI: −1.79, −1.02; $P < .001$), and postoperative month 3 (WMD: −0.80; 95% CI: −1.56, −0.04; $P = .038$).

Discussion

Our review of the literature indicates that the use of perioperative duloxetine in lower extremity TJA may effectively decrease pain and postoperative opioid use. These findings are similar to a meta-analysis published recently by Branton et al. [10], which found lower postoperative opioid use with duloxetine at 24 and 48 hours in patients undergoing elective orthopaedic surgery. The nonsignificant difference in 24-hour opioid use in this meta-analysis is due to the inclusion of unpublished data from a recently published study [26]. The safety data and lack of severe adverse events observed presently is also consistent with other reviews, which have shown that duloxetine is generally safe and well-tolerated, with few serious side effects reported, particularly at doses not exceeding 60 mg/d [27–30]. While study heterogeneity precludes strong recommendations regarding the optimal patient population and dosing schedule, this quantitative meta-analysis provides the strongest evidence to date that duloxetine improves postoperative pain without causing major adverse events in lower extremity TJA.

Table 1
Overview of included studies. Trial success determined based on weather or not the study achieved statistical significance of their registered primary outcome.

Study	Methodology				Intervention		Outcomes		
	Registration	Surgery	Patients per study arm	Screening questionnaire	Presurgery dosing	Postsurgery dosing	Primary outcome	Statistically Significant Secondary Outcomes	Statistically insignificant Secondary outcomes
Ho, 2020 [21]	Not registered	TKA	Duloxetine (n = 25); placebo (n = 25)	None	60 mg, 2 h preoperative	60 mg on POD 1	N/A	Opioid consumption	Pain at all time points; Adverse events
YaDeau, 2016 [22]	Methodology consistent with registration	TKA	Duloxetine(n = 53) Placebo (n = 53)	None	60 mg, 30 min preoperative	60 mg/ d until POD 14	Failed	Opioid consumption	NRS-pain length of stay; disposition at discharge; HADS; painDETECT; Knee Society Score; number of manipulations; adverse events
Rienstra, 2021 [23]	Methodology consistent with registration	THA or TKA	Duloxetine (n = 54); No tx (n = 57)	m-PDQ	10 wk total: 60 mg for 7 wk; 30 mg for 1 wk dose escalation; 2 wk taper	None	Failed	None	KOOS or HOOS; mPDQ
Kim, 2021 [24]	Trial ended prematurely	TKA	Duloxetine(n = 20); placebo (n = 20)	CSI	30 mg for 2 wk	8 wk	Failed	Postoperative opioid use; VAS-pain up to 6 weeks; BPI at 2, 6 and 12 wk; wound temp	ROM; rate of wound complications; CRP level; VSS score; adverse events
Koh, 2019 [18]	Methodology consistent with registration	TKA	Duloxetine (n = 40); no tx (n = 40)	CSI; HAMD	30 mg, starting 1 d before surgery	30 mg/d for 6 wk	Success -Reduced pain up to 12 wk	BPI subdomains; SF-36 from 2 to 12 wk; satisfaction at 12 wk	Opioid consumption; adverse events
Li, 2021 [19]	Failed to specify which VAS subscore would primary or their outcome timepoints; otherwise consistent with registration	THA	Duloxetine (n = 48); no tx (n = 48)	HAMD; HAMA	60 mg, 2 d preoperative	60 mg/d for 14 d	Partial success; reduced pain up to 3 wk and opioid consumption up to 1w	Patient satisfaction; opioid consumption	MCID for pain; pain scores at 3 months; length of hospital stay; VAS-resting pain after 3 mo; HHS knee score; adverse events
YaDeau, 2022 [25]	Methodology consistent with registration	TKA	Duloxetine (n = 80); no tx (n = 80)	None	60 mg, preoperative	60 mg/d for 14 d	Success − Reduced opioid use (d 14);reduced pain with movement (d 14)	Satisfaction, BPI, KOOS JR	PROMIS Depression and anxiety; length of stay; pain at rest; neuropathic pain; QoR9; compliance
Yuan, 2022	Methodology consistent with registration[a]	TKA	Duloxetine (n = 50); no tx (n = 50)	HAMD; HAMA	60 mg starting on preoperative d 2	60 mg/day for 14 d	Success - Reduced pain at rest and with movement (d 1 and 14); reduced opioid consumption (d 1 and 14)	Active and passive ROM (up to 6 and 5 d, respectfully), nausea/ vomiting and constipation (placebo group); drowsiness (duloxetine group)	Other AEs (dizziness, bleeding, sweating, fatigue, dry mouth); Note: authors failed to report the following prespecified secondary outcomes: Timed Up & Go Test, KSS, WOMAC, SF-12

TKA, total knee arthroplasty; POD, postoperative day; N/A, not applicable; NRS, numeric rating scale; HADS, hospital anxiety and depression scale; THA, total hip arthroplasty; HOOS, hip dysfunction and osteoarthritis outcome score for joint replacement; KOOS JR, knee dysfunction and osteoarthritis outcome score for joint replacement; m-PDQ, modified PainDETECT questionnaire; CSI, central sensitization inventory; VAS, visual analog scale; BPI, brief pain inventory; ROM, range of motion; CRP, C-reactive protein; VSS, Vancouver Scar Scale; SF, short form; KSS, Knee Society Score; WOMAC, The Western Ontario and McMaster Universities Arthritis Index Hamilton Depression Scale (HAMD); HAMA, Hamilton Anxiety Scale; MCID, minimum clinically important difference; HSS, hospital for special surgery; PROMIS, patient-reported outcomes measurement information system; QoR9, quality of recovery-9.

[a] Outcome timepoints not specified on Chinese Clinical Trial Registry.

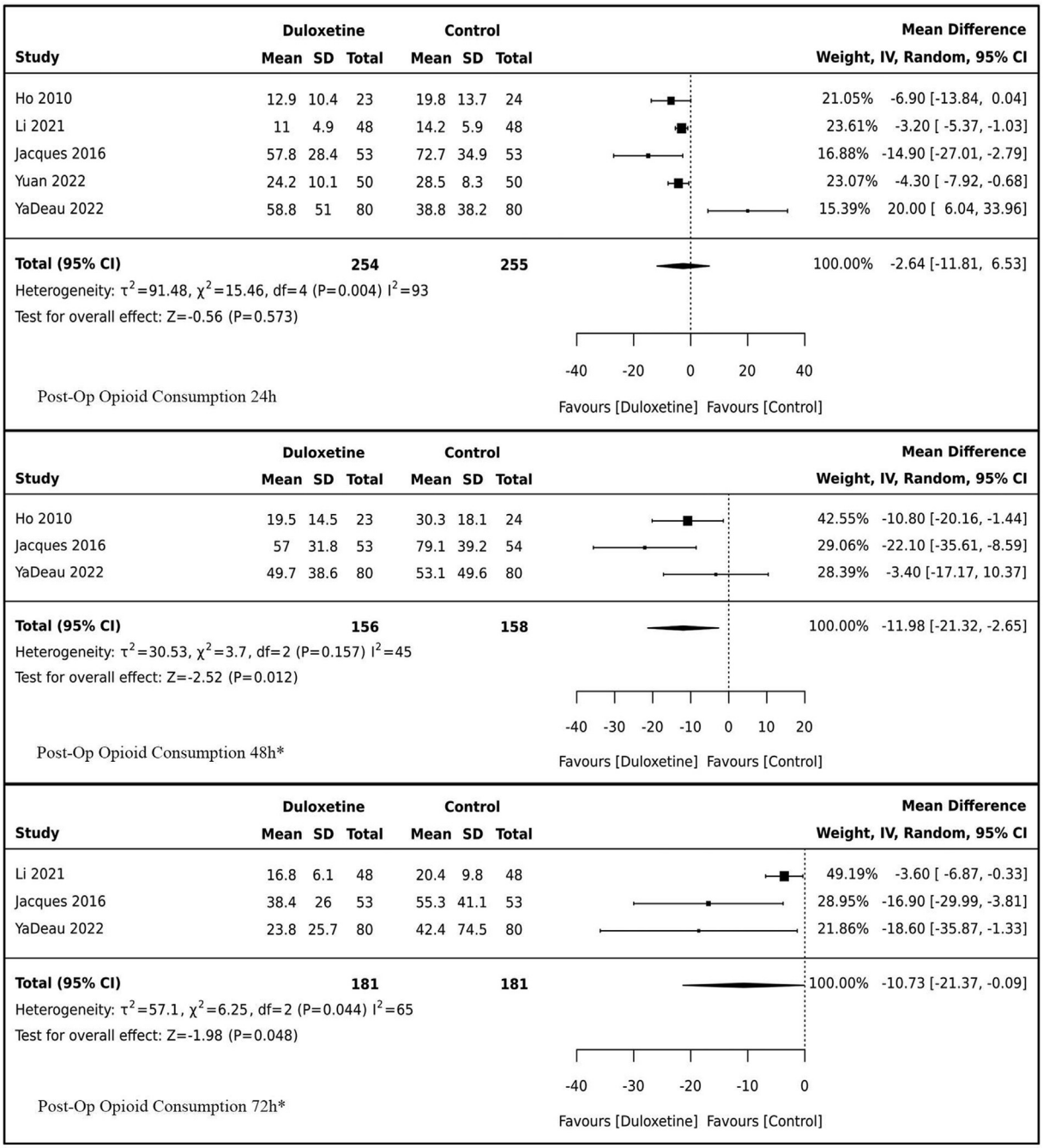

Figure 2. Forest plot of the weighted mean difference (WMD) in 24, 48, and 72-hour postoperative opioid consumption.

The findings presented in this meta-analysis should be carefully considered in the context of the dosing regimen used in each individual study, which includes the total dose given as well as the dose duration and timing relative to surgery. The dosage of duloxetine should be ≥ 60 mg when treating neuropathic pain [12]. However, almost a third of the studies included in this review used 30mg. Interestingly, Koh et al. was among the studies that used a 30-mg dose yet produced some of the most promising data [17]. This could be due to a greater relative importance of the duration and timing of duloxetine employed than the dose utilized. It has been shown that it takes ≥6 weeks of duloxetine use before peak improvements in osteoarthritic pain are attained [12,31,32]. The findings of Koh et al. [17] and Kim et al. [26] (both of whom used 30 mg of duloxetine daily) provides support for this hypothesis. Koh et al. started dosing patients 1 day before surgery. While they failed to show a difference in opioid consumption or pain at 72 hours, they had better performance across pain metrics between 2 and 12 weeks. In contrast, Kim et al. [26] dosed patients for 2 weeks prior to surgery and observed an inverse finding—decreased opioid consumption and postoperative pain at 72 hours but no difference in pain at 12 weeks.

Further support for the importance of dosing schedule comes from the largest study included in this review [26]. Patients were given a 60-mg dose for 14 days starting on POD 0. The primary outcomes of pain and opioid use at 14 days showed significant benefit compared to the placebo, but pain scores at earlier time

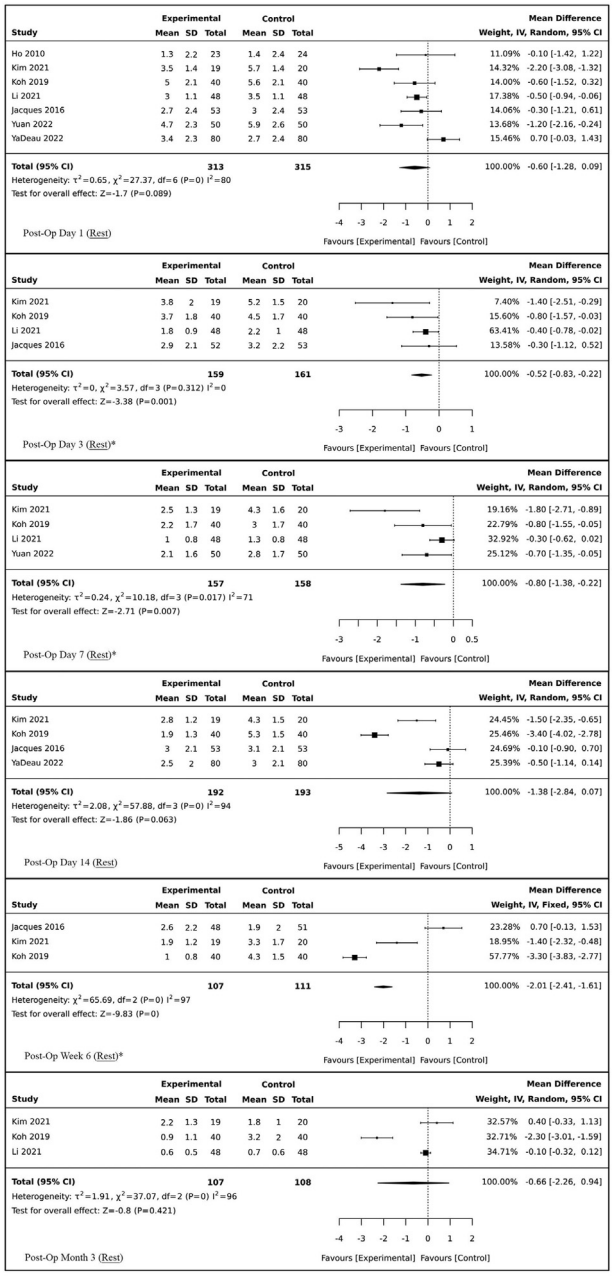

Figure 3. Forest plot of the weighted mean difference (WMD) in pain at rest between platelet-rich duloxetine and comparator treatments. Statistically significant time points are marked with an asterisk.

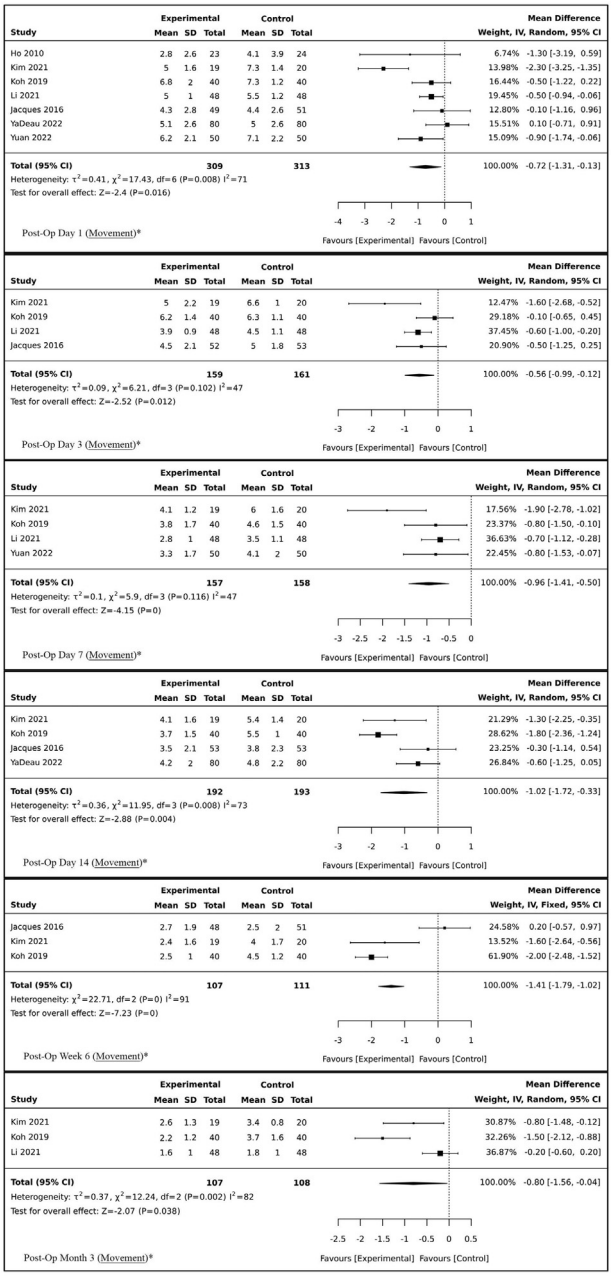

Figure 4. Forest plot of the weighted mean difference (WMD) in pain with movement between platelet-rich duloxetine and comparator treatments. Statistically significant time points are marked with an asterisk.

points were noninferior. Prior to inclusion of the data by YaDeau et al., several earlier time points had been significant and the effect size for pain scores at POD 14 had been notably larger. In their study, the general lack of significant differences during the first postoperative week is reasonable given that dosing did not start until POD 0. As discussed, the benefits of duloxetine would be expected to start around POD 14 and would not be expected to peak for another several weeks. This hypothesis is supported by the fact that they found significant improvements knee pain and the Knee Dysfunction and Osteoarthritis Outcome Score for Joint Replacement at 3 months. It should also be emphasized that these improvements occurred in patients well after the effects of treatment should have subsided. This suggests long-term benefits of treatment beyond the effects of the drug alone, which have yet to be explained.

One of the prevailing questions when considering the use of duloxetine in the surgical setting is whether it decreases central and/or peripheral sensitization. This was explicitly investigated by Rienstra et al. [23], who hypothesized that targeted treatment aimed at desensitization prior to surgery would reduce chronic residual pain postoperatively. In their unblinded trial, duloxetine was given for 10 weeks then stopped prior to surgery. A difference was not demonstrated, leading the authors to conclude that preoperative targeted treatment with duloxetine does not influence postoperative chronic, residual pain after TKA or THA. In contrast, Koh et al. [17] dosed patients for 6 weeks postoperatively and found significant differences in pain at 12 weeks, well after the drug had been discontinued. Similarly, YaDeau et al. [26] dosed patients for 14 days after surgery and found significant

improvements in opioid consumption. The apparent difference suggests that managing pain in the postoperative period may be more important than in the preoperative period for limiting pain sensitization. Future large-scale follow-up studies aimed at reducing long-term pain should strongly consider continuing treatment during the postoperative period. However, preoperative dosing should not be discounted entirely. The dosing regime by Rienstra et al. [23] was atypical in how dosing was tapered in the weeks leading up to surgery. As discussed, preoperative dosing may be an important strategy for decreasing postoperative opioid use [24].

Among all surgeries, TKA has 1 of the widest ranges of postoperative pain [33]. As such, the success of future large-scale clinical trials will likely require target population optimization, which can be achieved through screening questionnaires. These questionnaires fall broadly into 2 categories: (1) those focused on identifying patients with underlying psychiatric pathology (eg, anxiety, depression) and (2) those aimed at identifying patients with preoperative pain catastrophizing. Attempts to target and/or exclude patients with psychiatric illness is reasonable given the proven efficacy of duloxetine in treating depression and anxiety, as well as potential transitory worsening of some symptoms when starting treatment [34]. Moreover, preoperative depression and anxiety are associated with heightened pain at 1 year for TKA, even in the absence of clinical or radiographic abnormalities [35]. Pain catastrophizing is a negative cognitive–affective response to anticipated or actual pain and has been associated with a number of important pain-related outcomes [36,37]. Surgery patients with high levels of preoperative pain catastrophizing have lower physical function, more pain, and worse overall health both before and after surgery [38–41].

In summary, duloxetine appears to safely decrease postoperative pain and opioid consumption following TJA. The major limitations of this study include inconsistent placebo use and heterogeneous dosing regimens. Nevertheless, this review provides sufficient safety and preliminary efficacy data to support large-scale clinical trials aimed at establishing the optimal dose, duration, and target population for duloxetine use in lower extremity TJA. In addition, the available data suggest that 3 principal factors be considered when designing future clinical trials. First, dosing should continue for at least 2 weeks postoperatively, and preoperative dosing should be considered for studies that aim to decrease opioid use in the first 24- to 72-hour postoperative period. Second, a dose of at least 60 mg should be considered, as this is the Food and Drug Administration–approved target dose for chronic musculoskeletal pain. Finally, at least 1 screening questionnaire aimed at assessing pain catastrophizing and/or anxiety should be implemented as a way to stratify patients and maximize effect size.

Conflicts of interest

The authors declare there are no conflicts of interest. For full disclosure statements refer to https://doi.org/10.1016/j.artd.2023.101097.

Acknowledgments

None.

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Appendix 1

Working collaboratively with a librarian (LSM), a three-step search strategy was implemented. First, an initial limited search of MEDLINE (PubMed) and Google Scholar was performed to identify articles on the topic. Second, the text words contained in the titles and abstracts of relevant articles and the MeSH (Medical Subject Headings) terms used to describe them were used to develop a full search strategy in the PubMed, Scopus, The Cochrane Central Register of Controlled Trials (CENTRAL), Web of Science, and CINAHL Complete via EBSCOhost electronic databases. This search strategy was adapted for each included database and/or information source and carried out on December 1st, 2021. Third, references of systematic reviews on the same or similar topic were examined. References from the included studies were also reviewed to identify new studies that were not found in database searches. Only full text articles published in English were included. No date restrictions on the search strategy were imposed. An updated search was performed on July 1st, 2022 to determine if new studies were published since the initial search was conducted.

PubMed search strategy:

#1 (duloxetine OR Cymbalta OR Irenka OR Duloxetine Hydrochloride) AND (Arthroplasty, Replacement OR Hip replacement OR knee replacement).

#2 (duloxetine OR Cymbalta OR Irenka OR Duloxetine Hydrochloride) AND Arthroplasty AND (Hip OR knee).

#3 (#1 OR #2) Filters: English.

Appendix 2

The following were the questions asked through JBI SUMARI to discern which studies would be included and which would be excluded:

1. Was true randomization used for assignment of participants to treatment groups?
2. Was allocation to treatment groups concealed?
3. Were treatment groups similar at the baseline?
4. Were participants blind to treatment assignment?
5. Were those delivering treatment blind to treatment assignment?
6. Were outcomes assessors blind to treatment assignment?
7. Were treatment groups treated identically other than the intervention of interest?
8. Was follow up complete and if not, were differences between groups in terms of their follow up adequately described and analyzed?
9. Were participants analyzed in the groups to which they were randomized?
10. Were outcomes measured in the same way for treatment groups?
11. Were outcomes measured in a reliable way?
12. Was appropriate statistical analysis used?
13. Was the trial design appropriate, and any deviations from the standard RCT design (individual randomization, parallel groups) accounted for in the conduct and analysis of the trial?