META-ANALYSIS

Perioperative Analgesic Interventions for Reduction of Persistent Postsurgical Pain After Total Hip and Knee Arthroplasty: A Systematic Review and Meta-analysis

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BACKGROUND: High pain levels immediately after surgery have been associated with persistent postsurgical pain. Still, it is uncertain if analgesic treatment of immediate postsurgical pain prevents the development of persistent postsurgical pain.
METHODS: We searched MEDLINE, CENTRAL, and Embase up to September 12, 2023, for randomized controlled trials investigating perioperative analgesic interventions and with reported pain levels 3 to 24 months after total hip or knee arthroplasty in patients with osteoarthritis. The primary outcome was pain score 3 to 24 months after surgery, assessed at rest and during movement separately. Two authors independently screened, extracted data, and assessed risk of bias using the Cochrane Risk of Bias 2 tool. We conducted meta-analyses and tested their robustness with trial sequential analyses and worst-best and best-worst case analyses.
RESULTS: We included 49 trials with 68 intervention arms. All but 4 trials were at high risk of bias for the primary outcome. Moreover, the included trials were heterogeneous in terms of exclusion criteria, baseline pain severity, and which cointerventions the participants were offered. For pain at rest, no interventions demonstrated a statistically significant difference between intervention and control. For pain during movement, perioperative treatment with duloxetine (7 trials with 641 participants) reduced pain scores at 3 to 24 months after surgery (mean difference −4.9 mm [95% confidence interval {CI}, −6.5 to −3.4] on the 0–100 visual analog scale) compared to placebo. This difference was lower than our predefined threshold for clinical importance of 10 mm.
CONCLUSIONS: We found no perioperative analgesic interventions that reduced pain 3 to 24 months after total hip or knee arthroplasty for osteoarthritis. The literature on perioperative analgesia focused little on potential long-term effects. We encourage the assessment of long-term pain outcomes. (Anesth Analg 2025;141:765–778)

KEY POINTS

- **Question:** Can perioperative analgesic interventions reduce persistent postsurgical after total hip or knee arthroplasty?
- **Findings:** Only few, heterogenous trials reported long-term pain outcomes and none of the meta-analyses suggested an important effect.
- **Meaning:** Currently, no perioperative analgesic interventions can reduce persistent postsurgical pain after total hip or knee arthroplasty for osteoarthritis (low certainty of evidence).

With improved health care accessibility and increased life expectancy, more patients with osteoarthritis are now offered total hip and knee arthroplasties.[1] Most patients recover well after surgery, yet up to 20% experience moderate to severe persistent postsurgical pain, that is, pain lasting >3 months after surgery.[2,3]

Persistent postsurgical pain has severe consequences for both patients and society and is difficult to manage clinically.[4,5] With general inadequacy of analgesic treatment options for persistent postsurgical pain,[6,7] patients are often prescribed opioids despite the risk of dependency, abuse, and well-known adverse effects.[8] Additionally, high pain intensity

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immediately after surgery has been associated with persistent postsurgical pain.[9] It is, however, unknown if analgesic treatment of immediate postsurgical pain prevents development of persistent postsurgical pain.[10–12] This stresses the need for interventions that can prevent persistent postsurgical pain after hip and knee arthroplasty, including existing perioperative analgesic treatments.

With this procedure-specific systematic review, we aimed to investigate if perioperative analgesic interventions, compared to placebo or no interventions reduce pain levels 3 to 24 months after total hip and knee arthroplasty.

METHODS

The reporting of this review followed the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) statement.[13] The Regional Institutional Review Board for the Capitol Region of Denmark waived approval for this study. We registered the review in the International Prospective Register of Systematic Reviews (PROSPERO) with identifier CRD42021284175 on November 19, 2021 and published the protocol.[14] The full dataset and statistical code is available from the corresponding author.

Eligibility Criteria

We included randomized controlled trials (RCTs) investigating medical interventions for immediate pain control after total hip or knee arthroplasty in adults with osteoarthritis. We excluded quasi-randomized trials, conference abstracts, and trials with crossover designs. We also excluded trials that explicitly included patients undergoing hip hemiarthroplasty, unicondylar knee arthroplasty, one-stage bilateral surgery, or patient operated for indications other than osteoarthritis. We sought to translate trials reported in languages other than English, which were included if translations were deemed accurate. Lastly, we excluded trials where none of the outcomes of interest to the present review were available, either from the trial reports or after contact to the trial's corresponding author.

Information Sources

We searched the CENTRAL, MEDLINE, and Embase for eligible trials from inception to September 12, 2023. Search strategies are available in Supplemental Digital Content 1, Appendix 1, http://links.lww.com/AA/F31.

Selection Process

Two authors (J.L. and A.K.) independently screened titles and abstracts. J.L. sent a standardized letter requesting summarized outcome data to authors of articles where pain outcomes between 3 and 24 months after surgery were not reported (Supplemental Digital Content 1, Appendix 2, http://links.lww.com/AA/F31). J.L. and A.K. independently assessed full text for eligibility. Disagreements regarding inclusion were resolved with help from M.M.

Data Collection Process

Two of 3 authors (J.L. and A.K./M.M.) independently extracted data from each included trial into a predefined extraction spreadsheet. We assessed all supplementary materials and online trial registrations for relevant information. We screened reference lists to identify other potentially includable trials.

Data Items

For each trial, we registered *baseline data* (country and year of conduct, number of centers, type of anesthesia, type of surgery, exclusion criteria, and analgesic interventions imposed on both groups), *participant data* (age, sex, body mass index [BMI], American Society of Anesthesiologists [ASA] score, and preoperative pain score) and *intervention data* (dose, intensity, duration, and timing).

The primary outcome was pain scores at 3 to 24 months after surgery. Persistent postsurgical pain is defined in the International Classification of Diseases, 11th Revision (ICD-11) as pain "persisting beyond the healing process, i.e. at least 3 months after surgery or tissue trauma."[3] We added a 24-month upper limit to reduce interference with other pain conditions, for example, pain from the contralateral joint. We extracted and reported pain scores at rest and during ambulation separately. When the state of pain measurement (ie, at rest or during movement) was not explicitly reported, we categorized the pain score as "at rest." When pain scores were reported during multiple states of movement, for example, walking, running, or climbing stairs, we used the movement that produced the highest pain scores to increase assay sensitivity. We converted compatible pain scores to millimeters on the 0 to 100 mm visual analog scale. A 10-mm difference in mean pain score between groups was considered the minimal important difference.[15,16]

The review had 2 secondary outcomes: (1) the number of patients with either persistent pain or opioid use 3 to 24 months after surgery, because we expected some trialists would report this rather than mean pain scores.[17] (2) The number of patients experiencing 1 or more serious adverse events (SAE) within 24 months after surgery.[18] An arbitrary minimal important difference of 10% relative difference was chosen for the 2 secondary outcomes.[16]

We used the earliest reported assessment between 3 and 24 months. When summary statistics were not reported as numbers, we approximated the estimate

and variation from figures using Plot Digitizer (www.plotdigitizer.com).

Trial Risk of Bias Assessment

Two of 3 authors (J.L. and A.K./M.M.) evaluated each reported outcome in all trials for risk of bias using Cochrane's Risk of Bias 2 Excel tool.[19] We evaluated 5 risk of bias domains: randomization process, deviations from intended interventions, missing outcome data, outcome measurement, and selection of the reported results. The overall risk of bias of an outcome was considered high if 1 or more of these domains were deemed at high risk or "some concerns." We contacted authors of trials where clarification could change the overall risk of bias assessment.

Effect Measures

We presented differences in pain scores between groups as mean differences with 95% confidence intervals (CIs). We presented secondary outcomes as risk ratios with 95% CIs.

Synthesis Methods

We grouped the interventions based on type of drug and route of administration before any meta-analyses were conducted. We originally planned to conduct meta-analyses of only 2 comparable trials but chose post hoc to only conduct meta-analyses when 3 or more grouped trials reported the same outcome. The reported summary statistics were converted (eg, from median to mean, CI to standard deviation, etc) in R statistical software (R Core Team, R Foundation for Statistical Computing) according to the methods proposed in the Cochrane Handbook.[20] We used the R package *meta* to conduct meta-analyses and create forest plots.[21]

Estimates were presented with 95% CIs in both fixed- and random-effects models. Conclusions were based on the most conservative estimate.[22] Statistical heterogeneity was evaluated by visual inspection of forest plots; χ^2 tests; and I^2, and tau statistics.

Repeated meta-analyses, for example, each time a new trial is published, are prone to type I errors (false positives) and type 2 errors (false negatives).[23,24] To control for these errors, we conducted trial sequential analyses. We used an alpha-value of 5%, a beta-value of 20%, and for the primary outcome: a mean difference of 10 mm on the 0 to 100 VAS scale. For our secondary dichotomous outcomes, we used a relative risk difference of 10%. The proportion of patients at risk in the control group and statistical diversity were derived from the meta-analyses.

We scored the clinical differences between grouped trials with the Clinical Diversity In Meta-analyses (CDIM) tool[25] and conducted subgroup analyses based on type of surgery (hip versus knee arthroplasty), type of anesthesia (general versus regional anesthesia), and risk of bias assessment (low versus high risk of bias trials). We also planned to conduct meta-regression analyses on the timing of outcome assessment, when >10 grouped trials reported an outcome at more than 1 timepoint within 3 to 24 months after surgery.

To assess the robustness of the results, we conducted best-worst and worst-best-case analyses.[22] These analyses measure the impact of missing data, by assigning patients lost to follow-up beneficial outcome values in the intervention group and detrimental values in the control group (best-worst case) and vice versa (worst-best case).

Assessment of Nonreporting Bias

We planned to use funnel plots and relevant quantitative tests (eg, Egger, Harbord, Rücker) to assess nonreporting bias, but only when at least 10 trials were included in a meta-analysis.

Certainty Assessment

We used the Grading of Recommendations, Assessment, Development and Evaluation (GRADE) approach to rate and present the evidence.[26,27] The GRADE assessment of certainty is based on 5 domains: risk of bias, inconsistency, indirectness, imprecision, and publication bias.

RESULTS

Trial Selection

We screened a total of 44,206 citations (Figure 1). Of the 1003 citations that were reviewed in full-text, the main reason for exclusion was no reporting of long-term pain outcomes (778 trials; 78%). We included 49 trials with 68 intervention arms. No included trials used cluster randomization. We focused on pooled estimates from meta-analyses to avoid repeating already reported findings. Thus, results from interventions with outcome data from only 1 or 2 trials were not presented.

Trial Characteristics

A list of included studies can be found in Supplemental Digital Content 1, Appendix 3, http://links.lww.com/AA/F31. The characteristics of the individual intervention arms are presented in the Table. Of note, interventions were grouped primarily by type of drug and place of administration. Thus, the dose, timing, and duration of the intervention may vary considerably between interventions in the same intervention group. The included trials also differed in terms of exclusion criteria, baseline pain severity, and which cointerventions the participants were offered (ranging from 'as needed' medication alone, to comprehensive

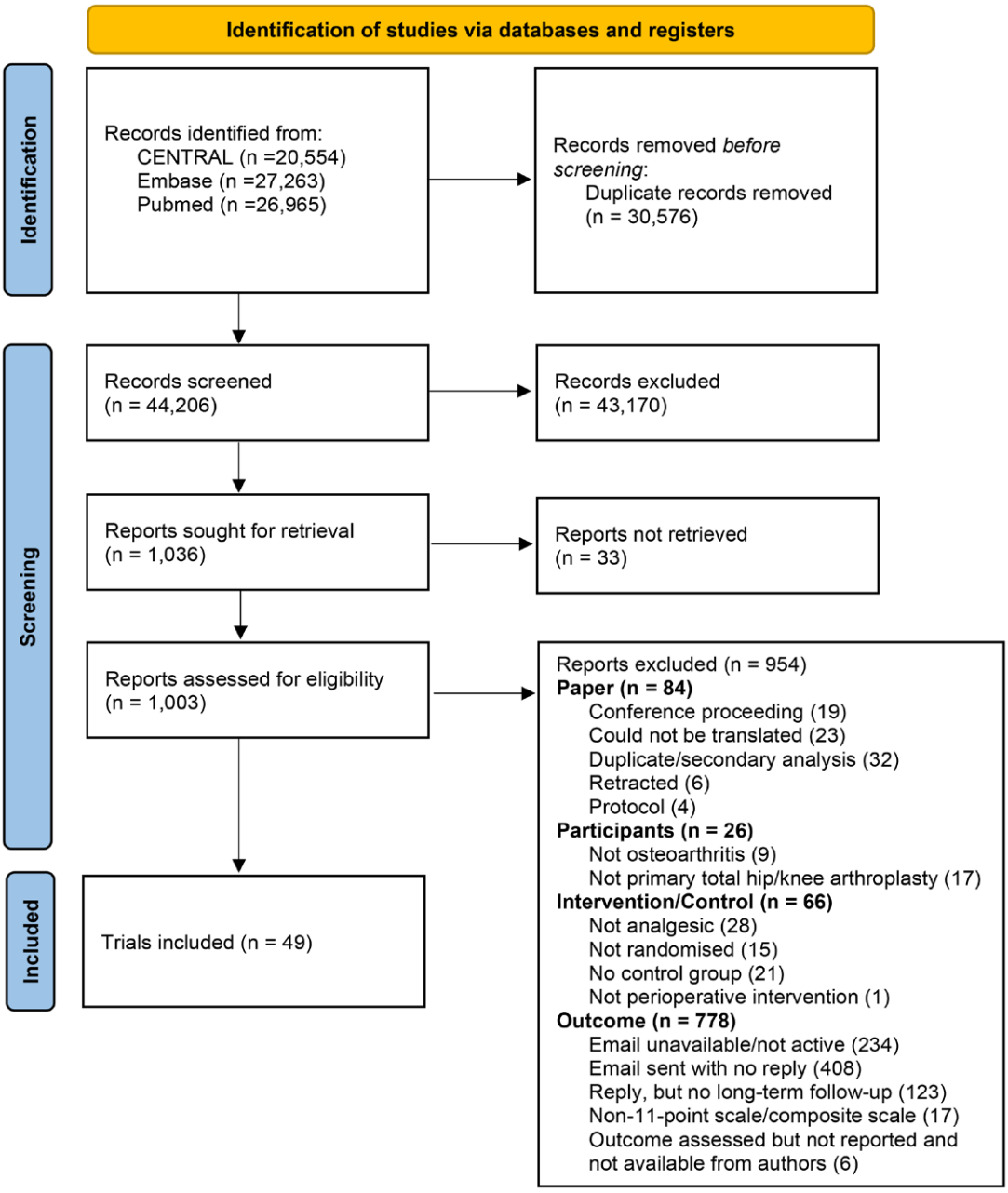

Figure 1. PRISMA flow chart.

multimodal analgesia). Overall, this resulted in moderate clinical diversity in most meta-analyses (Supplemental Digital Content 1, Appendix 4, http://links.lww.com/AA/F31).

Risk of Bias

Four trials were rated as low risk of bias for at least 1 outcome (Supplemental Digital Content 1, Appendix 5, http://links.lww.com/AA/F31). The most frequent reasons for high risk of bias ratings were lack of a predefined statistical analysis plan or lack of blinding. Consequently, all meta-analyses in this review were based on high risk of bias trials.

Pain Scores Assessed 3 to 24 Months After Surgery

Pain scores at rest were reported in 6 glucocorticoid trials, 6 local infiltration analgesia trials, 5 duloxetine, and 4 nonsteroidal anti-inflammatory drug (NSAID) trials (Figure 2). Pain scores during ambulation were reported in 4 glucocorticoid trials, 5 local infiltration analgesia trials, and 7 duloxetine trials (Figure 3).

Only the meta-analysis of perioperative treatments with duloxetine resulted in a statically significant reduction in pain score during movement 3–24 months after surgery (mean difference –4.9 mm [95% CI –6.5 to –3.4 and trial sequential analysis-adjusted: –6.6 to –3.3]). This difference was lower than our predefined threshold for

Table. Characteristics of Trial Interventions

Type of intervention	First author, publication year (country)	Brief description of intervention	Presurgical pain at rest (0–100)[a]	Anesthesia	Surgery	Components of the acute analgesic regimen (rescue analgesia)	Postsurgical pain scores intervention group versus control group	Total patients analyzed (% of randomized)
Systemic pharmacological interventions								
Chlorzoxazone	Skrejborg 2020 (Denmark)[b]	750 mg chlorzoxazone from surgery to POD7	34	Regional	THA	PCM, NSAID (Mixed opioids)	12-month pain score at rest: 5 (1) vs 5 (1) 12-month pain score during movement: 7 (1) vs 7 (1)	178 (91%)
Chlorzoxazone	Skrejborg 2020 (Denmark)[b]	750 mg chlorzoxazone from surgery to POD7	35	Regional	TKA	PCM, NSAID, LIA (Mixed opioids)	12-month pain score at rest: 9 (2) vs 10 (1) 12-month pain score during movement: 7 (1) vs 7 (1)	173 (87%)
Dexmedetomedine	Gao 2022 (China)	1 μg/kg dexmedetomidine bolus + infusion 0.4 μg/kg/h during surgery + dexmedetomidine in PCA (0.027 μg/kg/h + boli) to POD2	14	General	TKA	NSAID, LIA, femoral nerve block (PCA sufentanil with baseline infusion)	12-month pain score at rest: 9 (7) vs 10 (7) 12-month pain score during movement: 33 (9) vs 37 (9)	95 (97%)
Duloxetine	Ding 2023 (China)	60 mg/d duloxetine from surgery to POD7	31	General	THA	NSAID, LIA (IV morphine)	3-month pain score at rest: 5 (5) vs 5 (5) 3-month pain score during movement: 6 (8) vs 10 (10)	67 (95%)
Duloxetine	Kim 2021 (Korea)	30 mg/d duloxetine from 2 wk before surgery to POD56	41	General	TKA	PCM, NSAID, pregabalin, LIA (PCA fentanyl with baseline infusion)	3-month pain score at rest: 22 (13) vs 28 (10) 3-month pain score during movement: 26 (13) vs 34 (8)	39 (97%)
Duloxetine	Koh 2019 (Korea)	30 mg/d duloxetine 1 d before surgery to POD42	NA	General	TKA	PCM, NSAID, pregabalin (PCA fentanyl with baseline infusion)	3-month pain score at rest: 9 (11) vs 19 (17) 3-month pain score during movement: 22 (12) vs 37 (16)	80 (100%)
Duloxetine	Rienstra 2021 (the Netherlands)	60 mg/d of duloxetine for 7 wk before surgery	53	NA	THA/TKA	NA (NA)	6-month pain score at rest: 21 (30) vs 16 (29) 6-month pain score during movement: 25 (30) vs 21 (29)	111 (100%)
Duloxetine	YaDeau 2016 (USA)	60 mg/d duloxetine from surgery to POD14	32	Regional	TKA	NSAID, adductor canal block (PO PCM and oxycodone)	3-month pain score during movement: 23 (23) vs 20 (19)	96 (90%)
Duloxetine	YaDeau 2022 (USA)	60 mg/d duloxetine from surgery to POD14	55	Regional	TKA	PCM, NSAID, LIA, adductor canal block, IPACK (PO oxycodone)	3-month pain score during movement: 17 (15) vs 27 (21)	148 (92%)
Duloxetine	Yuan 2022 (China)	60 mg/d duloxetine since preoperative day 2 to POD14	32	General	TKA	NSAID, LIA (Opioids, unspecified)	3-month pain score at rest: 8 (5) vs 10 (5) 3-month pain score during movement: 8 (5) vs 12 (5)	100 (100%)
Gabapentinoids	Ayad 2022 (USA)	600 mg gabapentin enacarbil x 2 daily, from 1 d presurgically to POD3	45	Regional	THA/TKA	No cointerventions (Opioids, unspecified)	No pain scores reported. Number of patients with persistent pain at 3 mo: 7/23 vs 3/28	51 (47%)
Gabapentinoids	Clarke 2009 (Canada)	600 mg gabapentin before surgery	NA	Regional	THA	PCM, NSAID (PCA morphine)	6-month pain score at rest: 31 (19) vs 34 (16)	17 (26%)
Gabapentinoids	Clarke 2009 (Canada)	600 mg gabapentin after surgery	NA	Regional	THA	PCM, NSAID (PCA morphine)	6-month pain score at rest: 31 (15) vs 34 (16)	14 (22%)
Gabapentinoids	Clarke 2014 (Canada)	600 mg gabapentin before surgery	NA	Regional	TKA	NSAID, femoral nerve block, sciatic nerve block (PCA morphine)	3-month pain score during movement: 16 (17) vs 12 (17)	145 (81%)

(*Continued*)

Table. Continued

Type of intervention	First author, publication year (country)	Brief description of intervention	Presurgical pain at rest (0–100)[a]	Anesthesia	Surgery	Components of the acute analgesic regimen (rescue analgesia)	Postsurgical pain scores intervention group versus control group	Total patients analyzed (% of randomized)
Gabapentinoids	Motififard 2023 (Iran)	900 mg/d gabapentin from 3 d before surgery and up to surgery	NA	Regional	TKA	PCM (PCA morphine)	0 (0) vs3 (6) 3-month pain score during movement:	129 (95%)
Gabapentinoids	YaDeau 2015 (USA)	100 mg/d pregabalin from surgery and until POD14 + 50 mg pregabalin on POD15 and POD16	NA	Regional	TKA	NSAID, femoral nerve block (PO PCM and oxycodone)	3-month pain score during movement: 20 (23) vs 20 (15)	35 (87%)
Gabapentinoids	YaDeau 2015 (USA)	200 mg/d pregabalin from surgery and until POD14 + 100 mg pregabalin on POD15 and POD16	NA	Regional	TKA	NSAID, femoral nerve block (PO PCM and oxycodone)	3-month pain score during movement: 19 (19) vs 20 (15)	38 (95%)
Gabapentinoids	YaDeau 2015 (USA)	300 mg/d pregabalin from surgery and until POD14 + 150 mg pregabalin on POD15 and POD16	NA	Regional	TKA	NSAID, femoral nerve block (PO PCM and oxycodone)	3-month pain score during movement: 17 (19) vs 20 (16)	38 (95%)
Glucocorticoids	Chan 2020 (China)	8 mg IV dexamethasone before surgery	NA	Regional	TKA	PCM, NSAID, pregabalin, LIA (PCA morphine)	3-month pain score at rest: 2 (0–5) vs 2 (0–5)	69 (100%)
Glucocorticoids	Chan 2020 (China)	16 mg IV dexamethasone before surgery	NA	Regional	TKA	PCM, NSAID, pregabalin, LIA (PCA morphine)	3-month pain score at rest: 2 (0–3) vs 2 (0–5)	68 (100%)
Glucocorticoids	Cheng 2019 (China)	125 mg IV methylprednisolone during surgery	6	Regional	TKA	PCM, NSAID, gabapentin, LIA (PCA morphine)	4-month pain score at rest: 12 (33) vs 7 (37)	60 (100%)
Glucocorticoids	Lei 2020 (China)	20 mg dexamethasone before surgery	23	General	THA	NSAID, pregabalin, LIA (IM morphine)	3-month pain score at rest: 0 (1) vs 1 (3) 3-month pain score during movement: 2 (4) vs 2 (5)	83 (100%)
Glucocorticoids	Lei 2020 (China)	10 mg dexamethasone before surgery +10 mg dexamethasone after surgery	23	General	THA	NSAID, pregabalin, LIA (IM morphine)	3-month pain score at rest: 1 (2) vs1 (3) 3-month pain score during movement: 2 (4) vs 2 (5)	82 (100%)
Glucocorticoids	Lei 2022 (China)	20 mg dexamethasone before surgery	24	General	TKA	NSAID, LIA (IM morphine)	3-month pain score at rest: 0 (1) vs 1 (2) 3-month pain score during movement: 2 (4) vs 2 (4)	96 (94%)
Glucocorticoids	Lei 2022 (China)	10 mg dexamethasone before surgery +10 mg dexamethasone after surgery	23	General	TKA	NSAID, LIA (IM morphine)	3-month pain score at rest: 1 (2) vs 1 (2) 3-month pain score during movement: 3 (4) vs 2 (4)	101 (99%)
Glucocorticoids	Sculco 2016 (USA)	20 mg prednisolone before surgery +100 mg IV hydrocortisone 8 and 16 h after first dose	NA	Regional	THA	- (NA)	3-month pain score at rest: 5 (7) vs 9 (8)	27 (67%)
Glucocorticoids	Wu 2023 (China)	10 mg dexamethasone in LIA +10 mg IV dexamethasone during surgery +10 mg IV dexamethasone after surgery	52	General	TKA	NSAID, LIA, PO oxycodone (SC morphine)	3-month pain score at rest: 21 (9) vs 20 (9)	87 (96%)
Glucocorticoids	Xu 2018 (China)	20 mg IV dexamethasone before surgery	NA	General	TKA	NSAID, LIA (PO oxycodone)	3-month pain score during movement: 2 (4) vs 2 (3)	90 (100%)
Glucocorticoids	Xu 2018 (China)	20 mg IV dexamethasone before surgery +10 mg IV dexamethasone on POD1 and POD2	NA	General	TKA	NSAID, LIA (PO oxycodone)	3-month pain score during movement: 1 (3) vs 2 (3)	92 (100%)

(*Continued*)

Table. Continued

Type of intervention	First author, publication year (country)	Brief description of intervention	Presurgical pain at rest (0–100)[a]	Anesthesia	Surgery	Components of the acute analgesic regimen (rescue analgesia)	Postsurgical pain scores intervention group versus control group	Total patients analyzed (% of randomized)
Glucocorticoids, additional dose	Lei 2020 (China)	10 mg IV dexamethasone 24 h post-op (in supplement to 10 mg pre-op)	23	General	THA	NSAID, LIA (IM morphine)	3-month pain score at rest: 1 (2) vs 1 (3) 3-month pain score during movement: 3 (1) vs 3 (5)	75 (100%)
Glucocorticoids, additional dose	Lei 2020 (China)	10 mg IV dexamethasone 24 h and 48 h post-op (in supplement to 10 mg pre-op)	23	General	THA	NSAID, LIA (IM morphine)	3-month pain score at rest: 0 (1) vs 1 (3) 3-month pain score during movement: 2 (4) vs 3 (5)	75 (100%)
Ketamine	Aveline 2014 (France)	0.2 mg/kg IV ketamine after induction +120 µg/kg/h ketamine during surgery +60 µg/kg/h ketamine to POD2	17	General	TKA	PCM, NSAID (PCA morphine)	6-month pain score at rest: 20 (10–30) vs 25 (11–34) 6-month pain score during movement: 30 (21–38) vs 35 (30–45)	35 (94%)
Lidocaine IV	Martin 2008 (France)	1.5 mg/kg lidocaine IV at induction +1.5 mg/kg/h lidocaine until 1 h postoperatively	39	General	THA	- (PCA morphine)	3-month pain score at rest: 6 (12) vs 5 (8) 3-month pain score during movement: 12 (11) vs 21 (25)	56 (93%)
Nefopam	Aveline 2014 (France)	0.2 mg/kg nefopam bolus after induction, 120 µg/kg/h nefopam during surgery, and 60 µg/kg/h nefopam until POD2	18	General	TKA	PCM, NSAID (PCA morphine)	6-month pain score at rest: 21 (10–34) vs 25 (11–34) 6-month pain score during movement: 31 (22–40) vs 35 (30–45)	34 (89%)
NSAIDs	Jianda 2016 (China)	400 mg celecoxib before surgery	62	Both	TKA	NSAID, LIA (SC morphine)	3-month pain score at rest: 0 (0) vs 0 (0) 3-month pain score during movement: 0 (0) vs 0 (0)	75 (100%)
NSAIDs	Meunier 2007 (Sweden)	400 mg/d celecoxib from surgery to POD21	54	Regional	TKA	PCM, PO tramadol (IV or SC ketobemidone)	3-month pain score at rest 15 (15) vs 8 (7)	44 (88%)
NSAIDs	Motififard 2023 (Iran)	400 mg/d celecoxib from 3 d presurgically to surgery	NA	Regional	TKA	PCM (PCA morphine)	3-month pain score at rest: 0 (2) vs 3 (6)	129 (95%)
NSAIDs	Vielpeau 1999 (France)	750 mg/d naproxen from surgery to POD42	NA	NA	THA	- (NA)	6-month pain score at rest: 30 (37) vs 38 (55)	30 (71%)
NSAIDs	Vielpeau 1999 (France)	75 mg/d indomethacin from surgery to POD42	NA	NA	THA	- (NA)	6-month pain score at rest: 27 (52) vs 38 (55)	33 (78%)
Opioids	Wang 2023 (China)	10 mg extended-release oxycodone hydrochloride before surgery	45	General	TKA	NSAID, pregabalin, LIA, adductor canal block (SC morphine)	3-month pain score at rest: 18 (8) vs 17 (7) 3-month pain score during movement: 28 (12) vs 26 (12)	100 (100%)
Regional anesthesia								
Adductor canal block	Mou 2022 (China)	Adductor canal block 20 ml 0.25% ropivacaine and 2.0 mg/mL epinephrine added to IPACK	23	General	TKA	NSAID, pregabalin, IPACK (PO oxycodone)	3-month pain score at rest: 10 (6) vs 10 (8) 3-month pain score during movement: 12 (8) vs 12 (8)	60 (100%)
Continuous femoral nerve block	Choi 2016 (Canada)	Continuous femoral nerve block with 0.2% 5 ml/h ropivacaine until POD 2	60	Regional	TKA	PCM, NSAID, gabapentin, femoral nerve block, PO hydromorphone (PCA hydromorphone)	4.5-month pain score at rest: 24 (25) vs 21 (20)	72 (91%)

(*Continued*)

Table. Continued

Type of intervention	First author, publication year (country)	Brief description of intervention	Presurgical pain at rest (0–100)[a]	Anesthesia	Surgery	Components of the acute analgesic regimen (rescue analgesia)	Postsurgical pain scores intervention group versus control group	Total patients analyzed (% of randomized)
Continuous femoral nerve block	Dixit 2018 (USA)	Continuous femoral nerve block 0.2% ropivacaine (infusion rate chosen by the anesthesiologist). Unknown time frame	NA	Regional	TKA	PCM, NSAID, gabapentin, LIA, femoral nerve block (PO oxycodone)	3-month pain score at rest: 10 (17) vs 10 (17)	85 (85%)
Continuous Sciatic Nerve Block	Wegener 2013 (the Netherlands)	Continuous Sciatic Nerve Block with 20 mL of levobupivacaine 0.375% and levobupivacaine 0.125% 10 mL/h to POD2	63	General	TKA	PCM NSAID, femoral nerve block (IV morphine)	3-month pain score at rest: 10 (0–30) vs 0 (0–20) 3-month pain score during movement: 23 (5–50) vs 15 (0–50)	41 (91%)
Femoral and sciatic nerve block	Martin 2008 (France)	Sciatic (20 ml 0.75% ropi) and continuous femoral nerve block (20 ml 0.75% ropi +0.2% ropi 0.15 mg/kg/h for 48 hrs)	18	General	TKA	PCM (PCA morphine)	3-month pain score at rest 0 (0) vs 27 (17) 3-month pain score during movement: 33 (20) vs 30 (15)	38 (95%)
IPACK	Mou 2022 (China)	IPACK 20 mL 0.25% ropivacaine and 2.0 mg/mL of epinephrine added to adductor canal block	23	General	TKA	NSAID, pregabalin, adductor canal block (PO oxycodone)	3-month pain score at rest: 10 (6) vs 9 (10) 3-month pain score during movement: 12 (8) vs 11 (9)	60 (100%)
IPACK	Tang 2023 (China)	iPACK (20–70 mL of 0.25% ropivacaine and 2.0 mg/mL epinephrine) added to LIA	23	General	TKA	NSAID, pregabalin, LIA (PO oxycodone)	3-month pain score at rest: 9 (6) vs 10 (10) 3-month pain score during movement: 10 (9) vs 10 (10)	60 (100%)
Obturator nerve block	Wang 2021 (China)	Obturator nerve block 5 ml 0.2% ropivacaine and 2.0 mg/mL of epinephrine	41	General	TKA	NSAID, LIA, adductor canal block, IPACK (SC morphine)	3-month pain score at rest: 20 (5) vs 19 (5) 3-month pain score during movement: 25 (18) vs 24 (20)	74 (98%)
Obturator and lateral femoral cutaneous nerve block	Wang 2021 (China)	Obturator (5 ml 0.2% ropivacaine and 2.0 mg/mL of epinephrine) and lateral femoral cutaneous nerve block (5 ml 0.2% ropivacaine and 2.0 mg/mL)	40	General	TKA	NSAID, LIA, adductor canal block, IPACK (SC morphine)	3-month pain score at rest: 20 (5) vs 19 (5) 3-month pain score during movement: 23 (15) vs 24 (20)	75 (100%)
Sciatic nerve block	Wegener 2013 (the Netherlands)	Sciatic nerve block with 20 mL of levobupivacaine 0.375%	65	General	TKA	PCM NSAID, femoral nerve block (IV morphine)	3-month pain score at rest: 15 (0–40) vs 0 (0–20) 3-month pain score during movement: 50 (20–68) vs 15 (0–50)	36 (80%)
Peri/intraarticular pharmacological interventions								
Dexamethasone in LIA	Wang 2021 (China)	80 ml 0.1 mg/mL dexamethasone in LIA	48	General	TKA	NSAID, LIA (SC morphine)	3-month pain score at rest: 17 (7) vs 16 (9) 3-month pain score during movement: 31 (10) vs 33 (14)	102 (100%)
Dexmedetomidine in LIA	Zhao 2023 (China)	2.0 mg/kg dexmedetomidine in LIA	17	General	TKA	NSAID, pregabalin, LIA (PO oxycodone)	3-month pain score at rest: 7 (8) vs 5 (6) 3-month pain score during movement: 14 (7) vs 13 (7)	56 (93%)
Epinephrine in LIA	Zhao 2023 (China)	Epinephrine 2.0 mg/mL in LIA	15	General	TKA	NSAID, pregabalin, LIA (PO oxycodone)	3-month pain score at rest: 5 (6) vs 5 (6) 3-month pain score during movement: 12 (9) vs 13 (7)	58 (96%)

(*Continued*)

Table. Continued

Type of intervention	First author, publication year (country)	Brief description of intervention	Presurgical pain at rest (0–100)[a]	Anesthesia	Surgery	Components of the acute analgesic regimen (rescue analgesia)	Postsurgical pain scores intervention group versus control group	Total patients analyzed (% of randomized)
Intraarticular infusion	Ali 2015 (Sweden)	Intraarticular infusion ropivacaine (7.5 mg/mL) 2 mL/h for 48 h added to LIA	60	Both	TKA	PCM, NSAID, LIA, buprenorphine patch (PO oxycodone)	3-month pain score at rest: 19 (21) vs 17 (19)	192 (96%)
Intraarticular infusion	Williams 2013 (Canada)	Intraarticular infusion 0.5% bupivacaine 2 mL/h for 48 h added to LIA	57	Regional	TKA	PCM, NSAID, gabapentin, LIA, PO oxycodone (PCA morphine)	6-month pain score at rest: 12 (13) vs 12 (12)	45 (67%)
Ketorolac in LIA	Andersen 2013 (Denmark)	30 mg ketorolac in LIA +15 mg ketorolac in intraarticular boli every 6 h to POD2	NA	Regional	TKA	PCM, LIA (PCA morphine)	4-month pain score at rest: 3 (1–4) vs 2 (0–18) 4-month pain score during movement: 3 (3–12) vs 4 (1–21)	57 (95%)
LIA	Aso 2019 (Japan)	LIA consisting of 20 ml of 0.75% ropivacaine, 20 ml saline and 6.6 mg of dexamethasone	21	General	TKA	PCM, NSAID, femoral nerve block (PCA fentanyl)	3-month pain score at rest: 5 (2) vs 6 (4) 3-month pain score during movement: 3 (1) vs 6 (2)	40 (100%)
LIA (and intraarticular injection at 21h postoperatively)	Essving 2010 (Sweden)	LIA consisting of 400 mg ropivacaine, 30 mg ketorolac, and 0.5 mg epinephrine + intraarticular injection 21h postoperatively of 200 mg ropivacaine, 30 mg ketorolac, and 0.1 mg epinephrine	4	General	TKA	PCM (PCA morphine)	3-month pain score at rest: 0 (0) vs 0 (0) 3-month pain score during movement: 0 (0) vs 0 (0)	43 (89%)
LIA	Jules-Elysee 2023 (USA)	"Deep" LIA consisting of 0.5% bupivacaine with epinephrine; morphine, 8 mg; methylprednisolone, 40 mg; and cefazolin, 500 mg	NA	Regional	THA	PCM, NSAID, SNRI, LIA (PO oxycodone)	3-month pain score at rest: 6 (13) vs 3 (7) 3-month pain score during movement: 14 (21) vs 6 (12)	54 (60%)
LIA	Tan 2019 (Australia)	LIA consisting of 2.5 mL/kg 0.2% ropivacaine	43	Regional	THA	PCM, NSAID, PO oxycodone (PO oxycodone)	No pain scores reported. Number of patients with opioid use at 3 mo: 3/72 vs 2/74	146 (94%)
LIA	Tang 2023 (China)	LIA consisting of 50 ml 0.25% ropivacaine and 2.0 mg/mL epinephrine added to iPACK	22	General	TKA	NSAID, pregabalin, IPACK (PO oxycodone)	3-month pain score at rest: 9 (6) vs 9 (7) 3-month pain score during movement: 10 (9) vs 10 (10)	60 (100%)
LIA	Xiao 2021 (China)	"Deep and superficial" LIA 80 ml of 0.25% ropivacaine	7	General	THA	NSAID (PO oxycodone)	3-month pain score at rest: 1 (3) vs 1 (3) 3-month pain score during movement: 7 (7) vs 7 (7)	59 (98%)
LIA	Xiao 2021 (China)	"All-layers" LIA 80 ml of 0.25% ropivacaine	7	General	THA	NSAID (PO oxycodone)	3-month pain score at rest: 1 (3) vs 1 (3) 3-month pain score during movement: 7 (6) vs 7 (7)	60 (100%)
LIA	Zoric 2014 (France)	LIA 80 ml of 0.2% ropivacaine	NA	General	THA	PCM, NSAID (Mixed opioids and more NSAID)	3-month pain score at rest: 4 (0–27) vs 0 (0–1)	56 (91%)
Magnesium sulphate in LIA	Zhao 2023 (China)	Magnesium sulphate (2.5 mg/mL) in LIA	43	General	TKA	NSAID, LIA (SC morphine)	No pain scores reported. Number of patients with persistent pain at 3 mo: 2/45 vs 6/45	90 (100%)
Other								
Glucocorticoids in iPACK and continuous adductor canal block	Akaravinek 2023 (Thailand)	40 mg methylprednisolone in IPACK +20 mg methylprednisolone in adductor canal block and methylprednisolone 0.7 mg/h in continuous infusion	13	Regional	TKA	PCM, NSAID, pregabalin, LIA, continuous adductor canal block, IPACK (IV morphine)	3-month pain score at rest: 5 (8) vs 4 (7) 3-month pain score during movement: 15 (15) vs 9 (12)	79 (98%)

(*Continued*)

Table. Continued

Type of intervention	First author, publication year (country)	Brief description of intervention	Presurgical pain at rest (0–100)[a]	Anesthesia	Surgery	Components of the acute analgesic regimen (rescue analgesia)	Postsurgical pain scores intervention group versus control group	Total patients analyzed (% of randomized)
Ketorolac in spinal	Wang 2014 (USA)	2 mg ketorolac in spinal anesthesia	17	Regional	THA	PCM (PCA morphine)	6-month pain score at rest: 4 (6) vs 1 (2)	51 (89%)
Patient-controlled epidural analgesia	Jules-Elysee 2023 (USA)	Patient-controlled epidural analgesia (bupivacaine 0.06%)	NA	Regional	THA	PCM, NSAID, SNRI, LIA (PO oxycodone)	3-month pain score at rest: 6 (13) vs 3 (8) 3-month pain score during movement: 12 (21) vs 7 (13)	64 (71%)

Abbreviations: IM, intramuscularly; IPACK, infiltration of local anesthetic between the popliteal artery and capsule of the knee; IQR, interquartile range; IV, intravenously; LIA, local infiltration analgesia; NSAID, nonsteroidal anti-inflammatory drug; PCA, patient-controlled analgesia; PCM, paracetamol/acetaminophen; PO, perorally; POD, postoperative day; SC, subcutaneously; SD, standard deviation; SNRI, serotonin and noradrenaline reuptake inhibitor; THA, total hip arthroplasty; TKA, total knee arthroplasty.

[a]The mean presurgical pain scores were similar between intervention and control groups. Therefore, the presurgical pain score are presented as the mean between the 2 groups.

[b]Some trial groups were divided into different rows, due to more than 2 trial arms. For example, in a trial with 2 intervention groups and 1 control groups, each intervention group is compared to half the control group.

clinical importance of 10 mm. The meta-analysis yielded a Tau^2 value of 32.9 and an I^2 value of 71%, suggesting significant statistical heterogeneity. Visually, the statistical heterogeneity of all other analyses was small, as no trial demonstrated a statistically significant finding of > 10 mm on the visual analog scale.

Subgroup analyses (Supplemental Digital Content 1, Appendixes 6 and 7, http://links.lww.com/AA/F31) did not reveal statistically significant differences between type of surgery (hip versus knee arthroplasty), type of anesthesia (general versus regional anesthesia) or risk of bias assessment (low versus high risk of bias trials). However, duloxetine's statistically significant reduction of pain scores 3 to 24 months after surgery during movement was primarily driven by TKA-trials (5 trials, mean difference −7.0 [95% CI −12.4 to −1,6]. None of the interventions resulted in 10 mm reduction of the pain score at 3 to 24 months in any subgroup.

The worst-best case analyses revealed that treatment with duloxetine perioperatively may not have produced a statistically significant reduction in persistent during movement and had all patients been analyzed (Supplemental Digital Content 1, Appendix 8, http://links.lww.com/AA/F31). All remaining analyses of pain scores were largely unaffected in best-worst and worst-best case analyses (Supplemental Digital Content 1, Appendixes 8 and 9, http://links.lww.com/AA/F31).

Number of Patients With Persistent Postsurgical Pain 3 to 24 Months After Surgery

We were unable to find 3 or more eligible trials investigating the same intervention that reported the number of patients with persistent postsurgical pain.

Number of Patients Experiencing Serious Adverse Events After Surgery

We were unable to find 3 or more eligible trials investigating the same intervention that reported SAEs.

Meta-Regression Analyses

We did not conduct the planned meta-regression analyses to investigate differences in effect between follow-up times as we included <10 trials in all analyses. Also, almost all trials assessed pain at 3 months (Table).

Reporting Biases

Since <10 trials were available for all meta-analyses, we did not use funnel plots or other tests to assess nonreporting bias. Thus, reporting bias could not be assessed systematically.

Trial Sequential Analyses

For all meta-analyses, the trial sequential analysis suggested that further trials were unlikely to change the conclusion (Supplemental Digital Content 1, Appendix 10 and 11, http://links.lww.com/AA/F31).

Certainty of Evidence

For all outcomes, the GRADE rating was downgraded to low certainty of evidence due to high risk of bias and possible reporting bias, as most studies were excluded from this review due to nonreporting of the outcomes assessed and because nonreporting bias could not be assessed.

DISCUSSION

We reviewed published RCTs on perioperative analgesic interventions for reduction of persistent postsurgical pain after total hip and knee arthroplasty for osteoarthritis. We showed that analgesic treatments limited to the perioperative period resulted in little to no difference in the level of pain after 3 to 24 months. Only 49 trials with 68 intervention arms were included in the review because we excluded most RCTs for the sole reason that they failed to report long-term pain outcomes. All meta-analyses included trials at high risk of bias and the results should be interpreted with caution.

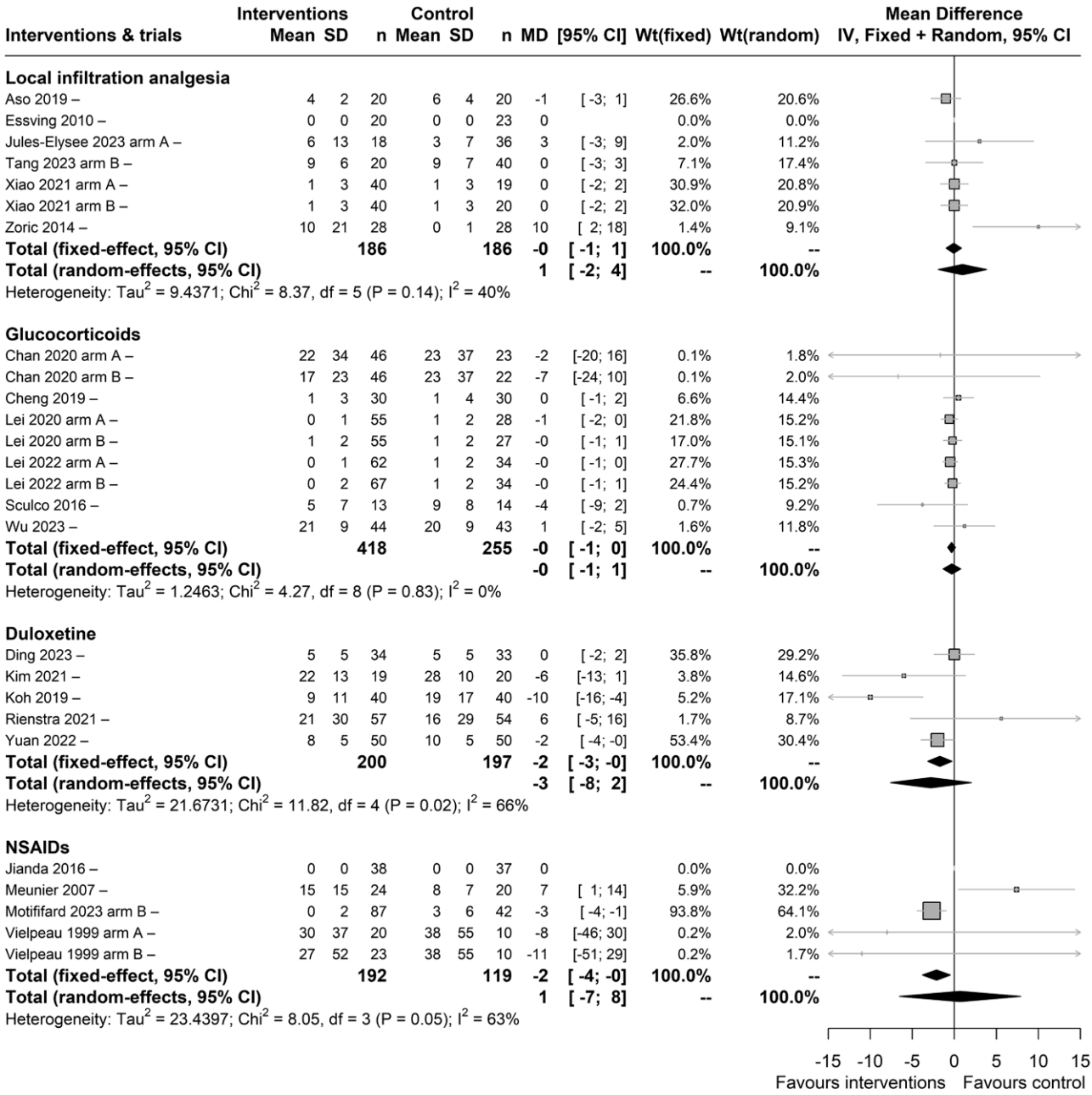

Figure 2. Meta-analysis of pain scores at rest.

No procedure-specific systematic reviews have investigated the effect of perioperative systemic analgesic interventions or regional anesthesia on persistent pain after major orthopedic surgery. Still, other reviews have addressed research questions similar to ours.[28–34] These have investigated perioperative pharmacological interventions on a range of surgical procedures, and found modest results for ketamine,[28,29,33] intravenous lidocaine,[28,30] gabapentinoids[28,30] and NSAIDs.[30] Although pooling trials on various surgeries increases the amount of available data, these reviews may be hard to interpret due to differences in patient populations, incidence, and types of persistent pain.[35]

We only included RCTs investigating patients with osteoarthritis undergoing total hip or knee arthroplasty. In a systematic review from 2019, Beswick et al reviewed the effect of perioperative interventions, including nonanalgesic interventions, for persistent pain after total knee arthroplasty.[32] Beswick et al were unable to synthesize results due to heterogeneity in interventions and outcomes, but narratively described the results of the included trials. Based on few included trials, they found statistically significant, but clinically irrelevant reductions in persistent pain with local infiltration analgesia and pregabalin.[32]

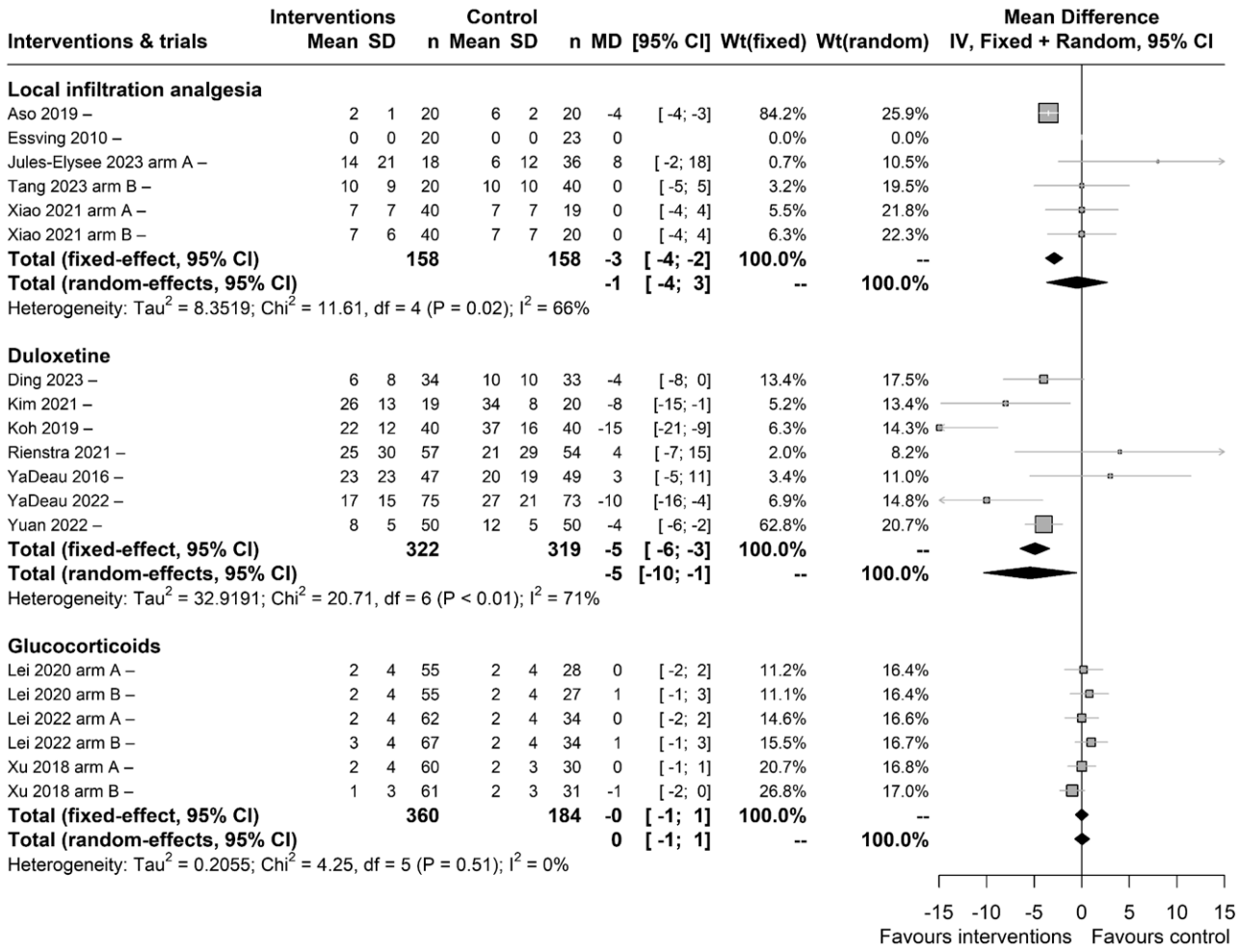

Figure 3. Meta-analysis of pain scores during movement.

Finally, 2 reviews have investigated direct comparisons between regional anesthesia and conventional opioid and nonopioid analgesics for prevention of persistent postsurgical pain.[31,34] Generally, the evidence favors regional anesthetic techniques; although the evidence for orthopedic procedures was sparse, further the reviews did not answer the question of whether acute analgesic intervening has long-term effects preventing persistent pain.[31,34] This is similar to the present review, where very few trials on regional anesthesia were included.

The discussed systematic reviews have found small effect sizes or low certainty of evidence. Researchers have speculated that immediate postsurgical pain may be causally linked to persistent postsurgical pain and that better perioperative analgesia reduces persistent postsurgical pain.[12,36] Still, even interventions that decrease immediate postsurgical pain significantly[37–40] did not affect the level of persistent pain in the current review. Instead, secondary analgesics like ketamine, gabapentinoids, intravenous lidocaine, and antidepressants have shown somewhat consistent benefits in previous reviews.[28–30,32,33] This may indicate that these effects are not directly driven by reductions in immediate postsurgical pain.[11,36]

It is unclear which pathophysiological mechanisms contribute to persistent pain after total hip and knee arthroplasty.[35,41] Factors may include genetic disposition, psychosocial factors, surgical approach, nerve injury, implant type, peripheral or central sensibilisation, and inflammation.[12,35,36,41] Also, persistent postsurgical pain may be an oversimplistic umbrella-term for a number of different pain conditions,[35] which could require different treatment strategies.[41]

STRENGTHS AND LIMITATIONS

A major strength of our study is that we only included studies on osteoarthritis patients undergoing total hip and knee arthroplasty as the patient populations and pain mechanisms produced from these surgeries are relatively similar. This gives more robust results. Also, we chose only to compare interventions to inactive controls because, in our opinion, the variation in baseline risk between trials limits the validity of results from network meta-analyses.[28,42,43]

Our results are mainly limited by heterogeneity in the included trials. First, both baseline and follow-up pain levels varied between trials. Second, the basic analgesic regimens ranged from no basic analgesics or paracetamol alone to a wide range of pharmacological and invasive analgesic cointerventions. Third, the individual interventions differed in dose and treatment regimens, but were grouped in the analyses based on the available trials. Last, the proportion of patients lost to follow-up were very different between trials, possibly due to different research practice or differences in reporting of trials.[44]

CONCLUSIONS

We found no perioperative analgesic interventions that reduced pain 3 to 24 months after total hip or knee arthroplasty for osteoarthritis. The literature on perioperative analgesia focused little on potential long-term effects. We encourage the assessment of long-term pain outcomes. ■

DISCLOSURES

Conflicts of Interest: None. **Funding:** J. Laigaard received a scientific scholarship from the local scientific committee at Bispebjerg and Frederiksberg Hospital. Aside from this, no external funding was received for the present review. **This manuscript was handled by:** Honorio T. Benzon, MD.

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