Reduction of opioid use after orthopedic surgery: a scoping review

Jessica Gormley, MD
Kyle Gouveia, MD
Seaher Sakha, BHSc
Veronica Stewart, MD
Ushwin Emmanuel, BHSc
Michael Shehata, MD
Daniel Tushinski, MD
Harsha Shanthanna, MD, PhD
Kim Madden, PhD

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Correspondence to:
K. Madden
Room G841, 50 Charlton Ave E
Hamilton ON L8N 4A6
maddenk@mcmaster.ca

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Background: The opioid epidemic is one of the biggest public health crises of our time, and overprescribing of opioids after surgery has the potential to lead to long-term use. The purpose of this review was to identify and summarize the available evidence on interventions aimed at reducing opioid use after orthopedic surgery.

Methods: We searched CENTRAL, Embase and Medline from inception until August 2019 for studies comparing interventions aimed at reducing opioid use after orthopedic surgery to a control group. We recorded demographic data and data on intervention success, and recorded or calculated percent opioid reduction compared to control.

Results: We included 141 studies (20 963 patients) in the review, of which 113 (80.1%) were randomized controlled trials (RCTs), 6 (4.3%) were prospective cohort studies, 16 (11.4%) were retrospective cohort studies, 5 (3.6%) were case reports, and 1 (0.7%) was a case series. The majority of studies (95 [67.4%]) had a follow-up duration of 2 days or less. Interventions included the use of local anesthetics and/or nerve blocks (42 studies [29.8%]), nonsteroidal anti-inflammatory drugs (31 [22.0%]), neuropathic pain medications (9 [6.4%]) and multimodal analgesic combinations (25 [17.7%]. In 127 studies (90.1%), a significant decrease in postoperative opioid consumption compared to the control intervention was reported; the median opioid reduction in these studies was 39.7% (range 5%–100%). Despite these reductions in opioid use, the effect on pain scores and on incidence of adverse effects was inconsistent.

Conclusion: There is a large body of evidence from randomized trials showing the promise of a variety of interventions for reducing opioid use after orthopedic surgery. Rigorously designed RCTs are needed to determine the ideal interventions or combination of interventions for reducing opioid use, for the good of patients, medicine and society.

Contexte : La crise des opioïdes est l'une des plus importantes crises de santé publique de notre époque et la surprescription d'opioïdes après la chirurgie comporte le risque d'entraîner leur utilisation prolongée. Le but de cette revue est de recenser et de résumer les données probantes sur les interventions visant à réduire le recours aux opioïdes après la chirurgie orthopédique.

Méthodes : Nous avons interrogé les réseaux CENTRAL, Embase et Medline, de leur mise sur pied à août 2019, pour trouver les études ayant comparé des groupes témoins à des groupes soumis à des interventions de réduction du recours aux opioïdes après la chirurgie orthopédique. Nous avons noté les données démographiques et les données sur la réussite des interventions, et nous avons consigné ou calculé le pourcentage de réduction de la consommation d'opioïdes en comparaison avec les groupes témoins.

Résultats : Notre revue a réuni 141 études (20 963 patients); 113 (80,1 %) d'entre elles étaient des essais randomisés et contrôlés (ERC), 6 (4,3 %) étaient des études de cohorte prospectives, 16 (11,4 %) étaient des études de cohorte rétrospectives, 5 (3,6 %) étaient des rapports de cas et 1 (0,7 %) était une série de cas. La majorité des études (95 [67,4 %]) avaient un suivi d'une durée de 2 jours ou moins. Les interventions incluaient l'utilisation d'anesthésiques locaux et/ou de blocs nerveux (42 études [29,8 %]), d'anti-inflammatoires non stéroïdiens (31 [22,0 %]), de médicaments pour la douleur neuropathique (9 [6,4 %]) et une analgésie multimodale (25 [17,7 %]. Dans 127 études (90,1 %), on a fait état d'une baisse significative de la prise d'opioïdes postopératoire comparativement aux groupes témoins; la réduction médiane de la consommation d'opioïdes dans ces études a été de 39,7 % (allant de 5 % à 100 %). Malgré cette consommation réduite des opioïdes, l'effet sur les scores de douleur et sur l'incidence des effets indésirables a été mitigé.

Conclusion : On dispose d'un volumineux ensemble de données tirées d'essais randomisés selon lesquelles diverses interventions de réduction de la consommation d'opioïdes après une chirurgie orthopédique sont prometteuses. Il faudra procéder à des ERC rigoureusement conçus pour déterminer quelles interventions utilisées seules ou ensemble sont idéales pour réduire le recours aux opioïdes, dans l'intérêt des patients, de la médecine et de la société.

The conflict and tension between the intended good and unintended harms of opioids have been recognized within the medical context since the early 1900s.[1] It is helpful to separate the harms broadly into 2 categories: short-term adverse effects, which are adverse drug effects experienced by the person using the drug, and long-term harms, which could be to the individual or to society (diversion). The immediate harms are considered under the term opioid-related adverse drug effects and they commonly include nausea/vomiting, sedation, itching, postoperative ileus and respiratory depression.[2] Secondarily, they can lead to increased length of stay, opioid dependence, death and rising costs.[3,4]

The long-term harms of opioids are specifically responsible for the ongoing opioid epidemic in North America, as well as in other parts of the world.[5] Over the past 20 years, opioid use disorder and opioid-related mortality have increased rapidly.[6] In 2013, drug overdose surpassed motor vehicle crashes to become the leading cause of preventable death in the United States, with more than 42 000 opioid overdose deaths in 2016 alone.[7,8] The number of opioid-related deaths has continued to rise, with an increase in deaths in Canada in 2017 of 30% from the previous year.[7] These trends are matched by a marked increase in patient opioid prescriptions. In Canada, the defined daily dose per million population per day of opioids increased threefold between 2001–2003 and 2012–2014, from 10 209 to 30 540.[7,8] This is second only to the US.[7]

In light of the current opioid epidemic, increased attention has been given to target areas to reduce opioid use and manage acute pain alternatively in the postoperative period. Owing to the substantial amount of pain after many orthopedic procedures, opioids have traditionally been used postoperatively in this field. There are many risks to consider when prescribing, which makes the issues at hand incredibly complex. Prescribing opioids peri- and postoperatively can trigger long-term use in people independent of opioid tolerance or previous use.[9] A retrospective cohort study from Ontario showed increased risk of long-term opioid use after receiving a prescription for a short-stay surgery in 44% of 400 000 patients.[9] In opioid-naive patients, a new opioid prescription after discharge from hospital increased the odds of long-term use 1 year later by 4.9 times (95% confidence interval 3.22–7.45).[10] Two of the 3 surgical interventions that were associated with highest long-term opioid use were total knee arthroplasty (TKA) and total hip arthroplasty (THA).[11] Other risks to consider include the possibility that the legal supply will be diverted to those with substance use disorder or people seeking illicit drugs.[12,13] Studies repeatedly show that more than 50% of prescribed opioids go unused, and the majority are never disposed of safely.[14]

Managing pain is a key component of patient care. For opioid-reduction programs to be successful, they must recognize the challenges around pain, particularly in older patients and those with chronic pain, including the potential for persisting pain after surgery and, hence, the necessity of providing alternative analgesic modalities that depend less on opioids. Programs that aim to reduce opioid use substantially should not only focus on the physiologic management of pain, but also consider education initiatives on opioid use and assess for patients at high risk. To reduce dependency on opioids, pain should be managed with a multimodal analgesia regimen. This includes the use of pharmacologic modalities such as peripheral nerve blocks (PNBs) or local anesthetic infiltration (LAI), acetaminophen and nonsteroidal anti-inflammatory drugs (NSAIDs) in all patients, and the use of gabapentinoids and cannabinoids in suitable patients. Nonpharmacologic modalities that are considered as adjuncts include acupuncture, electrotherapy and transcutaneous electrical nerve stimulation.[15–17] Evidence suggests that many of these modalities are underused.[18,19]

The goals of this scoping review were to 1) identify the current literature and level of evidence on reduction of opioid use after orthopedic surgery; 2) describe the interventions used; 3) summarize the results, noting the amount of opioid reduction and other postoperative outcomes; and 4) synthesize the results to highlight patterns seen with different interventions.

Methods

Protocol and registration

We conducted a scoping review of published literature on strategies to reduce opioid use in orthopedic surgery. The purpose of a scoping review is to map the current literature on a broad topic to identify gaps in the literature in order to plan future studies and to identify areas where there is enough information to conduct formal meta-analyses. This scoping review protocol was registered with the PROSPERO international prospective register of systematic reviews (CRD42020153418). The methodology of the review is in accordance with the PRISMA-ScR guidelines for scoping reviews.[20]

Literature search

We completed a comprehensive search of CENTRAL, Embase and Medline from database inception until August 2019 for studies aiming to eliminate or substantially reduce perioperative opioid use. Terms searched included common orthopedic interventions, analgesic options, alternative therapy options to manage acute pain and any phrases that suggest there has been a reduction in opioid use. We then performed an extensive manual search of reference lists from the included literature to seek any additional relevant studies. Our search strategy for each of the 3 databases is presented in Appendix 1 (available at www.canjsurg.ca/lookup/doi/10.1503/cjs.023620/tab-related-content).

Studies were included if at least 25% of the population were orthopedic surgery patients; they were original reports focused on perioperative and/or acute postoperative pain management (i.e., not chronic pain); the primary objective of the study was to reduce or eliminate perioperative or postoperative opioid use; and full-text articles were available. Studies were excluded if they were animal or preclinical studies, were in a language other than English, focused on cancer pain, focused exclusively on pediatric populations, or were opinion pieces, editorials or synthesis of literature, including reviews.

We managed references using Rayyan QCRI software (Qatar Computing Research Institute). Two reviewers (J.G., V.S.) independently screened titles identified by the literature search first and then all remaining abstracts. Any study that was distinctly irrelevant based on the eligibility criteria was excluded. At both the title and the abstract stage, a study was included if at least 1 of the 2 reviewers chose to include it. Full texts were obtained for all remaining studies when available. Both reviewers screened the remaining references independently. Any initial discrepancies at the full-text stage were resolved by discussion between the reviewers until agreement on inclusion or exclusion of the study in question was reached.

We extracted the data using a collaborative online spreadsheet (Google Sheets). The form included study characteristics (design, date, location, sample size, demographic characteristics and level of evidence), description of the population, intervention, comparator (if applicable) and relevant outcomes at final follow-up. The spreadsheet was piloted by 2 reviewers (J.G., V.S.) before data extraction. Each reviewer's data were audited by the other reviewer using a random spot-check method.

Data analysis

As this was a scoping review, we presented our analysis and results in a descriptive fashion. We used frequencies and proportions for categoric data, and means and standard deviations, or median and range (depending on data distribution) for continuous data. We grouped studies based on type of orthopedic procedure: arthroplasty procedures (knee and/or hip), arthroscopy operations, spinal procedures and other peripheral limb procedures. We reported the category of opioid-sparing strategy used as pharmacologic or nonpharmacologic, and noted the type of interventions used within these categories as NSAIDs, acetaminophen derivatives, adjunct analgesic medications (gabapentinoids), PNBs, LAI, physical modalities, psychologic modalities and other. We noted the amount of opioid sparing or reduction as per the study reporting, including the dosage and duration of opioid therapy.

RESULTS

The initial literature search yielded 20 309 studies; after removal of duplicates, this number was reduced to 14 121. Systematic screening and assessment of eligibility yielded 141 full-text articles that satisfied the criteria for inclusion (Figure 1).

Study quality

Of the 141 studies, 113 (80.1%) were randomized controlled trials (RCTs) (level I evidence), 6 (4.3%) were prospective cohort studies (level II evidence), 16 (11.3%) were retrospective cohort studies (level III evidence), 5 (3.5%) were case reports (level IV evidence), and 1 (0.7%) was a case series (level IV evidence).

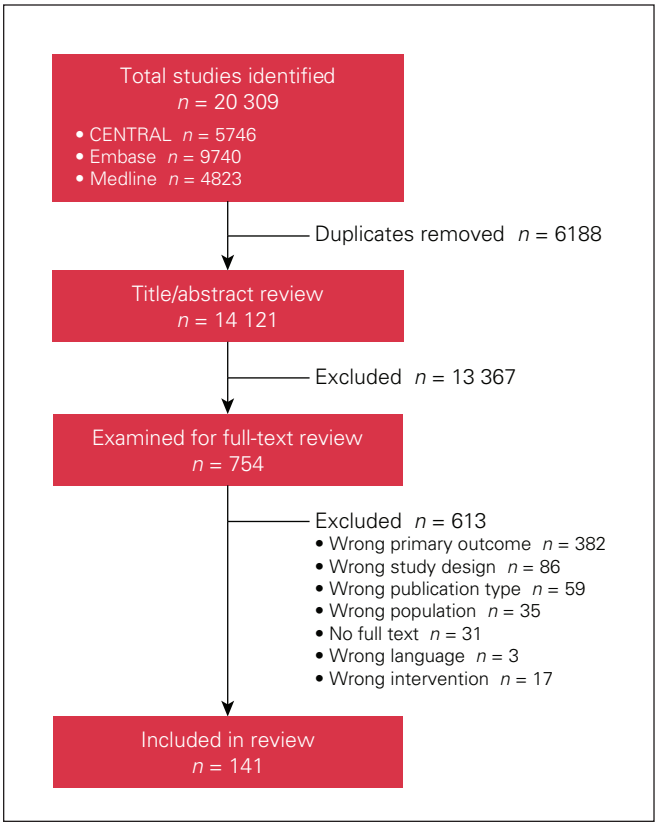

Fig. 1. Flow diagram showing study selection.

Study characteristics

The 141 studies included in this review involved 20 963 patients (Table 1). The number of included patients per study ranged from 1 to 4046 (median 68). In the studies that reported gender, 9585/17 511 patients (54.7%) were female. The overall mean age was 57.8 (range 16–94) years. The length of follow-up ranged from 0.83 to 365 days, with 95 studies (67.4%) having 2 days or less of follow-up, 24 studies (17.0%) having 3–7 days of follow-up, and 12 studies (8.5%) having more than 7 days of follow-up.

There were 158 total intervention arms aimed at reducing opioid use, of which 145 (91.8%) were pharmacologic. The most commonly used pharmacologic interventions, either alone or in some combination, were PNB/LAI, acetaminophen, NSAIDs and additional analgesics (most commonly gabapentin). In 25 studies (17.7%), the use of a multimodal regimen (defined as the use of ≥ 2 analgesics) aimed at reducing opioid use was reported. Nonpharmacologic interventions included education (4 studies[115,132,155,160]), transcutaneous electrical nerve stimulation (3 studies[69,112,126]), transcranial direct current stimulation (2 studies[24,97]) and, in 1 study each, auricular acupressure, cryotherapy and millimetre wave therapy.[33,48,49]

Of the 141 studies, 139 (98.6%) (19 795 patients) included only patients who had orthopedic procedures. The most common procedures performed were lower limb total joint arthroplasty, with 38 studies (7124 patients) involving TKA, 25 studies (2346 patients) involving THA and 7 studies (730 patients) involving both, for a total of 70 studies (49.6%) examining pain control specifically after lower limb arthroplasty. The next most common surgical procedures were spinal surgery (29 studies [20.6%], 5013 patients) and arthroscopic surgery (15 studies [10.6%], 1160 patients). There were 27 studies on other surgical procedures, including fracture fixation.

In 127 studies (90.1%), a significant decrease in postoperative opioid consumption compared to the control intervention was reported; the median opioid reduction in these studies was 39.7% (range 5%–100%).

Procedures

Total knee arthroplasty

Among the 38 TKA studies, PNB/LAI was used in 15 (40%), NSAIDs were used in 5 (13%), a nonpharmacologic intervention was used in 4 (10%), and additional adjuvant analgesics were used in 5 (13%) (Table 1). Multimodal analgesia was used in 9 studies (24%).

A statistically significant reduction in opioid use compared to the control group was reported in 34 studies (90%) (Table 2). Percent opioid reduction ranged from 10% to 100% (median 37.8%). Twenty-three studies (60%) showed at least a 30% reduction in opioid use, and 12 (32%) showed more than a 50% reduction.

Of the 36 studies in which pain scores were reported, 26 (72%) showed significantly lower scores compared to the control intervention. Postoperative length of stay was reported in 5 studies, with all 5 showing significantly lower values compared to control. Mobilization was reported in 10 studies, of which 8 (80%) showed significant improvement compared to control. Patient satisfaction was reported in 2 studies,[29,32] 1 of which showed significantly higher satisfaction compared to control. The frequency of adverse events was reported in 17 studies, with 4 (24%) showing the intervention had a significantly positive effect; the remaining 13 studies (76%) showed no difference between the intervention and control groups.

Total hip arthroplasty

Among the 25 THA studies, PNB/LAI was used in 8 (32%), NSAIDs were used in 6 (24%), a nonpharmacologic intervention was used in 1 (4%),[69] and additional adjuvant analgesics were used in 5 (21%). Multimodal analgesia was used in 5 studies (21%).

Twenty-four studies (96%) showed a statistically significant reduction in opioid use compared to control. Percent opioid reduction ranged from 15% to 100% (median 40.3%). Eighteen studies (72%) showed at least a 30% reduction in opioid use, and 6 studies (24%) showed more than a 50% reduction.

Pain scores were reported in 20 studies, 13 (65%) of which showed significantly lower scores compared to the control intervention. Postoperative length of stay was reported in 3 studies,[77,80,83] all of which showed significantly lower values compared to control. Of the 2 studies in which mobilization was reported,[62,80] 1 showed significant improvement compared to control.[80] Patient satisfaction was reported in 2 studies;[59,75] both showed significantly higher satisfaction compared to control. The frequency of adverse events was reported in 16 studies, 6 (38%) of which showed a significantly lower incidence compared to control.

Total knee and total hip arthroplasty

Among the 7 studies in patients underwent THA or TKA, the intervention consisted of PNB/LAI in 1 (14%),[87] NSAIDs in 3 (43%),[86,88,89] acetaminophen in 1 (14%),[90] additional adjuvant analgesics in 1 (14%)[85] and multimodal analgesia in 1 (14%).[84] Six studies (86%) showed a statistically significant reduction in opioid use compared to control. Percent opioid reduction ranged from 23.4% to 89.3% (median 36.3%). Four studies (57%) showed at least a 30% reduction in opioid use, and 2 studies (29%) showed more than a 50% reduction.

Pain scores were reported in 4 studies, all of which showed a significant decrease. The frequency of adverse events was reported by 4 studies; all 4 indicated that the intervention had no impact on the frequency of adverse events.

Table 1 (part 1 of 6). Characteristics of included studies

Procedure; study	Study design	Level of evidence*	Type of surgery	Intervention	Control	No. of participants	Mean age, yr	% female	Length of follow-up, d
Total knee arthroplasty									
Allen et al.,[21] 1998	RCT	I		Femoral 3-in-1 block	Spinal anesthetic block	44	72.3	53.9	2
Andersen et al.,[22] 2010	RCT	I		Ropivacaine + ketorolac + epinephrine LAI	Placebo	49	68	35	3
Badner et al.,[23] 1996	RCT	I		Bupivacaine LAI before or after wound closure	Placebo	80	68.3	64.3	1
Borckardt et al.,[24] 2013	RCT	I		tDCS	Placebo	40	67	74.4	2
Buvanendran et al.,[25] 2003	RCT	I		Rofecoxib	Placebo	70	61	67	1.75
Chan et al.,[26] 2015	RCT	I		Dexmedetomidine	Placebo	40	66.15	70	1
Essving et al.,[27] 2010	RCT	I		Ropivacaine + ketorolac + epinephrine LAI	Placebo	48	71	54.2	2
Essving et al.,[28] 2011	RCT	I		Ropivacaine + ketorolac + epinephrine LAI	Morphine	50	71	64	2
Goyal et al.,[29] 2013	RCT	I		0.5% bupivacaine, 300 mL (intra-articular infusion)	Placebo	150	64.8	56.7	3
Gomez-Cardero et al.,[30] 2010	RCT	I		0.2% ropivacaine, 300 mL (intra-articular infusion)	Placebo	50	71.3	62	3
Hanson et al.,[31] 2014	RCT	I		0.2% ropivacaine ACB	Placebo	80	67	NR	2
He et al.,[32] 2013	RCT	I		Auricular acupressure	Placebo	90	62.1	62.2	7
Ho et al.,[33] 2010	RCT	I		Duloxetine, 60 mg	Placebo	50	65.5	70.2	2
Huang et al.,[34] 2007	RCT	I		Celecoxib, 400 mg then 200 mg every 12 h + morphine PCA	PCA	80	70	NR	3
Hubbard et al.,[35] 2003	RCT	I		Parecoxib, 20 or 40 mg	Placebo	195	68.9	NR	2
Inan et al.,[36] 2007	RCT	I		Lornoxicam, 16 mg (intravenously) 15 min before surgery, and 8 mg at 12th and 24th h postoperatively	Placebo	46	63	85	2
Jenstrup et al.,[37] 2012	RCT	I		0.75% ropivacaine ACB	Placebo	75	47.9	34	1
Kampitak et al.,[38] 2019	RCT	I		ONB + TNB	ONB or TNB	90	70.8	86.5	8
Lamplot et al.,[39] 2014	RCT	I		0.5% bupivacaine + magnesium sulfate, 10 mg + ketorolac + tramadol LAI	PCA	36	64.6	50	21
Leung et al.,[40] 2018	RCT	I		ACB	Placebo	165	64.6	77.5	0.83
Mont et al.,[41] 2018	RCT	I		Liposomal bupivacaine LAI	Bupivacaine	140	66	59	3
Nader et al.,[42] 2016	RCT	I		0.25% bupivacaine + epinephrine ACB	Placebo	40	68	70	1.5
Pham Dang et al.,[43] 2005		RCT		FNB + SNB	FNB	28	71.7	83	2
Runge et al.,[44] 2016	RCT	I		ONB + FTB	Placebo	75	71.3	50.7	2
Sahin et al.,[45] 2014	RCT	I		FNB	Placebo	110	60	68.3	2
Samona et al.,[46] 2017	RCT	I		Dexamethasone	Placebo	102	63.8	56.9	3
Sarridou et al.,[47] 2014	RCT	I		Parecoxib (intravenously) + FNB	Placebo	90	70.5	83.3	1.5

Table 1 (part 2 of 6). Characteristics of included studies

Procedure; study	Study design	Level of evidence	Type of surgery	Intervention	Control	No. of participants	Mean age, yr	% female	Length of follow-up, d
Thijs et al.,[48] 2018	RCT	I		Cryotherapy	Placebo	60	65.1	46.7	42
Usichenki et al.,[49] 2007	RCT	I		MWT	Placebo	80	66.5	63.7	9
Venditolli et al.,[50] 2006	RCT	I		Ropivacaine + etodolac + adrenaline LAI	Placebo	52	NR	57.7	5
Williams et al.,[51] 2013	RCT	I		Bupivacaine (intra-articular infusion)	Placebo	67	66.5	58.9	2
Banerjee[52] 2014	RCS	III		0.2% ropivacaine + epinephrine + ketorolac, 30 mg LAI	Placebo	64	70.9	67.2	2
Chin et al.,[53] 2020	ROS	III		Gabapentin	Placebo	4046	NR	62	NR
Klement et al.,[54] 2019	RCR	III		ACC + iPACK	Single-shot FNB + LB-PAI	264	66.2	56.4	2
Kuo et al.,[55] 2017	RCR	III		PIA	Placebo	76	67.3	5.3	1
Xiao et al.,[56] 2018	RCR	III		Celecoxib or flurbiprofen axetil	Placebo	300	61.8	33.7	365
Horlocker et al.,[57] 2002	Case report	IV		Acetaminophen + ketorolac LPB	Placebo	1	74	100	2
Stevenson et al.,[58] 2018	Case report	IV		Acetaminophen, 325 g + diclofenac sodium gel + meloxicam	Acetaminophen + oxycodone	1	77	100	120
Total hip arthroplasty									
Aguirre et al.,[59] 2012	RCT	I		0.3% ropivacaine LAI	Placebo	76	58	48.6	2
Becchi et al.,[60] 2008	RCT	I		0.75% ropivacaine psoas catheter	Morphine + ketorolac	73	70	55.7	2
Bilir et al.,[61] 2007	RCT	I		Fentanyl + magnesium epidural	Fentanyl	50	60.4	52	1
Camu et al.,[62] 2002	RCT	I		Valdecoxib, 20 or 40 mg	Placebo	217	66.3	62.2	2
Clarke et al.,[63] 2009	RCT	I		Gabapentin	Placebo	126	61.3	46.2	2
Desmet et al.,[64] 2017	RCT	I		0.5% ropivacaine, 40 mL, longitudinal suprainguinal FICB	Placebo	88	63.5	61.1	1
Fogarty et al.,[65] 1995	RCT	I		Ketorolac, 30 mg (intramuscularly)	Placebo	60	65	57	1
Hwang et al.,[66] 2010	RCT	I		Magnesium sulfate	Placebo	40	47	45	2
Köroglu et al.,[67] 2008	RCT	I		0.25% bupivacaine, 40 mL femoral 3-in-1 block	Placebo	30	57.2	30	2
Laitenan et al.,[68] 1992	RCT	I		Diclofenac	Placebo	40	63.3	52	1
Lan et al.,[69] 2012	RCT	I		TENS on acupoints (bilateral P6, L14; ST36, GB31 ipsilateral to surgery site)	Placebo	68	75.5	55	2
Malan et al.,[70] 2003	RCT	I		Parecoxib, 20 or 40 mg	Placebo	201	63	42	1.5
Martinez et al.,[71] 2013	RCT	I		Ketamine and/or pregabalin	Placebo	142	52.2	40.4	2
Murphy et al.,[72] 2012	RCT	I		Levobupivacaine (periarticular infusion)	Placebo	45	57.4	42.9	3
Remérand et al.,[73] 2009	RCT	I		Ketamine	Placebo	154	64.5	49.1	7
Serpell et al.,[74] 1989	RCT	I		Piroxicam	Placebo	24	67.5	41.7	2
Siddiqui et al.,[75] 2007	RCT	I		LPB	PCA	34	55.5	52.9	1.5

Table 1 (part 3 of 6). Characteristics of included studies

Procedure; study	Study design	Level of evidence	Type of surgery	Intervention	Control	No. of participants	Mean age, yr	% female	Length of follow-up, d
Stevens et al.,[76] 2007	RCT	I		0.5% bupivacaine, 30 mL + epinephrine + clonidine, 150 μg + 0.9% saline, 9 mL FICB	Placebo	44	67.8	41	1
Ward et al.,[77] 2012	RCT	I		FNB	Placebo	40	38.4	58.3	1.5
Gurkan et al.,[78] 2018	RCT	I		Ibuprofen, 800 mg (intravenously)	Placebo	40	49	70	1
Post et al.,[79] 2010	PCS	II		Acetaminophen, 975 mg + celecoxib, 400 mg + pregabalin, 75 mg every 12 h	Placebo	116	62.7	57	2
Banerjee et al.,[80] 2011	RCS	III		0.2% ropivacaine + epinephrine + ketorolac, 30 mg LAI	Placebo	204	69.6	58.4	2
Maheshwari et al.,[81] 2006	RCR	III		Multimodal therapy regimen	Placebo	144	65.1	55.7	3
Uusalo et al.,[82] 2019	RCS	III		Dexmedetomidine, 50 μg (intranasally)	Placebo	120	57.5	NR	2
VanWagner et al.,[83] 2019	RCS	III		Bupivacaine LAI	Placebo	170	65.3	NR	3
Total knee arthroplasty and total hip arthroplasty									
Alexander et al.,[84] 2002	RCT	I		Diclofenac, 75 mg + ketorolac, 60 mg	Placebo	102	65.2	63.8	1
Arcioni et al.,[85] 2007	RCT	I		Magnesium sulfate (intrathecally and/or epidural) + spinal	Placebo	120	59.5	57.2	1.5
Boeckstyns et al.,[86] 1992	RCT	I		Piroxicam	Placebo	117	NR	NR	10
Oberhofer et al.,[87] 2011	RCT	I		Levobupivacaine spinal	Placebo	40	67.9	60	1
Kazerooni et al.,[88] 2012	RCT	I		Celecoxib, 200 mg twice daily	Placebo	141	64.2	5.7	NR
Singla et al.,[89] 2010	RCT	I		Ibuprofen	Placebo	34	55.5	52.9	1.5
Raiff et al.,[90] 2014	RCS	III		Acetaminophen (intravenously)	Placebo	176	62	37.5	1
Spinal surgery									
Aveline et al.,[91] 2006	RCT	I	Lumbar disc surgery	Morphine and/or ketamine	Placebo	69	45.8	52.9	2
Cassinelli et al.,[92] 2008	RCT	I	Primary multilevel lumbar decompression surgery	Ketorolac	Placebo	25	62.3	NR	1
Farag et al.,[93] 2013	RCT	I	Spinal surgery	Lidocaine (intravenously)	Placebo	116	58	61.4	2
Fujita et al.,[94] 2016	RCT	I	Posterior lumbar interbody fusion	Pregabalin, 75 or 150 mg	Placebo	97	62.1	64.1	2
Garcia et al.,[95] 2013	RCT	I	Lumbar decompression surgery	Celecoxib + pregabalin + oxycodone	Morphine	22	68.6	NR	1
Garg et al.,[96] 2016	RCT	I	Elective spinal surgery	Dexmedetomidine, 0.5 μg/kg bolus then 0.3 μg/kg per hour infusion	Placebo	66	36.5	34.9	2
Glaser et al.,[97] 2016	RCT	I	Lumbar spine procedures	tDCS	Placebo	27	59.5	63	NR
Gottschalk et al.,[98] 2004	RCT	I	Lumbar spine surgery	0.1% ropivacaine, 12 mL/h epidural catheter	Placebo	30	58.1	42.3	3

Table 1 (part 4 of 6). Characteristics of included studies

Procedure; study	Study design	Level of evidence	Type of surgery	Intervention	Control	No. of participants	Mean age, yr	% female	Length of follow-up, d
Hernández-Palazón et al.,[99] 2001	RCT	I	Spinal fusion	Propacetamol, 2 g every 6 h (intravenously)	Placebo	44	40.5	45.1	3
Jirarattanaphochai et al.,[100] 2007	RCT	I	Lumbar spine surgery	Methylprednisolone–bupivacaine LAI	Placebo	103	52	53.4	2
Karst et al.,[101] 2003	RCT	I	Single-level microdiscectomy	Celecoxib, 200 mg twice daily	Placebo	34	44.26	38.2	2
Kesmici et al.,[102] 2011	RCT	I	Laminectomy	Dexketoprofen	Placebo	50	42.2	44	1
Kim et al.,[103] 2013	RCT	I	Posterior decompression + posterior lumbar interbody fusion	Ketamine, 0.5 mg/kg bolus then 1 or 2 μg/kg per minute infusion	Placebo	60	57	53.8	2
Naik et al.,[104] 2016	RCT	I	Thoracic or lumbar spine surgery	Dexmedetomidine	Placebo	142	64	NR	3
Pandey et al.,[105] 2004	RCT	I	Lumbar discectomy	Gabapentin, 300 mg	Placebo	56	38.8	32.15	2
Rajpal et al.,[106] 2010	RCT	I	Spinal surgery	Oxycodone + gabapentin + acetaminophen + dolasetron	PCA	200	55.3	57	1
Riest et al.,[107] 2006	RCT	I	Spinal, breast or orthopedic surgery	Rofecoxib, 50 mg peri- and postoperatively	Placebo	540	NR	NR	3
Rowe et al.,[108] 1992	RCT	I	Lumbar laminectomy	Indomethacin	Placebo	30	NR	NR	1
Singh et al.,[109] 2019	RCT	I	Elective lumbar spine surgery	ESPB	Placebo	40	35.2	12.5	1
Turan et al.,[110] 2004	RCT	I	Elective lumbar discectomy or spinal fusion surgery	Gabapentin	Placebo	50	46.5	44	1
Unterrainer et al.,[111] 2008	RCT	I	Elective posterior intervertebral body fusion of 2 or 3 lumbar vertebrae	0.25% levobupivacaine, 10 mL LAI	Piritramide	40	61.8	NR	1
Unterrainer et al.,[112] 2010	RCT	I	Spinal surgery	TENS pre- and/or postoperatively	Placebo	38	60.9	53.8	1
Yamashita et al.,[113] 2006	RCT	I	Spinal fusion therapy	Flurbiprofen axetil pre- or postoperatively	Placebo	36	61.7	NR	1
Ali et al.,[114] 2019	PCS	II	Elective spinal or peripheral nerve surgery	ERAS protocol	Placebo	275	61.1	46.2	30
Lovecchio et al.,[115] 2019	OCS	II	Lumbar spine surgery (decompression and fusion)	Educational conference	No education	2479	57.5	44.2	NR
Bohl et al.,[116] 2016	RCS	III	ACDF	MAP	PCA	239	48.5	47.3	NR
Smith et al.,[117] 2014	RCS	III	Spinal surgery	Acetaminophen (intravenously)	Placebo	68	50.4	75	3
Soffin et al.,[118] 2019	RCR	III	Lumbar decompression	Acetaminophen + gabapentin	Fentanyl	36	60.8	44	1
Chin et al.,[119] 2019	Case Report	IV	Posterior spinal fusion	Acetaminophen + baclofen ESPB	Placebo	1	35	100	11
Arthroscopy									
Ahn et al.,[120] 2016	RCT	I	Shoulder arthroscopy	Pregabalin, 150 mg	Placebo	60	53	57	2
Butterfield et al.,[121] 2001	RCT	I	ACL reconstruction	0.25% bupivacaine + epinephrine LAI	Placebo	24	31.5	22.3	NR
Ekman et al.,[122] 2016	RCT	I	Knee arthroscopy	Celecoxib, 400 mg	Placebo	200	45.2	42.6	1
Hoenecke et al.,[123] 2002	RCT	I	ACL reconstruction	0.25% bupivacaine (intra-articular infusion)	Placebo	26	36.3	26.8	2
Ilan et al.,[124] 2004	RCT	I	Knee arthroscopy	Rofecoxib, 50 mg	Placebo	50	NR	NR	1
Lierz et al.,[125] 2012	RCT	I	Therapeutic knee arthroscopy	Etoricoxib, 120 mg	Placebo	66	54	60.6	1

Table 1 (part 5 of 6). Characteristics of included studies

Procedure; study	Study design	Level of evidence	Type of surgery	Intervention	Control	No. of participants	Mean age, yr	% female	Length of follow-up, d
Mahure et al.,[126] 2017	RCT	I	Arthroscopic Bankart repair	TENS	Placebo	68	58.7	51.3	7
Mardani-Kivi et al.,[127] 2013	RCT	I	ACL reconstruction and meniscectomy	Celecoxib, 40 mg (ACL or meniscectomy)	Placebo	130	29.4	73.1	1
Mardani-Kivi et al.,[128] 2016	RCT	I	Arthroscopic Bankart repair	Gabapentin, 600 mg	Placebo	76	28.3	24.1	1
Montazeri et al.,[129] 2007	RCT	I	Knee arthroscopy	Gabapentin, 300 mg	Placebo	70	34.7	33.9	1
Ringrose et al.,[130] 1984	RCT	I	ACL reconstruction	0.5% bupivacaine FNB	Placebo	100	71.3	40.4	1
Saritas et al.,[131] 2015	RCT	I	Arthroscopic shoulder surgery	Magnesium sulfate	Placebo	67	40.7	48.3	1
Syed et al.,[132] 2018	RCT	I	Arthroscopic rotator cuff repair	Education (preoperatively)	No education	140	58.6	32.1	90
Matheny et al.,[133] 1993	RCR	III	ACL reconstruction	0.5% lidocaine LPB	PCA	58	23.6	25.8	2
Edkin et al.,[134] 1995	Case report	IV	ACL reconstruction	0.5% bupivacaine, 2–3 mg/kg + epinephrine femoral 3-in-1 block	None	25	NR	37.5	1
Other orthopedic surgery									
Argoff et al.,[135] 2016	RCT	I	Bunionectomy	Diclofenac, 18 or 35 mg or celecoxib	Placebo	421	39.7	87	9
Bech et al.,[136] 2011	RCT	I	Internal fixation (femoral neck fractures)	Ropivacaine (intra-articular infusion) + LAI	Placebo	50	85	NR	NR
Delbos et al.,[137] 1995	RCT	I	Knee ligamentoplasty	Propacetamol, 2 g every 6 h over 24 h (intravenously)	Placebo	60	26	7	1
Diaz-Borjon et al.,[138] 2017	RCT	I	Major orthopedic surgery	Parecoxib, 40 mg then 20 mg every 12 h	Placebo	281	58.7	51.9	3
El-Kerdawy et al.,[139] 2008	RCT	I	Lower extremity orthopedic surgery	5% magnesium, 50 mg (intrathecally + spinal anesthetic) + 2% magnesium, 100 mg/h infusion	Placebo	80	51.8	46.3	1
Fredman et al.,[140] 2000	RCT	I	Subcapital fracture of femur ORIF	Diclofenac	Placebo	40	77.5	75	1
Gehling et al.,[141] 2009	RCT	I	Elective orthopedic surgery	Morphine, 0.1 or 0.2 mg + bupivacaine (intrathecally)	Placebo	188	64.2	52.4	3
Hamal et al.,[142] 2015	RCT	I	Lower extremity orthopedic surgery	Gabapentin, 600 mg	Placebo	52	36.9	32.7	1
Jones et al.,[143] 1985		I	Fixation of ICF (compression screw or pin and plate)	LCNB	Placebo	19	81	94.7	1
Kinsella et al.,[144] 1992	RCT	I	Major or minor orthopedic surgery	Ketorolac trometamol	Placebo	65	53.1	52.3	1
Mattila et al.,[145] 2010	RCT	I	First metatarsal osteotomy	Dexamethasone, 9 mg	Placebo	60	50	93	3
Mostafa et al.,[146] 2018	RCT	I	Femur ORIF	Levobupivacaine FICB	Fentanyl PCA	60	59.1	30	1
Park et al.,[147] 1996	RCT	I	Major knee surgery (TKA or hemiarthroplasty of knee)	Clonidine	Placebo	39	57.5	59	1.5
Sanzone et al.,[148] 2016	RCT	I	Hip fracture fixation	Acetaminophen (intravenously)	Acetaminophen (orally)	332	NR	NR	1
Southworth et al.,[149] 2009	RCT	I	Elective single-site orthopedic or abdominal surgery	Ibuprofen, 400 or 800 mg	Placebo	406	45.3	78.4	7

Table 1 (part 6 of 6). Characteristics of included studies

Procedure; study	Study design	Level of evidence	Type of surgery	Intervention	Control	No. of participants	Mean age, yr	% female	Length of follow-up, d
Twiston-Davies et al.,[150] 1990	RCT	I	Hip or foot surgery	Indomethacin	Placebo	85	NR	67.3	2
Waikakula et al.,[151] 2011	RCT	I	Major orthopedic surgery	Celecoxib and/or gabapentin	Placebo	99	49.6	46.5	1
Weinbroum,[152] 2002	RCT	I	Inguinal hernia repair or joint arthroscopy	General anesthesia or epidural + dextromethorphan	Placebo	75	53.3	NR	3
Xu et al.,[153] 2016	RCT	I	Lower limb orthopedic trauma surgery	Ketorolac PCA	PCA	63	49.9	47.6	2
Zhao et al.,[154] 2016	RCT	I	Multiple-fracture surgery	Propofol + remifentanil + Ringer solution or dexmedetomidine	Placebo	86	45.4	57.5	1
Dwyer et al.,[155] 2018	PCS	II	CTR or distal radius ORIF	Educational handout, pain diary, pain catastrophizing questionnaire	No education	145	63.4	63.6	14
McLaughlin et al.,[156] 2018	PCS	II	TSA	NSAID + gabapentin interscalene block	Placebo	150	70	44	2
Robbins et al.,[157] 2015	PCS	II	Forefoot surgery	Liposomal bupivacaine LAI	Placebo	40	58	82.5	NR
Ayling et al.,[158] 2014	RCR	III	Major lower limb amputation	Perineural stump catheter with local anesthetic	Placebo	198	51.1	69.9	3
Cao et al.,[159] 2018	RCS	III	Abdominal or orthopedic surgery	Acetaminophen (intravenously) intra- and postoperatively	Placebo	147	62	46.3	1
Stepan et al.,[160] 2019	RCS	I	Ambulatory hand surgery	Education	Pre-education	1348	NR	NR	NR
Maurer et al.,[161] 2002	Case report	IV	Bilateral distal radius fracture	Ropivacaine BPD	Placebo	1	21	100	NR

ACB = adductor canal block; ACC = adductor canal catheter; ACDF = anterior cervical discectomy and fusion; ACL = anterior cruciate ligament; BPD = brachial plexus block; CTR = carpal tunnel release; ERAS = Enhanced Recovery After Surgery; ESPB = erector spinae plane block; FICB = fascia iliaca compartment block; FNB = femoral nerve block; FTB = femoral triangle block; ICF = intertrochanteric fracture; iPACK = infiltration between popliteal artery and capsule of the knee; LAI = local anesthetic infiltration; LB-PAI = liposomal bupivacaine pericapsular injection; LCNB = lateral cutaneous nerve block; LPB = lumbar plexus block; MAP = multimodal analgesia protocol; MWT = millimetre wave therapy; NR = not reported; NSAID = nonsteroidal anti-inflammatory drug; OCS = observational cohort study; ONB = obturator nerve block; ORIF = open reduction internal fixation; PCA = patient-controlled analgesia; PCS = prospective cohort study; PIA = preimplantation immersion anesthesia; RCS = retrospective cohort study; RCT = randomized controlled trial; ROS = retrospective observational study; SNB = sciatic nerve block; tDCS = transcranial direct current stimulation; TENS = transcutaneous electrical nerve stimulation; TNB = tibial nerve block; TSA = total shoulder arthroplasty.
*Level I = RCTs, level II = prospective cohort studies, level III = retrospective cohort studies, level IV = case reports and case series.

Arthroscopy

Among the 15 arthroscopy studies, PNB/LAI was used in 5 (33%), NSAIDs were used in 4 (27%), a nonpharmacologic intervention was used in 2 (13%),[126,132] gabapentinoids were used in 3 (20%),[120,128,129] and additional adjuvant analgesics were used in 1 (7%).

Fourteen studies (93%) showed a statistically significant reduction in opioid use compared to control. Percent opioid reduction ranged from 14% to 89% (median 40.6%). Nine studies (60%) showed a reduction in opioid use of at least 30%, and 5 studies (33%) showed a reduction of more than 50%.

Pain scores were reported in 11 studies, of which 9 (82%) showed significantly lower scores compared to the control intervention. The 1 study[121] in which postoperative length of stay was reported indicated significantly lower values compared to control. Patient satisfaction was reported in 1 study,[125] which showed that the intervention had a significantly positive effect. The frequency of adverse events was reported in 7 studies, 1 (14%) of which showed a significantly lower incidence compared to control.

Spinal surgery

Among the 29 spinal surgery studies, the intervention consisted of PNB/LAI in 4 (14%), NSAIDs in 6 (21%), acetaminophen in 2 (7%),[99,117] a nonpharmacologic intervention in 3 (10%),[97,112,115] gabapentinoids in 3 (10%)[94,105,110] and additional adjuvant analgesics in 4 (14%). Multimodal analgesia was used in 7 studies (24%).

A statistically significant reduction in opioid use compared to control was reported in 27 studies (93%). Percent opioid reduction ranged from 8.5% to 100% (median 35.3%). Of the 29 studies, 19 (66%) showed at least a 30% reduction in opioid use, and 9 (31%) showed more than a 50% reduction.

Table 2 (part 1 of 4). Major outcomes of included studies*

Procedure; study	Opioid reduction	% opioid reduction	Pain score	Length of stay	Mobilization	Adverse events	Patient satisfaction
Total knee arthroplasty							
Allen et al.,[21] 1998	–	NR	+				
Andersen et al.,[22] 2010	+	66.7	+				
Badner et al.,[23] 1996							
Bupivacaine LAI after wound closure	+	27.2	–		+		
Bupivacaine LAI before wound closure	–	16	–		–		
Borckardt et al.,[24] 2013	+	46	–				
Buvanendran et al.,[25] 2003	+	37.6	+				
Chan et al.,[26] 2015	+	52.3					
Essving et al.,[27] 2011	+	51	+				+
Essving et al.,[28] 2010	+	79.3	+	+	+	–	
Goyal et al.,[29] 2013	+	26.5					
Gomez-Cardero et al.,[30] 2010	+	24	+	+			
Hanson et al.,[31] 2014	+	26.3	+		+	–	–
He et al.,[32] 2013	+	16.6	+		+		
Ho et al.,[33] 2010	+	35.6	–				
Huang et al.,[34] 2007	+	40	+		+	–	
Hubbard et al.,[35] 2003							
Parecoxib, 20 mg	+	15.6	+			–	
Parecoxib, 40 mg	+	27.8	+			–	
Inan et al.,[36] 2007	+	45.7	–			+	
Jenstrup et al.,[37] 2012	+	28.6	+				
Kampitak et al.,[38] 2019	+	NR	+			–	
Lamplot et al.,[39] 2014	+	57.1	+			+	
Leung et al.,[40] 2018	+	23.4	+		+		
Mont et al.,[41] 2018	+	77.7	+			–	
Nader et al.,[42] 2016	+	20	+				
Pham Dang et al.,[43] 2005	+	81	+		+	+	
Runge et al.,[44] 2016	+	10	+			–	
Sahin et al.,[45] 2014	+	52.8	+			–	
Samona et al.,[46] 2017	+	49.3	–				
Sarridou et al.,[47] 2014	+	32	+				
Thijs et al.,[48] 2018	+	53.8					
Usichenki et al.,[49] 2007	–	NR	–				
Venditolli et al.,[50] 2006	+	40	+			–	
Williams et al.,[51] 2013	–	NR	–		–	–	
Banerjee[52] 2014	+	30.5		+	+		
Chin et al.,[53] 2020	+	38	–				
Klement et al.[x54] 2019	+	54.6		+		+	
Kuo et al.,[55] 2017	+	34	+				
Xiao et al.,[56] 2018							
Flurbiprofen axetil	+	25	+	+		–	
Celecoxib	+	50	+	+		–	
Horlocker et al.,[57] 2002	+	NR	–				
Stevenson et al.,[58] 2018	+	100	+				
Total hip arthroplasty							
Aguirre et al.,[59] 2012	+	25.5	+				+
Becchi et al.,[60] 2008	+	34	+				
Bilir et al.,[61] 2007	+	24.9	–				
Camu et al.,[62] 2002							
Valdecoxib, 40 mg	+	43	+		–	–	
Valdecoxib, 20 mg	+	41	+		–	–	
Clarke et al.,[63] 2009	–	NR	–			–	

Table 2 (part 2 of 4). Major outcomes of included studies*

Procedure; study	Opioid reduction	% opioid reduction	Pain score	Length of stay	Mobilization	Adverse events	Patient satisfaction
Desmet et al.,[64] 2017	+	44.3	–			+	
Fogarty et al.,[65] 1995	+	50	+			–	
Hwang et al.,[66] 2010	+	NR	+			–	
Köroglu et al.,[67] 2008	+	36.1	+				
Laitenan et al.,[68] 1992	+	39.8	+			–	
Lan et al.,[69] 2012	+	30.3	–			+	
Malan et al.,[70] 2003							
Parecoxib, 20 mg	+	22.1	+			–	
Parecoxib, 40 mg	+	43.1	+			+	
Martinez et al.,[71] 2013	+	50.6	–			–	
Murphy et al.,[72] 2012	+	45.8	–			–	
Remérand et al.,[73] 2009	+	28				–	
Serpell et al.,[74] 1989	+	50					
Siddiqui et al.,[75] 2007	+	40.3	+			+	+
Stevens et al.,[76] 2007	+	44.6	–				
Ward et al.,[77] 2012	+	100	+	+		–	
Gurkan et al.,[78] 2018	+	32	+			–	
Post et al.,[79] 2010	+	50.4	+			+	
Banerjee et al.,[80] 2011	+	30.9`		+	+		
Maheshwari et al.,[81] 2006	+	15	+			+	
Uusalo et al.,[82] 2019	+	17.3					
VanWagner et al.,[83] 2019	+	61		+			
Total knee arthroplasty and total hip arthroplasty							
Alexander et al.,[84] 2002	+	29.6	+			–	
Arcioni et al.,[85] 2007	+	69.2				–	
Boeckstyns et al.,[86] 1992	+	23.4				–	
Oberhofer et al.,[87] 2011	+	89.3	+			–	
Kazerooni et al.,[88] 2012							
THA: celecoxib, 200 mg twice daily	+	39.8	+				
TKA: celecoxib, 200 mg twice daily	+	36.3	+				
Singla et al.,[89] 2010	+	30.9	+				
Raiff et al.,[90] 2014	–	NR					
Spinal surgery							
Aveline et al.,[91] 2006							
Ketamine	+	17.1	–			–	
Morphine + ketamine	+	57	+			–	
Cassinelli et al.,[92] 2008	+	74.1	+				
Farag et al.,[93] 2013	+	25.7	+	–		–	
Fujita et al.,[94] 2016							
Pregabalin, 75 mg	+	30	–			–	
Pregabalin, 150 mg	+	30.0	–			–	
Garcia et al.,[95] 2013	+	58.3	+	+		–	
Garg et al.,[96] 2016	+	22	+			–	
Glaser et al.,[97] 2016	+	23	–				
Gottschalk et al.,[98] 2004	+	38.2	+			–	+
Hernandez et al.,[99] 2001	+	46	–				
Jirarattanaphochai et al.,[100] 2007	+	12.5	+			–	
Karst et al.,[101] 2003	–	13.4	–				
Kesmici et al.,[102] 2011	+	35.6	–			–	
Kim et al.,[103] 2013							
Ketamine, 0.5 mg/kg bolus then 1 μg/kg per minute infusion	+	42.6	–			–	–
Ketamine, 0.5 mg/kg bolus then 2 μg/kg per minute infusion	–	8.5	–			–	–

Table 2 (part 3 of 4). Major outcomes of included studies*

Procedure; study	Opioid reduction	% opioid reduction	Pain score	Length of stay	Mobilization	Adverse events	Patient satisfaction
Pandey et al.,[105] 2004	+	35.1	+			–	
Rajpal et al.,[106] 2010	+	37.6	–			+	
Riest et al.,[107] 2006	+	20	+				
Rowe et al.,[108] 1992	+	30	+				
Singh et al.,[109] 2019	+	80.6	+				
Turan et al.,[110] 2004	+	61.9	+			+	
Unterrainer et al.,[111] 2008	+	30.8	–				
Unterrainer et al.,[112] 2010							
TENS postoperatively	+	NR					
TENS pre- and postoperatively	+	NR					
Yamashita et al.,[113] 2006							
Flurbiprofen axetil preoperatively	+	62.5	+			–	
Flurbiprofen axetil postoperatively	+	NS	–			–	
Ali et al.,[114] 2019	+	13.9			+		
Lovecchio et al.,[115] 2019	+	22.1					
Bohl et al.,[116] 2016	+	56.9	–			+	
Smith et al.,[117] 2014	+	45.1	–				
Soffin et al.,[118] 2019	+	93.6	–				
Chin et al.,[119] 2019	+	100					
Arthroscopy							
Ahn et al.,[120] 2016	+	31.4	+			–	
Butterfield et al.,[121] 2001	+	57.7		+		–	
Ekman et al.,[122] 2016	+	21.7	+				
Hoenecke et al.,[123] 2002	–	NR	+				
Ilan et al.,[124] 2004	+	47.8	–				
Lierz et al.,[125] 2012	+	62.5	+			–	+
Mahure et al.,[126] 2017	+	25.5	+				
Mardani-Kivi et al.,[127] 2013							
ACL: celecoxib, 40 mg	+	33.7	+			–	
Meniscectomy: celecoxib, 40 mg	+	59.9	+			–	
Mardani-Kivi et al.,[128] 2016	+	54	–			–	
Montazeri et al.,[129] 2007	+	14	+			–	
Ringrose et al.,[130] 1984	+	40					
Saritas et al.,[131] 2015	+	24.5	+				
Syed et al.,[132] 2018	+	41.2	+				
Matheny et al.,[133] 1993	+	89				+	
Edkin et al.,[134] 1995	+	NR					
Other orthopedic surgery							
Argoff et al.,[135] 2016							
Diclofenac, 35 mg	+	45.9				–	
Diclofenac, 18 mg	+	37.8				–	
Celecoxib	+	29.7				–	
Bech et al.,[136] 2011	–	100	–				
Delbos et al.,[137] 1995	+	24	–			–	
Diaz-Borjon et al.,[138] 2017	+	33	+				
El-Kerdawy et al.,[139] 2008	+	38.4	–			+	
Fredman et al.,[140] 2000	–	NR	–				
Gehling et al.,[141] 2009							
Morphine, 0.1 mg + bupivacaine intrathecally	+	20				–	
Morphine, 0.2 mg + bupivacaine intrathecally	+	40				–	
Hamal et al.,[142] 2015	+	40	+				
Jones et al.,[143] 1985	+	64.4					
Kinsella et al.,[144] 1992	+	66.7	–			–	
Mattila et al.,[145] 2010	+	28.9	+			–	

Table 2 (part 4 of 4). Major outcomes of included studies*

Procedure; study	Opioid reduction	% opioid reduction	Pain score	Length of stay	Mobilization	Adverse events	Patient satisfaction
Park et al.,[147] 1996	+	37	–			+	
Sanzone et al.,[148] 2016	+	31	+	+			
Southworth et al.,[149] 2009							
Ibuprofen, 400 mg	+	3	–			–	
Ibuprofen, 800 mg	+	21.0	+			–	
Twiston-Davies et al.,[150] 1990	+	73	+				
Waikakula et al.,[151] 2011	+	55.6	–			–	
Weinbroum,[152] 2002							
General anesthesia + dextromethorphan	+	44.9	+			–	
Epidural + dextromethorphan	+	50	+			–	
Xu et al.,[153] 2016	+	33.5	–			+	
Zhao et al.,[154] 2016	+	5	+			–	
Dwyer et al.,[155] 2018	+	54.5				–	
McLaughlin et al.,[156] 2018	+	44	–	+			
Robbins et al.,[157] 2015	–	NR					
Ayling et al.,[158] 2014	+	39.6	–			–	
Cao et al.,[159] 2018	+	46	+			–	
Stepan et al.,[160] 2019	+	52.3					
Maurer et al.,[161] 2002	+	NR					

NR = not reported; NS = not significant; TENS = transcutaneous electrical nerve stimulation; THA = total hip arthroplasty; TKA = total knee arthroplasty.
*+ represents a positive significant difference compared to control, and – represents no difference compared to control, when reported.

Pain scores were reported in 25 studies, of which 13 (52%) showed significantly lower scores compared to the control intervention. Of the 2 studies in which postoperative length of stay was reported,[93,95] 1 showed significantly lower values compared to control. Mobilization was reported in 1 study,[114] which showed a significant improvement compared to control. Patient satisfaction was reported in 2 studies,[98,103] with 1 showing significantly higher satisfaction compared to control.[98] The frequency of adverse events was reported in 15 studies, of which 3 (20%) indicated that the intervention had a significant improvement on the incidence of adverse events; the remaining studies showed no difference between the intervention and control groups.

Other orthopedic surgery

Among the 27 studies on other surgical procedures, PNB/LAI was used in 7 (26%), NSAIDs in 7 (26%), acetaminophen in 3 (11%),[137,148,159] a nonpharmacologic intervention in 2 (7%)[155,160] and additional adjuvant analgesics in 5 (18%). Multimodal analgesia was used in 3 studies (11%).[151,154,156]

Twenty-four studies (89%) showed a statistically significant opioid reduction compared to control. Percent opioid reduction ranged from 3% to 100% (median 40%). A reduction in opioid use of at least 30% was reported in 20 studies (74%), and a reduction in opioid use of more than 50% was reported in 9 studies (33%).

Pain scores were reported in 20 studies, with 10 (50%) showing significantly lower scores compared to the control intervention. Both studies[148,156] in which postoperative length of stay was reported indicated significantly lower values compared to control. The frequency of adverse events was reported in 16 studies, with 3 (19%) showing significantly lower values compared to control; in the remaining studies, no difference was observed between the intervention and control groups.

Discussion

Our review was a comprehensive review of the literature on reduction in opioid use after orthopedic surgery. It was conducted systematically with rigorous methodology, as outlined in the PRISMA extension for scoping reviews.[20] Although a majority (81.6%) of the included studies showed a reduction in opioid consumption of at least 25%, the reduction was not associated with a simultaneous positive effect on pain scores or the incidence of adverse events.

A majority (67.4%) of studies included a follow-up duration of 2 days or less, with only 8.5% having a follow-up duration of more than 7 days. This is a major drawback when one is trying to infer the potential for limiting persistent opioid use after orthopedic surgery.

Even among studies that reported a significant decrease in opioid use, a reduction in opioid-related adverse drug effects was reported or observed inconsistently. This may be a result of the particular type of intervention, as well as its potential to affect pain directly and its relative effect on adverse effects. For example, the use of gabapentin, although associated with decreased opioid

use, has been shown to be associated with substantial sedation and risk of adverse effects on its own.[162]

Opioid sparing is most possible with the use of a multimodal approach rather than a single, nonopioid substitute; however, this approach continues to be underused or applied inconsistently.[163–166] In our review, multimodal analgesia was used in less than 25% of studies within each procedure type.

It is also relevant to note that postsurgical pain can be influenced by many patient- and procedure-dependent factors. In addition, studies have shown significant variation in pain-resolution patterns,[167–170] and analgesic consumption is dynamic and changes with time.[171]

An important factor not reported in many studies is the use of preoperative screening based on known risk factors for long-term opioid use after surgery, including male sex, age more than 50 years, prior opioid use, alcohol abuse and mental illness.[11,172,173] As well, the use of benzodiazepines or antidepressants preoperatively has been found to be associated with a higher risk of long-term opioid use postoperatively.[11,174] Future trials should consider screening protocols to evaluate risk in potential patients.[175,176] One step toward this has been preoperative screening and referral to pain specialists for patients with preoperative long-term opioid use.[114,177]

The context of opioid use in hospital and its effect on long-term opioid use is still unclear. Although studies have shown a reduction in inpatient opioid consumption, especially with implementation of Enhanced Recovery After Surgery pathways,[178,179] there is no evidence to suggest that limiting intraoperative administration of opioids influences the risk of long-term opioid use postoperatively.[180–182] The most direct contributor to long-term opioid use identified in the literature is inappropriate physician prescribing.[11,171,183] An observational study showed that opioids are prescribed postoperatively to 98.3% of patients in North America, compared to 70.2% of patients in Europe, although the mean worst pain scores were higher in North American patients than in patients from Europe (7.4/10 v. 5.4/10).[184] Yet although opioid prescribing has been identified as the problem, it seems that very few investigators have incorporated this factor in their interventions. In a scoping review of opioid-free analgesia after major surgery, Fiore and colleagues[185] observed that a majority of RCTs compared opioid-free strategies only during the hospital stay, and only 7 targeted postdischarge analgesia.

In view of these challenges, education as a nonpharmacologic tool to reduce opioid consumption and alleviate pain may play an important role. However, in the present review, an educational intervention was used in only 4 studies (2.8%); all showed significant reduction in opioid use, ranging from 22.1% to 54.5%. Notably, these studies involved education in many different forms, whether for prescribers[115,160] or patients.[132] Bohl and colleagues[116] investigated the use of a multimodal analgesia protocol that included preoperative counselling in addition to a variety of different classes of analgesic medications pre-, intra- and postoperatively. Similarly, Ali and colleagues[114] used an Enhanced Recovery After Surgery protocol involving preoperative education and screening for long-term opioid use, as well as multimodal perioperative analgesia. Both studies showed significant positive effects on opioid consumption. A recent systematic review of institutional interventions such as education, counselling and prescribing guidelines showed that, on the patient side, educational programs were most effective, and on the provider side, the use of prescribing guidelines was most effective.[186] Although there is scant evidence available on these types of interventions, with only 13 studies being included in that systematic review, there is reason to believe that these institutional strategies will be crucial in tackling this complex problem.

Somewhat unexpectedly, the majority (80.1%) of studies that included evidence on reducing opioid consumption after orthopedic surgery in the present review were randomized studies. This not only suggests the importance of this problem in this surgical specialty, but also identifies opportunities for synthesis of available information in the form of appropriate meta-analyses and network meta-analyses to investigate the relative merits and effect size of opioid reduction with individual interventions or combination of interventions.[16,187,188]

Future trials should also consider methodologic issues in surgical trials looking at opioid reduction. Measuring opioid use, for either relative increase or decrease, in postsurgical trials can be challenging: apart from the weak correlation between pain intensity and opioid use, there may also be issues of sedation accompanying adjuvant analgesics.[189,190] Ideally, there should be some integrated measure of pain intensity and analgesic (opioid) demand.[191]

Limitations

One limitation of this review is the inclusion of all levels of evidence instead of only evidence from RCTs. As well, much of the data gathered were reported simply in terms of whether or not there was improvement, with many studies reporting little quantitative data. However, the purpose of this scoping review was to identify literature and general results, with the goal of directing areas for future research, as well as guiding the development of study protocols incorporating a variety of both pharmacologic and nonpharmacologic interventions. Included studies were relatively small, with a median sample of 68 participants, and relatively short, with a median follow-up duration of 2 days. Last, there was a wide variety of procedures with varying levels of postoperative pain represented in the included studies.

Conclusion

This scoping review showed that there is a large body of evidence, much of it from randomized trials, that shows the promise of both pharmacologic and nonpharmacologic interventions in the goal of reduction of opioid use after orthopedic surgery. However, rigorously designed RCTs incorporating evidence-based pharmacologic and nonpharmacologic interventions in a multimodal regimen are needed to evaluate the goal of reducing opioid use, for the good of patients, medicine and society.

Affiliations: From the Michael G. DeGroote School of Medicine, McMaster University, Hamilton, Ont. (Gormley, Gouveia, Stewart, Shehata); the Faculty of Science, McMaster University, Hamilton, Ont. (Sakha, Emmanuel); the Department of Surgery, McMaster University, Hamilton, Ont. (Tushinski, Madden); the Hamilton Health Sciences – Juravinski Hospital, Hamilton, Ont. (Tushinski); the Department of Anesthesia, McMaster University, Hamilton, Ont. (Shanthanna); and St. Joseph's Healthcare Hamilton, Hamilton, Ont. (Shanthanna, Madden).

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