ANESTHESIOLOGY

Pharmacotherapy for the Prevention of Chronic Pain after Surgery in Adults: An Updated Systematic Review and Meta-analysis

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EDITOR'S PERSPECTIVE

What We Already Know about This Topic

- Chronic postsurgical pain is a common problem that can severely affect a patient's quality of life
- Many medications have been examined for their utility in preventing chronic postsurgical pain, but we do not understand which may be effective

What This Article Tells Us That Is New

- Seventy randomized controlled trials were identified published since a previous meta-analysis involving drugs to prevent chronic postsurgical pain
- Overall effects of the drugs were small and of uncertain clinical relevance

ABSTRACT

Background: Chronic postsurgical pain can severely impair patient health and quality of life. This systematic review update evaluated the effectiveness of systemic drugs to prevent chronic postsurgical pain.

Methods: The authors included double-blind, placebo-controlled, randomized controlled trials including adults that evaluated perioperative systemic drugs. Studies that evaluated same drug(s) administered similarly were pooled. The primary outcome was the proportion reporting any pain at 3 or more months postsurgery.

Results: The authors identified 70 new studies and 40 from 2013. Most evaluated ketamine, pregabalin, gabapentin, IV lidocaine, nonsteroidal anti-inflammatory drugs, and corticosteroids. Some meta-analyses showed statistically significant—but of unclear clinical relevance—reductions in chronic postsurgical pain prevalence after treatment with pregabalin, IV lidocaine, and nonsteroidal anti-inflammatory drugs. Meta-analyses with more than three studies and more than 500 participants showed no effect of ketamine on prevalence of any pain at 6 months when administered for 24 h or less (risk ratio, 0.62 [95% CI, 0.36 to 1.07]; prevalence, 0 to 88% ketamine; 0 to 94% placebo) or more than 24 h (risk ratio, 0.91 [95% CI, 0.74 to 1.12]; 6 to 71% ketamine; 5 to 78% placebo), no effect of pregabalin on prevalence of any pain at 3 months (risk ratio, 0.88 [95% CI, 0.70 to 1.10]; 4 to 88% pregabalin; 3 to 80% placebo) or 6 months (risk ratio, 0.78 [95% CI, 0.47 to 1.28]; 6 to 68% pregabalin; 4 to 69% placebo) when administered more than 24 h, and an effect of pregabalin on prevalence of moderate/severe pain at 3 months when administered more than 24 h (risk ratio, 0.47 [95% CI, 0.33 to 0.68]; 0 to 20% pregabalin; 4 to 34% placebo). However, the results should be interpreted with caution given small study sizes, variable surgical types, dosages, timing and method of outcome measurements in relation to the acute pain trajectory in question, and preoperative pain status.

Conclusions: Despite agreement that chronic postsurgical pain is an important topic, extremely little progress has been made since 2013, likely due to study designs being insufficient to address the complexities of this multifactorial problem.

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Chronic postsurgical pain has been recognized as a disabling complication that can have a severe impact on patient health and quality of life, with pain that can sometimes last for a significant amount of time after surgery. On average, 10% of patients undergoing common surgical procedures will suffer from chronic pain.[1–3] Given the difficulty in managing chronic postsurgical pain, many efforts to prevent the transition from acute to chronic pain have been evaluated, including perioperative administration of various systemic pharmacologic interventions. The aim of this review is to synthesize available evidence from placebo-controlled, randomized controlled trials on the effectiveness and safety of systemically administered drugs that aim to prevent the development of chronic postsurgical pain in adults

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undergoing elective surgeries. This systematic review is the first update of an original review we published in 2013[4] and it will describe results of an updated search of new studies published since then. The rationale for updating the review is to provide the most current and best available evidence to inform clinical decision-making for this highly relevant issue.

Materials and Methods

This systematic review was conducted according to the original study protocol,[5] and in a consistent manner with the original review.[4] Procedures were guided by Cochrane Collaboration recommendations[6] and followed the principles of Preferred Reporting Items for Systematic Reviews and Meta-analysis[7] and A Measurement Tool to Assess Systematic Reviews.[8]

Data Sources and Search Strategy

Using the originally published search strategy (Supplemental Digital Content 1, appendix A, http://links.lww.com/ALN/C628),[4] the following databases were searched for trials since the previous review (July 17, 2013, to July 1, 2019): Cochrane Central Register of Controlled Trials, MEDLINE, and EMBASE. We conducted hand searches of trial registries using each intervention as the key word (*e.g.,* ketamine and pregabalin, among others) and filtered results by interventional studies, age group (18 to 65+ yr), and outcomes (*e.g.,* chronic pain OR persistent pain OR persistent postsurgical pain). No limits were placed regarding date, language, or status of the publications. Backward reference searching was conducted by screening reference lists of included studies and relevant systematic reviews. Authors of included studies and experts were asked about recent or forthcoming studies that fit our eligibility criteria.

Study Selection

We included double-blind, placebo-controlled, randomized controlled trials that involved participants 18 yr and older undergoing a planned surgical procedure, that evaluated one or more drugs administered systemically immediately before, during, or after the procedure by any dose, route, or frequency, and that included data on a patient-reported measure of pain 3 or more months postsurgery. This review only included randomized controlled trials because "randomization is the only way to prevent systematic differences between baseline characteristics of participants in different intervention groups in terms of both known and unknown (or unmeasured) confounders."[6]

Data Extraction and Assessment of Risk of Bias

The following was extracted for each study: drug name; trial methods; trial registration; participant demographics; preoperative pain status and analgesic use; type of surgery; dosing including route, timing, and duration; dropouts due to treatment-emergent adverse effects; concomitant standardized analgesic approach; planned dichotomous outcomes; proportion of patients reporting any pain (more than 0 out of 10) or moderate to severe pain (greater than or equal to 4 out of 10) at 3, 6, and 12 months postsurgery. We reviewed trial registries when available, and in the case of secondary publications, original papers were reviewed. If a study reported parametric measures of pain intensity but not dichotomous measures of proportions of participants reporting pain, we contacted corresponding authors for supplementary data. Extraction was performed by M.E.C. and I.G. by reading each included study and completing the data extraction form.

Eligible studies were evaluated independently by two reviewers (M.E.C., I.G.) for risk of bias using the Cochrane risk of bias tool.[9] Any discrepancies could be resolved by a third coauthor (E.V.); however, this did not occur. Attrition bias was assessed as "low-risk" for studies where the dropout rate was less than 20%.[10] Studies with higher dropout rates that included intention-to-treat analyses were assessed as "unclear" or "high risk of bias." Chronic pain was rarely the prespecified primary outcome and most included trials were underpowered for this outcome; therefore, "other potential sources of bias" were assessed as high-risk in studies that had fewer than 50 participants per arm.[11] While it could be argued that, for pain prevention trials, this number should even be higher than 50 participants per arm, there is currently no consensus for a specific higher threshold for trial size in this setting.[12]

Outcome Measures

The primary outcome for the review was the proportion of participants reporting any pain at the anatomical site of the procedure or pain referred to the surgical site, or both, 3 months or more after the surgery.[2] Secondary outcomes were the number of participants reporting moderate to severe pain at the anatomical site of the procedure or pain referred to the surgical site—or both—6 months or more after surgery, as well as the number of participants who dropped out of the study due to treatment-related adverse effects. All results reported represent aggregate data from the 2013 and current review, unless otherwise specified.

Statistical Analysis

Comparing the study drug(s) with placebo was the primary objective. Studies were grouped if they evaluated the same drug(s) administered in a similar manner (*i.e.,* dosage, route of administration, and treatment duration). Given the potential effect on outcome of surgical procedure and underlying condition, timing of outcome measurement, and duration of the intervention, subgroup analyses were conducted according to these parameters. Given the diverse features of the studies included in the review, not all were necessarily represented in a meta-analysis.

Statistical analyses were conducted using Review Manager v5.3.[13] Dichotomous data were analyzed using Mantel–Haenszel fixed-effects model for risk ratio with 95% CI. Heterogeneity was evaluated by visual examination of forest plots and use of the I^2 statistic. In cases of moderate to considerable heterogeneity (*i.e.,* 30 to 100%) the random-effects model was employed.[6] For studies with multiple intervention arms, we split the "shared" (placebo) group into two or more groups with smaller sample size, and included two or more (reasonably independent) comparisons.[6] Sensitivity analyses were conducted to evaluate robustness of a result by omitting studies considered to be outliers with respect to study quality, drug dose and duration, or pain measurement scales.

Results

The search identified 6,709 citations, with first level screening based on title and abstract yielding 115 studies for full text review, of which 70 new studies fulfilled the inclusion criteria (fig. 1). The majority of the 45 excluded studies did not follow participants for at least 3 months (n = 15), were not placebo controlled (n = 9), were not double-blinded (n = 7), were not relevant to the prevention of chronic postsurgical pain (n = 6), or did not evaluate drugs administered systemically (n = 4). Full details regarding the excluded studies are summarized in Supplemental Digital Content 2 (appendix B, http://links.lww.com/ALN/C629). Our trial database searches yielded 46 ongoing and unpublished studies. Ongoing studies are evaluating ketamine (n = 12), pregabalin (n = 11), IV lidocaine (n = 8), dexamethasone (n = 4), gabapentin (n = 3), dexmedetomidine (n = 2), magnesium (n = 2), acetyl-salicylic acid (n = 1), cannabinoids (n = 1), clonidine (n = 1), duloxetine (n = 1), lamotrigine (n = 1), meloxicam (n = 1), midazolam (n = 1), propranolol (n = 1), sevoflurane (n = 1), and tramadol-paracetamol (n = 1). A summary of the 46 ongoing studies is included in Supplemental Digital Content 3 (appendix C, http://links.lww.com/ALN/C630).

Characteristics of Included Studies

Characteristics of the 110 included studies (70 new plus 40 from the previous review)[4] are summarized in Table 1 and Supplemental Digital Content 4 (appendix D, http://links.lww.com/ALN/C631). Studies (new and from previous review) involved various surgeries including breast (n = 19), total hip or knee arthroplasty (n = 16), thoracotomy (n = 14), spine (n = 14), abdominal or pelvic (n = 12), heart (n = 8), limb amputation (n = 5), thyroidectomy (n = 5), inguinal herniorrhaphy (n = 4), caesarean section (n = 3), carpal tunnel (n = 2), brain (n = 1), mandibular fracture (n = 1), and a combination of surgeries (n = 6) (table 1).

Of all the new and previous studies, only 37 studies included patients that were free of pain before surgery. Patients taking various analgesics were excluded from 36 trials. Preoperative pain or analgesic use was unclear in 11 studies. Patients with preexisting pain were included in 26 studies (table 1).

Studies received financial support from research granting agencies (n = 28), institutional and/or departmental sources (n = 18), pharmaceutical companies (n = 10), and granting agencies and pharmaceutical companies (n = 1); 10 studies stated that no funding was received; and the source of funding was not reported for 43 studies (Supplemental Digital Content 4, appendix D, http://links.lww.com/ALN/C631). Insufficient reporting prohibits further investigation of possible correlations between sources of financial support and study outcomes and it is beyond the scope and preplanned objectives of the current review. Seventy-nine of 110 (71.8%) included studies had at least four of seven items that qualified as low risk of bias (Supplemental Digital Content 5, appendix E, http://links.lww.com/ALN/C632). Most studies were of small sample size having fewer than 50 participants per arm (n = 70 [64%]), greater than or equal to 50 and fewer than 100 per arm (n = 29 [26%]), and greater than or equal to 100 per arm (n = 11 [10%]).

Ketamine

Thirteen new studies (n = 1,283 participants)[14–27] evaluated ketamine or (S)-ketamine (total, 27 studies; n = 2,757).[14–41] Nine of 27 studies reported prevalence of any pain at 3 months,[16,20,22,26,29,37,39–41] 16 studies at 6 months,[14–17,22,24–26,30,33–37,40,41] and five studies at 12 months.[14–16,28,30] Prevalence of any pain at 3 months ranged from 5.6 to 72.2% (mean, 35.0%) in the placebo arm and 5.6 to 83.3% (mean, 31.5%) in the ketamine arm. No treatment effect of ketamine was observed on prevalence of any pain regardless of outcome timing, duration of drug administration, or surgical procedure (fig. 2). Forest plots for studies evaluating ketamine are included in Supplemental Digital Content 6 (appendix F, http://links.lww.com/ALN/C633). In 2013, subgroup analysis based on duration of treatment suggested a significant effect of ketamine compared to placebo (odds ratio, 0.37 [95% CI, 0.14 to 0.98]; two studies; 135 participants) on the prevalence of any pain at 3 months for studies evaluating ketamine treatment for more than 24 h; however, the current review did not demonstrate a similar treatment effect (risk ratio, 0.83 [95% CI, 0.58 to 1.18]; five studies; 331 participants).

Two studies reported prevalence of moderate to severe pain at 3 months (placebo: range, 14.7 to 16.7%; mean, 15.7; ketamine: range, 9.1 to 32.3%; mean 20.7),[16,22] six studies at 6 months (placebo: range, 0.0 to 39.1%; mean, 17.9; ketamine: range, 3.2 to 26.7%; mean, 12.2),[14,16,22,33,35,37] and two studies at 12 months (placebo: range, 7.1 to 26.1%; mean, 16.6; ketamine: range, 0.0 to 12.5%; mean, 6.3).[14,16] No treatment effect of ketamine was observed on prevalence of moderate to severe pain regardless of outcome timing, duration of drug administration, or surgical

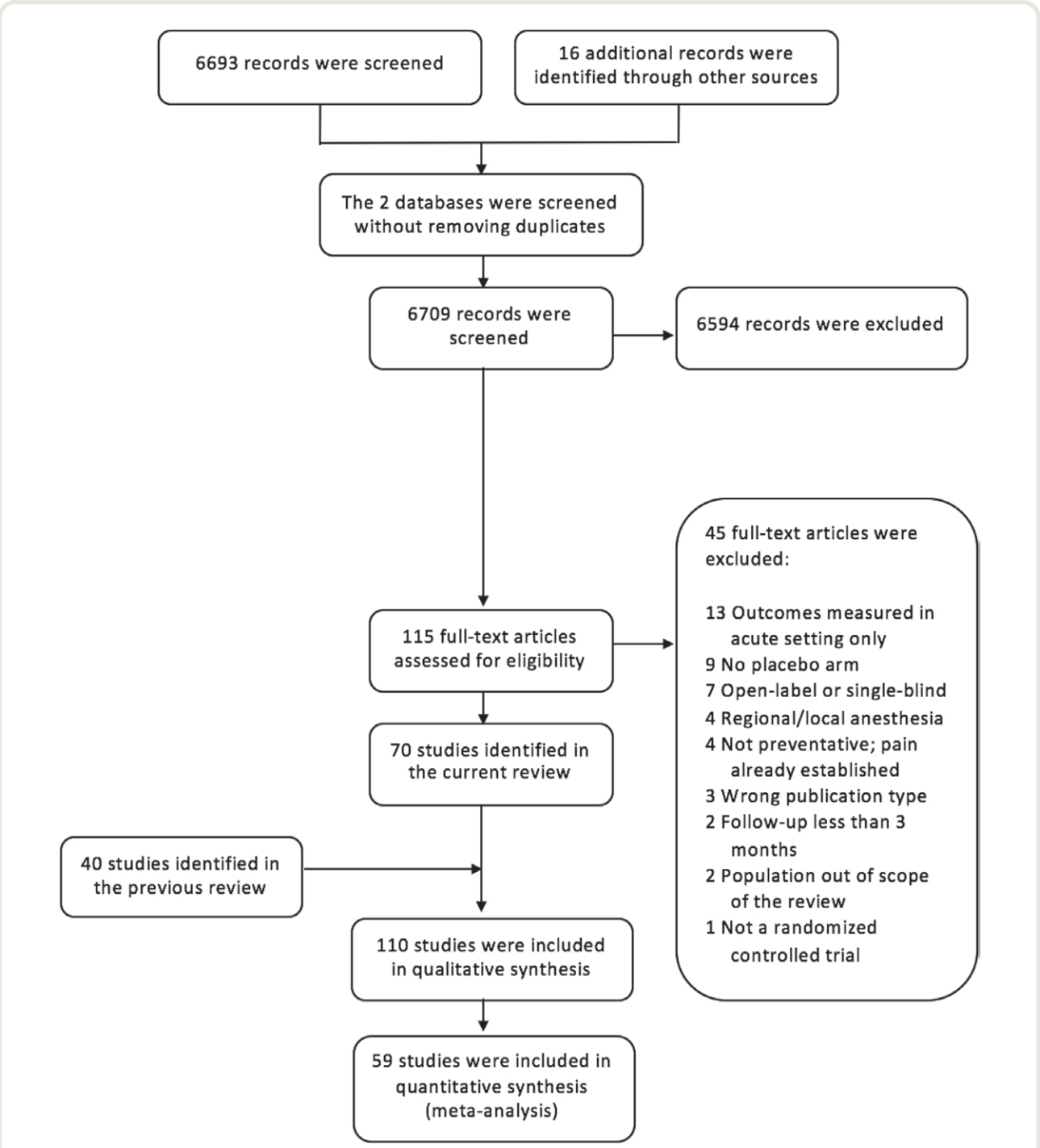

Fig. 1. Study flow diagram.

procedure (fig. 2). Only two of the 27 ketamine studies provided data regarding dropouts due to treatment-related adverse effects. Of those, 4 of 70 (5.7%) received ketamine and 4 of 70 (5.7%) received placebo. Adverse events included hallucinations, delayed emergence, dizziness, diplopia, and confusion.[19,25]

Ketamine has been evaluated in three recent reviews for orthopedic surgery,[42,43] and thoracotomy.[44] Consistent with the current review, the majority (two of three) indicated results to be inconclusive.[43,44] In disagreement, one narrative systematic review evaluating various interventions for adults receiving primary total knee arthroplasty concluded

Table 1. Characteristics of Included Studies

Drug	Surgery	No. of Patients	Allowed Patients with Pain	Follow-up, mo	Preoperative Dose	Intraoperative Dose	Postoperative Dose	Cumulative Dose*	Study ID
Ketamine	Total knee arthroplasty	75	Yes	12	200 μg/kg	120 μg · kg^{-1} h^{-1}	60 μg/kg for 48 h	3,305 μg/kg†	Aveline *et al.*,[14] 2014 (new)
Ketamine	Cesarean	140	No	12	250 μg/kg	None	None	250 μg/kg	Bilgen *et al.*,[15] 2012 (new)
					500 μg/kg	None	None	500 μg/kg	
					1,000 μg/kg	None	None	1,000 μg/kg	
Ketamine	Breast augmentation	106	No	12	420 μg/kg	200 μg · kg^{-1} · h^{-1}	None	820 μg/kg†	Chaparro *et al.*,[28] 2010 (2013 review)
Ketamine	Thoracotomy	77	No	12	100 μg/kg	100 μg/kg for 96 h		9,700 μg/kg	Chumbley *et al.*,[16] 2019 (new)
Ketamine	Breast	36	Long-term analgesic or anti-inflammatory treatment excluded	3	500 μg/kg	250 μg · kg^{-1} · h^{-1}	None	908 μg/kg†	Crousier *et al.*,[29] 2008 (2013 review)
Ketamine	Major lower back	160	Yes	12	250 μg/kg	250 μg/kg for ~1 h; down to 100 μg/kg until end of postanesthesia care unit stay		900 μg/kg†	Czarnetzki *et al.*,[27] 2020 (new)
Ketamine	Rectal cancer	100	Unclear	12	250 μg/kg	125 μg · kg^{-1} · h^{-1}	None	772 μg/kg†	De Kock *et al.*,[30] 2001 (2013 review)
					500 μg/kg	250 μg · kg^{-1} · h^{-1}	None	1,595 μg/kg†	
Ketamine	Thoracotomy	86	No	4	1,000 μg/kg	1,000 μg · kg^{-1} · h^{-1}	1,000 μg/kg for 24h	3,000 μg/kg†	Duale *et al.*,[31] 2009 (2013 review)
Ketamine	Orthopedic	120	Taking psychoactive drugs or opiates excluded	3	150 μg/kg	None	None	150 μg/kg	Dullenkopf *et al.*,[32] 2009 (2013 review)
					500 μg/kg	None	None	500 μg/kg	
Ketamine	Amputation	45	Yes	6	500 μg/kg	150 μg/kg for 72 h		11,300 μg/kg	Hayes *et al.*,[33] 2004 (2013 review)
Ketamine	Thoracotomy	81	Taking neuropathic pain drugs, antidepressants, anticonvulsants, NSAIDs, or opioids excluded	6	1,000 μg/kg	120 μg/kg for 72 h		9,640 μg/kg	Hu *et al.*,[17] 2014 (new)
Ketamine	Nephrectomy	63	No	3	150 μg/kg	100 μg · kg^{-1} · h^{-1}	100 μg/kg for 24 h	22,350 μg/kg†	Jendoubi *et al.*,[18] 2017 (new)
Ketamine	Thoracotomy	60	No	3	500 μg/kg	180 μg · kg^{-1} · h^{-1}	90 μg/kg for 48 h	5,356 μg/kg†	Joseph *et al.*,[19] 2012 (new)
Ketamine	Radical prostatectomy	160	Chronic opioid use excluded	6	200 μg/kg	175 μg/kg in 70 min	None	375 μg/kg	Katz *et al.*,[34] 2004 (2013 review)
					None	200+175 μg/kg in 70 min	None	375 μg/kg	
Ketamine	Thyroidectomy	64	No	3	150 μg/kg	120 μg · kg^{-1} · h^{-1}	None	472 μg/kg†	Lee *et al.*,[20] 2018 (new)
Ketamine	Breast	100	Unclear	6	None	1,000/day for 48 h		2,000 μg/kg	Malek *et al.*,[35] 2006 (2013 review)
Ketamine	Total hip arthroplasty	142	Taking corticosteroids or opioids excluded	3	500 μg/kg	3 μg · kg^{-1} · h^{-1}	None	506 μg/kg†	Martinez *et al.*,[21] 2014 (new)
Ketamine	Thoracotomy	66	Unclear	6	None	100 μg/kg for 60 h		6,000 μg/kg	Mendola *et al.*,[22] 2012 (new)
Ketamine	Lumbar fusion	150	Yes	6	500 μg/kg	250 μg · kg^{-1} · h^{-1}	None	1,042 μg/kg†	Nielsen *et al.*,[23,24] 2017; 2019 (new)
Ketamine	Total knee arthroplasty	16	Taking >10 mg morphine equivalent excluded	6	500 μg/kg	240 μg · kg^{-1} · h^{-1}	None	1,002 μg/kg†	Perrin *et al.*,[36] 2009 (2013 review)
Ketamine	Abdominal, thoracic, breast, or inguinal herniorrhaphy	80	No	6	500 μg/kg	250 μg · kg^{-1} · h^{-1}	100 μg/kg for 24h	3,558 μg/kg†	Peyton *et al.*,[25] 2017 (new)
Ketamine	Total hip arthroplasty	160	Taking neuropathic pain drugs or >10 mg morphine equivalent excluded	6	500 μg/kg	120 μg/kg for 24 h		3,380 μg/kg†	Remerand *et al.*,[37] 2009 (2013 review)
Ketamine	Hysterectomy	60	No	6	300 μg/kg	50 μg · kg^{-1} · h^{-1}	None	363 μg/kg†	Sen *et al.*,[38] 2009 (2013 review)
Ketamine	Hemorrhoidectomy	83	Regular use of opioids excluded	3	350 μg/kg	300 μg · kg^{-1} · h^{-1}	None	452 μg/kg†	Spreng *et al.*,[39] 2010 (2013 review)

(*Continued*)

Table 1. (Continued)

Drug	Surgery	No. of Patients	Allowed Patients with Pain	Follow-up, mo	Preoperative Dose	Intraoperative Dose	Postoperative Dose	Cumulative Dose*	Study ID
Ketamine	Thoracotomy	50	Unclear	6	None	50 μg/kg for 72 h		3,600 μg/kg†	Suzuki *et al.*,[40] 2006 (2013 review)
Ketamine	Orthopedic	352	Taking opioids daily for >1 week excluded	6	None	None	1.5 mg‡	1,198 μg/kg§	Sveticic *et al.*,[41] 2008 (2013 review)
Ketamine	Thoracotomy	125	No	6	500 μg/kg	None	250 μg/kg for 48 h	12,500 μg/kg	Tena *et al.*,[26] 2014 (new)
Pregabalin	Cardiac	150	No	6	150 mg	None	150 mg for 14 days	2,250 mg	Anwar *et al.*,[45] 2019 (new)
Pregabalin	Cardiac	101	No	3	75 mg	None	None	75 mg	Bouzia *et al.*,[46] 2017 (new)
					150 mg	None	None	150 mg	
Pregabalin	Thoracotomy	114	No	3	300 mg	None	300 mg for 4 days	1,500 mg	Brulotte *et al.*,[47] 2015 (new)
Pregabalin	Spine	40	Yes	3	300 mg	None	300 mg for 1 day	600 mg	Burke *et al.*,[62] 2010 (2013 review)
Pregabalin	Total knee arthroplasty	240	Yes	6	300 mg	None	300 mg for 10 days, 150 mg for 2 days, 100 mg for 2 days	3,800 mg	Buvanendran *et al.*,[63] 2010 (2013 review)
Pregabalin	Spine	120	Yes	6	150 mg	None	300 mg for 3.5 days	1,200 mg	Choi *et al.*,[48] 2013 (new)
Pregabalin	Total hip arthroplasty	184	Taking chronic pain medications, >10 mg morphine equivalent, or anticonvulsants excluded	3	150 mg	None	150 mg for 9 days‖	1,500 mg	Clarke *et al.*,[64] 2015 (new)
Pregabalin	Hysterectomy/ myomectomy	80	No	3	450 mg	None	450 mg for 5 days	2,700 mg	Fassoulaki *et al.*,[49] 2012 (new)
Pregabalin	Spine	60	Taking opioids, sedatives, or anticonvulsants excluded	12	300 mg	None	300 mg for 2 days	900 mg	Gianesello *et al.*,[65] 2012 (2013 review)
Pregabalin	Cardiac	40	Taking anticonvulsants or antidepressants, or chronic analgesic use excluded	3	150 mg	None	150 mg for 2 days	450 mg	Joshi *et al.*,[50] 2013 (new)
Pregabalin	Breast	100	No	3	300 mg	None	150 mg for 9 days	1,650 mg	Khan *et al.*,[51] 2019 (new)
Pregabalin	Spine	90	Yes	3	75 mg	None	225 mg for 7 days	1,650 mg	Khurana *et al.*,[52] 2014 (new)
Pregabalin	Thyroidectomy	99	Taking pregabalin, gabapentin, or opioids excluded	3	150 mg	None	150 mg for 1 day	300 mg	Kim *et al.*,[66] 2010 (2013 review)
Pregabalin	Thoracotomy	100	No	9	300 mg	None	300 mg for 5 days	1,800 mg	Konstantatos *et al.*,[53] 2016 (new)
Pregabalin	Total hip arthroplasty	142	Taking corticosteroids or opioids excluded	3	150 mg	None	None	150 mg	Martinez *et al.*,[21] 2014 (new)
Pregabalin	Nephrectomy	80	Taking analgesics or sedatives excluded	12	150 mg	None	450 mg for 1 day	600 mg	Myhre *et al.*,[54] 2017 (new)
Pregabalin	Cardiac	70	No	3	150 mg	None	150 mg for 5 days	900 mg	Pesonen *et al.*,[67] 2011 (2013 review)
Pregabalin	Breast	200	No	6	75 mg	None	150 mg for 7 days	1,125 mg	Reyad *et al.*,[55] 2019 (new)
Pregabalin	Brain tumor	100	Yes	3	300 mg	None	300 mg for 3 days	1,200 mg	Shimony *et al.*,[56] 2016 (new)
Pregabalin	Thoracotomy	45	No	3	150 mg	None	150 mg for 5 days	900 mg	Sidiropoulou *et al.*,[57] 2016 (new)
Pregabalin	Hysterectomy	501	Unclear	6	150 mg	None	150 mg for 28 days	4,350 mg	Singla *et al.*,[58] 2015 Post- Hysterectomy (new)
					300 mg	None	300 mg for 28 days	8,550 mg	
Pregabalin	Inguinal hernia repair	425	Unclear	6	50 mg	None	50 mg for 7 days	400 mg	Singla *et al.*,[58] 2015 Post-Inguinal hernia repair (new)
					150 mg	None	150 mg for 7 days	1,200 mg	
					300 mg	None	300 mg for 7 days	2,400 mg	

(*Continued*)

Table 1. (Continued)

Drug	Surgery	No. of Patients	Allowed Patients with Pain	Follow-up, mo	Preoperative Dose	Intraoperative Dose	Postoperative Dose	Cumulative Dose*	Study ID
Pregabalin	Total knee arthroplasty	307	Unclear	6	150 mg	None	150 mg for 42 days	6,450 mg	Singla *et al.*,[58] 2015 Post-Total knee arthroplasty (new)
					300 mg	None	300 mg for 42 days	12,900 mg	
Pregabalin	Breast	80	Patients with chronic pain on analgesics or past/current use of gabapentinoids excluded	3	150 mg	None	150 mg for 7 days	1,200 mg	Vig *et al.*,[61] 2019 (new)
Pregabalin	Total knee arthroplasty	120	Chronic use of gabapentin, pregabalin, or opioids excluded	3	100 mg	None	100 mg for 14 days, 50 mg for 2 days	1,600 mg	YaDeau *et al.*,[59] 2015 (new)
					200 mg	None	200 mg for 14 days, 100 mg for 2 days	3,200 mg	
					300 mg	None	300 mg for 14 days, 150 mg for 2 days	4,800 mg	
Pregabalin	Spine	105	Use of opioids, pregabalin, or gabapentin within past 2 weeks excluded	12	300 mg	None	300 mg for 1 days	600 mg	Zarei *et al.*,[60] 2016 (new)
					300 mg	None	300 mg for 14 days	4,500 mg	
Gabapentin	Breast	150	Taking antidepressants, anticonvulsants, NSAIDS, or opioids excluded	6	300 mg	None	300 mg for 9 days	3,000 mg	Amr *et al.*,[78] 2010 (2013 review)
Gabapentin	Thyroidectomy	50	No	6	1,200 mg	None	None	1,200 mg	Brogly *et al.*,[79] 2008 (2013 review)
Gabapentin	Total hip arthroplasty	126	Taking chronic pain medications excluded	6	600 mg	None	None	600 mg	Clarke *et al.*,[80] 2009 (2013 review)
					None	None	600 mg	600 mg	
Gabapentin	Total knee arthroplasty	179	Taking chronic pain medications excluded	3	600 mg	None	600 mg for 4 days	3,000 mg	Clarke *et al.*,[71] 2014 (new)
Gabapentin	Breast	75	Taking analgesics, sedatives, hypnotics, or antidepressants excluded	3	1,200 mg	None	1,200 mg for 9 days	12,000 mg	Fassoulaki *et al.*,[81] 2002 (2013 review)
Gabapentin	Thoracotomy	104	No	6	1,200 mg	None	600 mg for 1 day, 900 mg for 1 day, 12,00 mg for 3 days	6,300 mg	Grosen *et al.*,[72] 2014 (new)
Gabapentin	Thoracotomy, total hip arthroplasty, total knee arthroplasty, or breast	422	Yes	24	1,200 mg	None	1,800 mg for 3 days	6,600 mg	Hah *et al.*,[73] 2018 (new)
Gabapentin	Spine	90	Yes	3	300 mg	None	900 mg for 7 days	6,600 mg	Khurana *et al.*,[52] 2014 (new)
Gabapentin	Thoracotomy	146	No	3	600 mg	None	None	600 mg	Kinney *et al.*,[82] 2011 (2013 review)
Gabapentin	Total knee arthroplasty	300	Taking gabapentinoids, antiepileptics, anxiolytics, antidepressants, systemic glucocorticoids, or opioids excluded	3–4 yr	900 mg	None	400 mg for 1 day, 1300 mg for 6 days	9,100 mg	KjaerPetersen *et al.*,[74] 2018 (new)
					600 mg	None	300 mg for 1 day, 900 mg for 6 days	6,300 mg	
Gabapentin	Caesarean	46	Taking analgesics in previous week excluded	3	600 mg	None	None	600 mg	Moore *et al.*,[83] 2011 (2013 review)

(*Continued*)

Table 1. (Continued)

Drug	Surgery	No. of Patients	Allowed Patients with Pain	Follow-up, mo	Preoperative Dose	Intraoperative Dose	Postoperative Dose	Cumulative Dose*	Study ID
Gabapentin	Amputation	46	Yes	6	None	None	300 mg for 1 day, 900 mg for 3 days, 1,200 mg for 2 days, 1,500 mg for 2 days, 1,800 mg for 2 days, 2,100 mg for 2 days, 2,400 mg for 18 days	75,600 mg	Nikolajsen *et al.*,[84] 2006 (2013 review)
Gabapentin	Inguinal hernia repair	100	Yes	24	300 mg	None	600 mg for 1 day, 900 mg for 1 day	1,800 mg	Quail *et al.*,[75] 2017 (new)
Gabapentin	Carpal tunnel	40	Yes	6	600 mg	None	None	600 mg	Sadatsune *et al.*,[76] 2016 (new)
Gabapentin	Hysterectomy	60	No	6	1,200 mg	None	None	1,200 mg	Sen *et al.*,[38] 2009a (2013 review)
Gabapentin	Inguinal herniorrhaphy	60	Unclear	6	1,200 mg	None	None	1,200 mg	Sen *et al.*,[85] 2009 (2013 review)
Gabapentin	Cesarean	132	No	3	600 mg 300 mg	None None	None None	600 mg 300 mg	Short *et al.*,[77] 2012 (new)
Gabapentin	Cardiac	40	Taking analgesics excluded	6	1,200 mg	None	1,200 mg for 2 days	3,600 mg	Ucak *et al.*,[86] 2011 (2013 review)
IV lidocaine	Colectomy	95	No	6	60 mg	60 mg/h for 48 h		43.2 mg/kg†	Beaussier *et al.*,[90] 2018 (new)
IV lidocaine	Thyroidectomy	90	No	3	2 mg/kg	3 mg · kg^{-1} · h^{-1}	None	9.4 mg/kg†	Choi *et al.*,[91] 2017 (new)
IV lidocaine	Breast	36	No	3	1.5 mg/kg	1.5 mg · kg^{-1} · h^{-1}	1.5 mg/kg for 1 h	4.5 mg/kg†	Grigoras *et al.*,[97] 2012 (2013 review)
IV lidocaine	Spine	44	Chronic opioid use excluded	3	2 mg/kg	3 mg · kg^{-1} · h^{-1}	None	7.4 mg/kg†	Ibrahim *et al.*,[92] 2018 (new)
IV lidocaine	Nephrectomy	63	No	3	1.5 mg/kg	1 mg · kg^{-1} · h^{-1}	1 mg/kg for 24 h	27.8 mg/kg†	Jendoubi *et al.*,[18] 2017 (new)
IV lidocaine	Breast	150	No	6	1.5 mg/kg	2 mg · kg^{-1} · h^{-1}	None	8.1 mg/kg†	Kendall *et al.*,[93] 2018 (new)
IV lidocaine	Breast	100	No	3	1.5 mg/kg	2 mg · kg^{-1} · h^{-1}	None	5.1 mg/kg†	Khan *et al.*,[51] 2019 (new)
IV lidocaine	Breast	126	No	3	2 mg/kg	2 mg · kg^{-1} · h^{-1}	None	6.3 mg/kg†	Kim *et al.*,[94] 2017 (new)
IV lidocaine	Total hip arthroplasty	60	Taking corticosteroids or opioids excluded	3	1.5 mg/kg	1.5 mg · kg^{-1} · h^{-1}	1.5 mg/kg for 1h	6.8 mg/kg†	Martin *et al.*,[95] 2008 (new)
IV lidocaine	Breast	80	No	6	1.5 mg/kg	2 mg · kg^{-1} · h^{-1}	2 mg/kg for 2 h	11.1 mg/kg†	Terkawi *et al.*,[96] 2015 (new)
Parecoxib	Thoracotomy	86	No	12	40 mg	None	80 mg for 2.5 days	240 mg	Ling *et al.*,[103] 2016 (new)
Parecoxib	Breast augmentation	219	Chronic analgesic use excluded	12	40 mg	None	None	40 mg	Romundstad *et al.*,[107] 2006 (2013 review)
Ibuprofen	Total hip arthroplasty	902	Taking NSAIDs within 48 h excluded	6–12	None	None	1,200 mg for 14 days	16,800 mg	Fransen *et al.*,[105] 2006 (2013 review)
Ibuprofen	Breast	30	Chronic use of aspirin or NSAIDs excluded	6	400 mg	None	1,600 mg for 2 days	2,000 mg	Lakdja *et al.*,[106] 1997 (2013 review)
Celecoxib	Total knee arthroplasty	107	Taking narcotics daily excluded	12	None	None	400 mg for 42 days	16,800 mg	Schroer *et al.*,[100] 2011 (new)
Dexketoprofen	Thoracotomy	60	Unclear	6	50 mg	None	50 mg	100 mg	Comez *et al.*,[101] 2015 (new)
Flurbiprofen axetil	Breast	60	No	12	50 mg	None	50 mg	100 mg	Sun *et al.*,[102] 2013 (new)
Parecoxib	Breast	138	No	12	40 mg	None	40 mg	80 mg	van Helmond *et al.*,[104] 2016 (new)
Celecoxib					None	None	200 mg for 5 days	1,000 mg	
Dexamethasone	Total hip arthroplasty	50	Yes	12	40 mg	None	None	40 mg	Bergeron *et al.*,[112] 2009 (2013 review)

(*Continued*)

Table 1. (Continued)

Drug	Surgery	No. of Patients	Allowed Patients with Pain	Follow-up, mo	Preoperative Dose	Intraoperative Dose	Postoperative Dose	Cumulative Dose*	Study ID
Dexamethasone	Spine	160	Taking steroids or strong opioids excluded	12	16 mg	None	None	16 mg	Nielsen *et al.*,[109,110] 2015; 2016 (new)
Dexamethasone	Spine	112	Yes	24	0.2 mg/kg	None	4 doses of 0.06 mg/kg	0.44 mg/kg	Jeyamohan *et al.*,[108] 2015 (new)
Hydrocortisone	Cardiac	36	Unclear	6	100 mg	240 mg for 1 day, 120 mg for 1 day, 60 mg for 1 day, 30 mg for 1 day		550 mg	Weis *et al.*,[113] 2006 (2013 review)
Methylprednisolone	Breast augmentation	219	Chronic analgesic use excluded	12	125 mg	None	None	125 mg	Romundstad *et al.*,[107] 2006 (2013 review)
Methylprednisolone	Cardiac	1,043	Yes	6	500 mg	None	None	500 mg	Turan *et al.*,[111] 2015 (new)
Acetaminophen	Hysterectomy	140	No	3	None	None	4,000 mg for 3 days	12,000 mg	Koyuncu *et al.*,[114] 2018 (new)
Acetaminophen	Cardiac	150	No	3	None	None	4,000 mg for 1 day	4,000 mg	Turan *et al.*,[115] 2017 (new)
Amantadine	Breast	22	No	6	200 mg	None	200 mg for 13 days	2,800 mg	Eisenberg *et al.*,[116] 2007 (2013 review)
Amantadine	Mandibular fracture	60	Opioid use or dependency excluded	6	100 mg	None	None	100 mg	Yazdani *et al.*,[117] 2016 (new)
Dexmedetomidine	Hysterectomy	80	No	12	0.5 $\mu g \cdot kg^{-1} \cdot h^{-1}$		N/A	0.70 μg/kg	Han *et al.*,[118] 2019 (new)
Dextromethorphan	Hysterectomy	50	No	3	750 mg	None	None	750 mg	Ilkjaer *et al.*,[119] 2000 (2013 review)
Duloxetine	Spine	101	Yes	3	30 mg for 5 days, 60 mg for 9 days	None	60 mg for 81 days	5,550 mg	Hyer *et al.*,[120] 2015 (new)
Duloxetine	Total knee arthroplasty	106	Chronic use of gabapentin, pregabalin, or opioids excluded	3	60 mg	None	60 mg for 14 days	900 mg	YaDeau *et al.*,[121] 2016 (new)
Etanercept	Inguinal herniorrhaphy	77	Yes	12	50 mg	None	None	50 mg	Cohen *et al.*,[122] 2013 (new)
Fentanyl	Amputation	65	Yes	6	58.3 μg/h	54.5 μg/h for 2 days		Variable	Karanikolas *et al.*,[123] 2011 (2013 review)
Magnesium	Breast	126	No	3	20 mg/kg + 20 mg $\cdot kg^{-1} \cdot h^{-1}$		63.2 mg/kg	Intraoperative	Kim *et al.*,[94] 2017 (new)
Memantine	Amputation	19	Yes	12	None	None	10 mg for 7 days, 20 mg for 7 days, 30 mg for 14 days	630 mg	Schley *et al.*,[124] 2007 (2013 review)
Mexiletine	Breast	100	Taking analgesics, sedatives, or antidepressants excluded	3	200 mg	None	400 mg for 6 days	2,600 mg	Fassoulaki *et al.*,[125] 2001 (2013 review)
Mexiletine	Breast	75	Taking analgesics, sedatives, hypnotics, or antidepressants excluded	3	200 mg	None	600 mg for 10 days	6,200 mg	Fassoulaki *et al.*,[81] 2002 (2013 review)
Minocycline	Carpal Tunnel	131	Yes	12	200 mg	None	200 mg for 5 days	1,200 mg	Curtin *et al.*,[127] 2017 (new)
Minocycline	Spine	100	Yes	3	200 mg	None	200 mg for 8 days	1,800 mg	Martinez *et al.*,[126] 2013 (new)
Nefopam	Total knee arthroplasty	75	Yes	12	0.2 mg/kg	120 $\mu g \cdot kg^{-1} \cdot h^{-1}$	60 $\mu g \cdot kg^{-1} \cdot h^{-1}$ for 2 days	3,128 μg/kg	Aveline *et al.*,[14] 2014 (new)
Nefopam	Thyroidectomy	58	Chronic use of opioids or any analgesic drugs >2 weeks excluded	3	0.2 mg/kg + 120 $\mu g \cdot kg^{-1} \cdot h^{-1}$		None	520 μg/kg	Kim *et al.*,[130] 2018 (new)
Nefopam	Breast	94	Taking any kind of analgesic excluded	3	20 mg	None	None	20 mg	Na *et al.*,[128] 2016 (new)

(*Continued*)

Table 1. (Continued)

Drug	Surgery	No. of Patients	Allowed Patients with Pain	Follow-up, mo	Preoperative Dose	Intraoperative Dose	Postoperative Dose	Cumulative Dose*	Study ID
Nitrous oxide	Numerous	2,050	Unclear	54	Intraoperative 70%		None	Intraoperative	Chan *et al.*,[132] 2011 (2013 review)
Nitrous oxide	Numerous	3,325	Yes	12	Intraoperative 70%		None	Intraoperative	Chan *et al.*,[131] 2016 (new)
Valproic acid	Amputation	128	Yes	3	250 mg	None	750 mg for 3.7 days	2,775 mg	Buchheit *et al.*,[133] 2019 (new)
Venlafaxine	Breast surgery	150	Taking antidepressants, anticonvulsants, NSAIDs, opioids excluded	6	37.5 mg	None	37.5 mg for 9 days	375 mg	Amr *et al.*,[78] 2010 (2013 review)
Vitamin C	Spinal fusion	123	Yes	12	None	Not reported	Not reported for 45 days	Not reported	Lee *et al.*,[134] 2017 (new)

*Cumulative doses have been estimated for comparative purposes only. †Calculation based on reported anesthesia duration. ‡1.5 mg of ketamine per each patient-controlled analgesia opioid bolus. §Calculation based on ketamine consumption and timing of administration. ||Duration of hospital stay postsurgery estimated at 2 days.
IV, intravenous; NSAID, nonsteroidal anti-inflammatory drug.

a treatment effect of ketamine claiming "good-quality evidence for a small benefit"[42]; however, their conclusion was based on one small randomized controlled trial.[14]

Pregabalin

Twenty-one new studies (n = 3,184)[21,45–61] evaluated pregabalin (total, 26 studies; n = 3,693).[21,45–67] Nineteen of 26 studies reported prevalence of any pain at 3 months,[21,45,47–51,53,57,58,61–63,65–67] six studies at 6 months,[45,48,54,58,63] and two studies at 12 months.[54,65] Prevalence of any pain at 3 months ranged from 3.1 to 80.0% (mean, 39.5%) in the placebo arm and 3.7 to 88.0% (mean, 31.9%) in the pregabalin arm. Subgroup analyses resulted in a statistically significant treatment effect of pregabalin 3 months after cardiac surgery (three trials; risk ratio, 0.25 [95% CI, 0.13 to 0.50]), and 3 months after total knee arthroplasty (three trials; risk ratio, 0.75 [95% CI, 0.58 to 0.97]). No treatment effects were observed for any pain evaluated at 3, 6, or 12 months when drug administration was for 24 h or less or more than 24 h or for other types of surgical procedures (fig. 3). Forest plots for studies evaluating pregabalin are included in Supplemental Digital Content 7 (appendix G, http://links.lww.com/ALN/C634). In 2013, only one study evaluated the prevalence of any pain at 6 months therefore no subgroup analyses were performed; in the current review, six studies were included in meta-analysis and did not demonstrate a treatment effect of pregabalin when drugs were administered for more than 24 h (risk ratio, 0.78 [95% CI, 0.47 to 1.28]).

Nine studies reported prevalence of moderate to severe pain at 3 months (placebo: range, 4.2 to 34.0%; mean, 20.2; pregabalin: range, 0.0 to 20.0%; mean, 8.7),[45,47,48,51,53,57,59,61,63] and three studies at 6 months (placebo: range, 11.3 to 28.0%; mean, 17.9; pregabalin: range, 2.7 to 8.8%; mean, 5.8).[45,48,63] When pregabalin was administered for more than 24 h the overall effectiveness risk ratio showed a statistically significant treatment effect of pregabalin compared to placebo at 3 months (nine trials; risk ratio, 0.47 [95% CI, 0.33 to 0.68]), and 6 months (three trials; risk ratio, 0.29 [95% CI, 0.14 to 0.58]) for varying surgical procedures, and 3 months after total knee arthroplasty (two trials; risk ratio, 0.42 [95% CI, 0.22 to 0.81]) (fig. 3). Only eleven of the 26 pregabalin studies provided data regarding dropouts due to treatment-related adverse effects. Of those, 56 of 1,295 (4.3%) received pregabalin and 27 of 819 (3.3%) received placebo. Adverse events included dizziness, nausea, vomiting, sedation, diplopia, somnolence, visual disturbances, fainting, fatigue, constipation, and allergic reaction.[45,47,49,56–58,62–64]

Pregabalin has been evaluated in four recent reviews for orthopedic surgery,[42] thoracotomy,[68] breast cancer surgery,[69] and various surgeries.[70] Consistent with the current review, half (two of four) of these reviews did not have sufficient evidence to make a clear recommendation.[69,70] Two reviews concluded a treatment effect of pregabalin. One narrative systematic review evaluating various

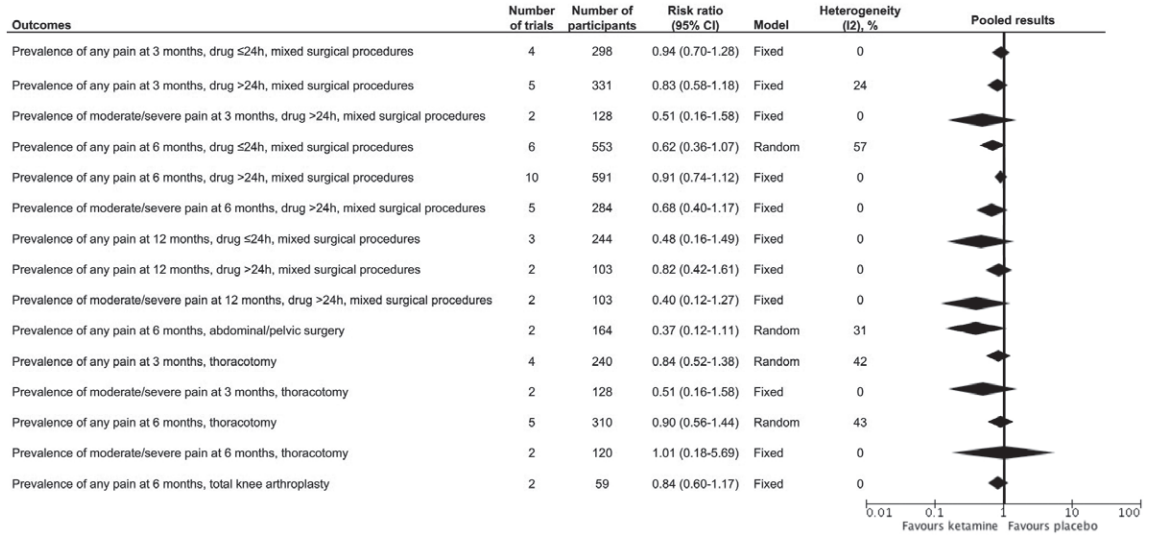

Fig. 2. Summary of ketamine meta-analyses. Data are presented as the pooled results for each outcome. Drug ≤ 24 h indicates drugs were administered for 24 h or less; drug > 24 h indicates drugs were administered for longer than 24 h.

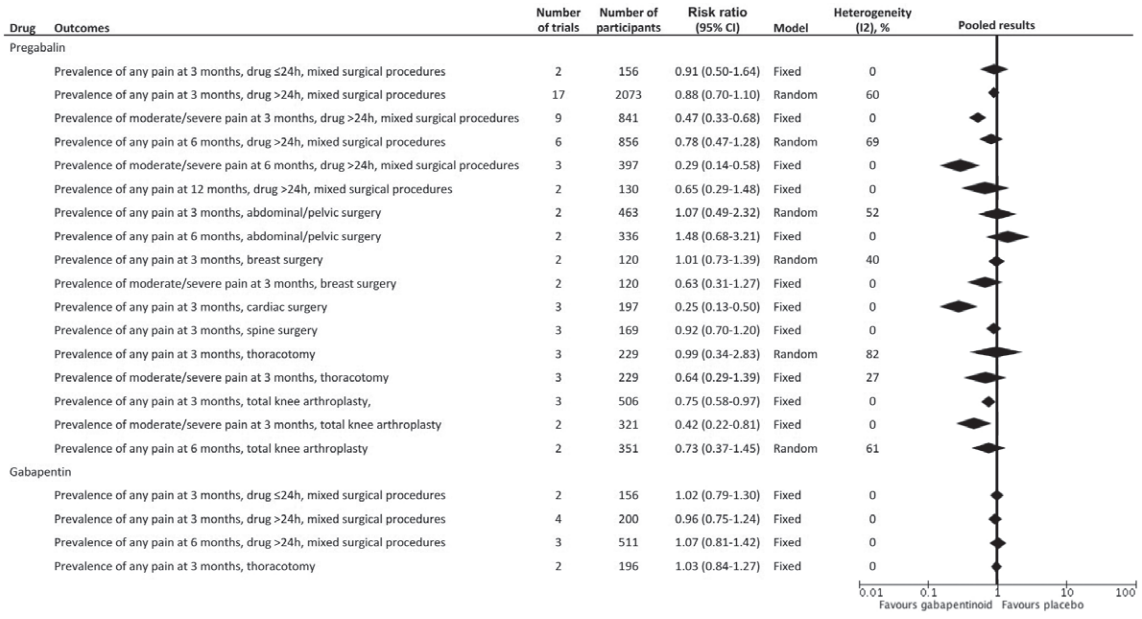

Fig. 3. Summary of gabapentinoid meta-analyses. Data are presented as the pooled results for each outcome. Drug ≤ 24 h indicates drugs were administered for 24 h or less; drug > 24 h indicates drugs were administered for longer than 24 h.

interventions for total knee arthroplasty[42] was limited to one randomized controlled trial from 2010[63] and the other review included nine studies for thoracotomy, seven of which were excluded from the present review due to lack of blinding, not placebo controlled, and lack of long term pain assessment.[68] Furthermore, two of the nine studies that were included in our review did not find a reduction in the prevalence of postsurgical chronic pain.[47,53] Despite the high proportion of studies lacking data on adverse events, consistent with our review adverse events included sedation,[42,70] dizziness,[68,70] drowsiness,[68,69] and visual disturbances.[70]

Gabapentin

Eight new studies (n = 1,367)[52,71–77] evaluated gabapentin (total, 18 studies; n = 2,166).[38,52,71–86] Six of 18 studies reported prevalence of any pain at 3 months,[72,81–84,86] four studies at 6 months,[72,73,80,84] and one study at 12 months.[73] Prevalence of any pain at 3 months ranged from 20.0 to 66.7% (mean, 49.9%) in the placebo arm and 12.5 to 70.2% (mean, 47.8%) in the gabapentin arm. No treatment effects were observed for any pain evaluated at 3 or 6 months (fig. 3). Forest plots for studies evaluating gabapentin are included in Supplemental Digital Content 8 (appendix H, http://links.lww.com/ALN/C635). Consistent with the 2013 review, meta-analyses of studies evaluating gabapentin failed to demonstrate statistical significance upon comparison to placebo at three or six months.

Two studies reported prevalence of moderate to severe pain at 3 and 6 months,[72,76] however results were not pooled given heterogeneity of timing and duration of administration. When drug administration was for 24 h or less, the prevalence of moderate to severe pain at 3 months was 21.1% in the placebo group and 22.2% in the gabapentin group and 10.5% and 16.7% at 6 months, respectively.[76] When drug administration was for more than 24 h, the prevalence of moderate to severe pain at 3 months was 13.5% in the placebo group and 12.8% in the gabapentin group and 8.1% and 16.7% at 6 months, respectively.[72] Only five of the 18 gabapentin studies provided data regarding dropouts due to treatment-related adverse effects. Of those, 32 of 506 (6.3%) received gabapentin and 18 of 401 (4.5%) received placebo. Adverse events included severe sedation, dizziness, nausea, syncope, paresthesia of the legs, and elevated serum creatinine.[72–74,83,84]

Gabapentin has been evaluated in two recent reviews for breast cancer surgery.[69,87] One review concluded low- to very-low–quality evidence that preoperative use of gabapentin does not reduce the rate of chronic postsurgical pain.[69] One review concluded that "preoperative use of gabapentin was able to reduce acute and chronic postoperative pain."[87] However, seven of nine studies were excluded from the current review; six due to follow-up for less than 3 months (range, 12 h to 1 month), and one was a clinical trial with one arm that combined topical analgesia and gabapentin. It is unclear why two of five studies were included in their meta-analysis evaluating chronic pain given their short timeline for follow-up (*i.e.*, 24 h and 7 days).[88,89] Furthermore, it is unclear why two studies included in the meta-analysis by Jiang *et al.*[87] show a treatment effect of gabapentin: Amr *et al.*[78] did not report dichotomous results for the incidence of chronic pain and concluded "gabapentin had no effect on chronic pain," and Fassoulaki *et al.*[81] reported no difference in the proportion of chronic pain between gabapentin 12 of 22 (54.5%) and pregabalin 14 of 24 (58.3%).

IV Lidocaine

Nine new studies (n = 808)[18,51,90–96] evaluated IV lidocaine (total, 10 studies; n = 844).[18,51,90–97] Six of 10 studies reported prevalence of any pain at 3 months,[51,90,91,93,94,97] three studies at 6 months,[90,93,96] and no studies at 12 months. Prevalence of any pain at 3 months ranged from 17.4 to 79.2% (mean, 41.6%) in the placebo arm and 11.8 to 92.3% (mean, 32.7%) in the IV lidocaine arm. One study could not be pooled in meta-analysis due to duration of drug administration for more than 24 h during colectomy.[90] Subgroup analyses of prevalence of any pain at 6 months based on duration of treatment being 24 h or less showed a statistically significant treatment effect of IV lidocaine after breast surgery (two trials; risk ratio, 0.43 [95% CI, 0.23 to 0.80]). No treatment effect of IV lidocaine was observed at 3 months after breast surgery or when the drug was administered for 24 h or less (fig. 4). Forest plots for studies evaluating IV lidocaine are included in Supplemental Digital Content 9 (appendix I, http://links.lww.com/ALN/C636).

Two studies reported prevalence of moderate to severe pain at 3 months (placebo: range, 10.0 to 20.8%; mean, 15.4; IV lidocaine: range, 4.7 to 7.7%; mean, 6.2),[51,93] and two studies at 6 months (placebo: range, 3.4 to 22.2%; mean, 12.8; IV lidocaine: range, 3.2 to 8.8%; mean, 6.0).[93,96] No treatment effect of IV lidocaine was observed for this outcome regardless of timing of outcome measurement or surgical procedure (fig. 4). Only 1 of the 10 IV lidocaine studies provided data regarding dropouts due to treatment-related adverse effects. Of those, 1 of 22 (4.5%) received IV lidocaine and 0 of 22 (0.0%) received placebo. One patient in the IV lidocaine group developed convulsions during injection of the loading dose.[92]

Intravenous lidocaine has been evaluated in two recent reviews for breast cancer surgery,[98] and various surgeries.[99] Both reviews were cautiously optimistic in support of IV lidocaine for preventing chronic postsurgical pain. However, higher quality evidence from large, definitive, multicenter clinical trials was called for before a widespread change in practice could be justified.[99]

Nonsteroidal Anti-inflammatory Drugs

Five new studies (n = 451) evaluated nonsteroidal anti-inflammatory drugs (NSAID) including one celecoxib,[100] one dexketoprofen,[101] one flurbiprofen axetil,[102] one parecoxib,[103] and one IV parecoxib in combination with oral celecoxib[104] (total, eight studies; n = 1,602).[100–107] Two of eight studies reported prevalence of any pain at 3 months,[103,104] three studies at 6 months,[102,104,106] and four studies at 12 months.[102–104,107] Prevalence of any pain at 3 months ranged from 48.8 to 59.1% (mean, 53.9%) in the placebo arm and 22.5 to 54.3% (mean, 38.4%) in the NSAID arm. Subgroup analysis did not show an effect of NSAIDs compared to placebo for studies evaluating treatment for more than 24 h at 3, 6, and 12 months; however, a statistically significant treatment effect was observed at 12 months when drugs were administered for 24 h or less (fig. 5). Forest plots for studies evaluating NSAIDS are included in Supplemental Digital Content 10 (appendix J, http://links.lww.com/ALN/C637).

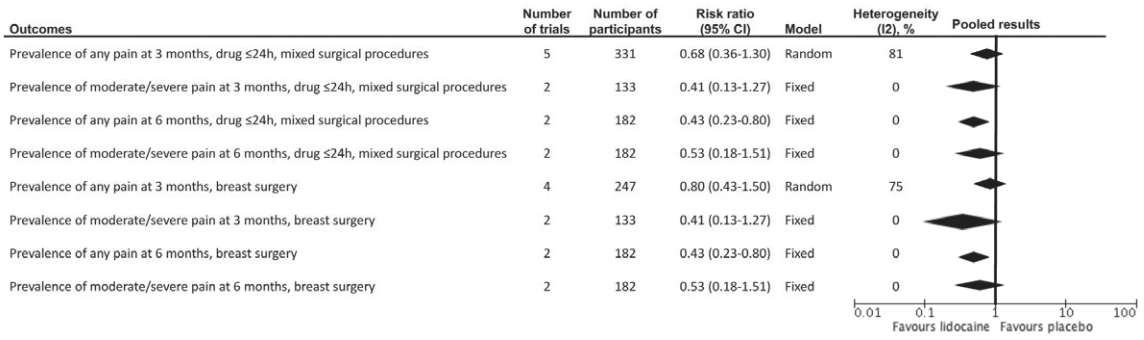

Fig. 4. Summary of intravenous lidocaine meta-analyses. Data are presented as the pooled results for each outcome. Drug ≤ 24 h indicates drugs were administered for 24 h or less; drug > 24 h indicates drugs were administered for longer than 24 h.

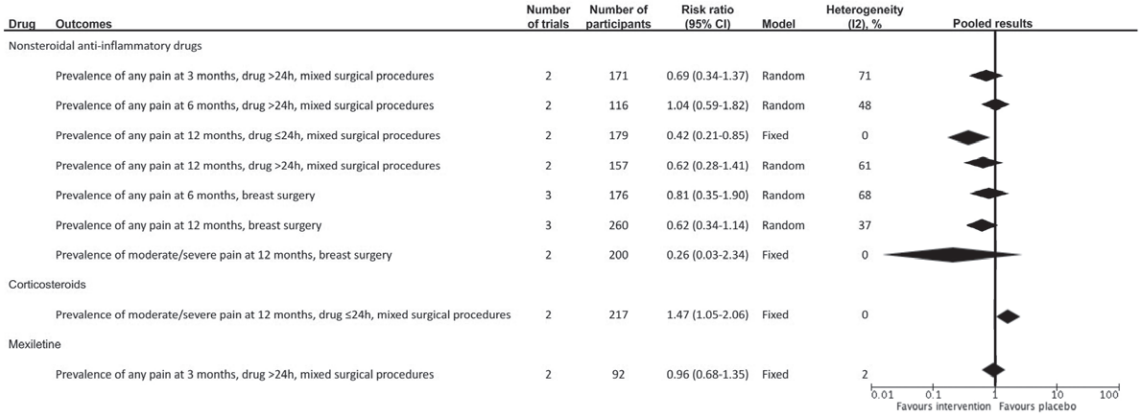

Fig. 5. Summary of other drugs meta-analyses. Data are presented as the pooled results for each outcome. Drug ≤ 24 h indicates drugs were administered for 24 h or less; drug > 24 h indicates drugs were administered for longer than 24 h.

One study reported prevalence of moderate to severe pain at 3 and 6 months and concluded no treatment effect of COX-2 inhibitors on persistent pain.[104] Two studies reported prevalence of moderate to severe pain at 12 months; however, results were not pooled due to heterogeneity of timing and duration of NSAID administration. When drug administration was for 24 h or less,[107] the prevalence of moderate to severe pain at 12 months was 3.2% in the placebo group and 0.0% in the NSAID group *versus* 2.4% *versus* 0.0%, respectively, when drug administration was for more than 24 h.[104] Only one of the eight NSAID studies provided data regarding dropouts due to treatment-related adverse effects. Of those, 51 of 440 (11.6%) received ibuprofen and 37 of 435 (8.5%) received placebo.[105]

Corticosteroids

Three new studies (n = 1,315) evaluated corticosteroids: two dexamethasone[108–110] and one methylprednisolone[111] (total, six studies; n = 1,620).[107–113] One of six studies reported prevalence of any pain at 3 months,[110] one at 6 months,[111] and one at 12 months.[107] Results were not pooled due to heterogeneity of the timing of outcome measurement.

Two of six studies reported the prevalence of moderate to severe pain at 12 months (placebo: range, 3.2 to 50.0%; mean, 26.6; corticosteroid: range, 5.4 to 72.7%; mean, 39.0).[107,109] Subgroup analysis at 12 months based on duration of treatment for 24 h or less resulted in a statistically significant treatment effect of placebo (two trials; risk ratio, 1.47 [95% CI, 1.05 to 2.06]) (fig. 5). Forest plots for studies evaluating corticosteroids are included in Supplemental Digital Content 11 (appendix K, http://links.lww.com/ALN/C638). No studies evaluating corticosteroids provided data regarding dropouts due to treatment-related adverse effects.

Other Drugs

Fewer studies evaluated acetaminophen (two new; n = 290),[114,115] amantadine (two studies, one new; n = 82),[116,117]

dexmedetomidine (one new; n = 80),[118] dextromethorphan (one study, not new; n = 50),[119] duloxetine (two new; n = 207),[120,121] etanercept (one new; n = 77),[122] fentanyl (one study, not new; n = 65),[123] magnesium (one new; n = 126),[94] memantine (one study, not new; n = 19),[124] mexiletine (two studies, not new; n = 175),[81,125] minocycline (two new; n = 231),[126,127] nefopam (four new; n = 307),[14,128–130] nitrous oxide (two studies, one new; n = 5,375),[131,132] valproic acid (one new; n = 128),[133] venlafaxine (one study, not new; n = 150),[78] and vitamin C (one new; n = 123).[134] Primary and secondary outcomes for drugs evaluated in fewer than five studies were inconclusive and shown in Supplemental Digital Content 12 (appendix L, http://links.lww.com/ALN/C639).

Discussion

This update reports on an escalating number of randomized controlled trials evaluating perioperative systemic drugs for the prevention of chronic postsurgical pain. The previous review in 2013 included 40 studies and the current one adds 70 new studies in just the last 6 yr. Most studies evaluated drugs that are used to treat acute postoperative pain—namely, ketamine, pregabalin, gabapentin, IV lidocaine, and NSAIDs. Overall, meta-analyses of available studies demonstrated superiority over placebo in 0 of 15 ketamine meta-analyses, 5 of 17 pregabalin meta-analyses, 0 of 4 gabapentin meta-analyses, 2 of 8 IV lidocaine meta-analyses, and 1 of 7 NSAID meta-analyses. Treatment-related adverse effects resulting in study dropouts were reported in only 2 of 27 ketamine studies, 11 of 26 pregabalin studies, 5 of 18 gabapentin studies, 1 of 10 IV lidocaine studies, 1 of 8 NSAID studies, and 0 of 6 corticosteroid studies. Insufficient reporting on the potential harms of each of the pharmacologic interventions was an impediment to conducting quantitative assessments to weigh the benefit–risk trade-offs.

The 110 included studies were of reasonably good quality with mostly low risks of bias related to randomization and blinding. Frequent risks of bias were related to small sample size (fewer than 50 participants).[11,135] Studies which were insufficiently blinded or uncontrolled were excluded as shown in the "Characteristics of Excluded Studies" table (Supplemental Digital Content 2, appendix B, http://links.lww.com/ALN/C629).

The studies included in this review varied with respect to pharmacologic interventions (*i.e.,* 28 different drugs and 16 drug classes); dosage, timing, and duration of drug administration; surgical procedures; participants (*e.g.*, with and without preoperative pain); sample size; outcome measurement tools; and timing of pain assessment (*e.g.*, 3, 6, and/or 12 months). These disparities restrict the amount of data that can be pooled in meta-analysis which presents major challenges in interpretation and applicability of the results. Therefore, caution is advised when generalizing the results beyond the boundaries of the subanalyses conducted in this review. This review should be considered in the setting of several potential limitations. Although 110 randomized controlled trials were included, only 59 studies allowed for direct comparisons in quantitative synthesis. Others were excluded due to variation in drugs evaluated, surgical procedures, pain assessment tools, and timing of pain outcome measurement. Although restriction of this review to double-blind, randomized controlled trials limits the potential for some sources of bias, the relatively small size of most of the studies (*i.e.,* 90% with fewer than 100 participants per arm), and high levels of withdrawals in some studies contribute other sources of bias that potentially overestimate treatment effect. Also, chronic pain was not necessarily the primary outcome for all included studies. Measures of pain at 3 or more months after surgery may have been secondary outcomes which may be a source of selective reporting bias. Furthermore, detailed assessment of pain and its consequences were often not reported beyond "Yes/No" since only a limited number of studies reported relevant moderate/severe pain. However, we believe all available results be considered for inclusion. The heterogeneity with respect to surgical procedures (*i.e.,* nerve *vs.* other tissue damage), participant populations (preexisting chronic pain, opioid use, and psychiatric morbidities), diverse underlying sources of pain after surgery (*e.g.,* incisional, nerve transection/injury, lymphedema, and deep tissue, among others, occurring after breast cancer surgery), and treatment dose/duration limit interpretation. This includes the question of whether the surgery was done to treat a pain condition, or otherwise, has not been addressed sufficiently in the literature. Other limitations come from heterogeneity regarding the study intervention (*e.g.*, drug dose [small/large], timing with respect to surgery [pre-, intra-, postoperative], and insufficient numbers of trials in each of these categories to conduct relevant subgroup analyses). Although this review did not reveal strong or consistent treatment effects for preventing chronic postsurgical pain, the observation of some statistically significant results points to the concern of multiplicity in systematic reviews where several different meta-analyses are conducted.[136] Although the Cochrane Collaboration[6] and other investigators do not generally recommend adjusting for multiple comparisons and is not generally done in meta-analyses—which seek to estimate intervention effects rather than test for them—this is still an area for future investigation.[136] Finally, lack of access to data from studies that remain unpublished may be an important source of publication bias to consider.

However, strengths of this review should be acknowledged: (1) this is the most up-to-date review of pharmacotherapy for prevention of chronic postsurgical pain with trials published as recently as 2019; (2) we conducted a comprehensive search for eligible randomized controlled trials in any language; (3) procedures throughout the review were conducted in a way that was rigorous,

transparent, and replicable; (4) this review follows definitive standard reporting criteria according to the Cochrane Collaboration,[6] Preferred Reporting Items for Systematic Reviews and Meta-analysis,[7] and A Measurement Tool to Assess Systematic Reviews[8]; (5) this is the only known systematic review in the past 5 yr that has considered all perioperative systemic drugs and was not limited by surgical procedure; (6) we reviewed a number of therapeutic agents in the same systematic manner; and (7) we used subgroup analyses according to dose/duration of treatment, surgical procedure, and timing of outcome measurements.

There is a need for better designed, large-scale, high-quality studies with adequate power to detect treatment effects of pharmacologic interventions on chronic pain outcomes 3 or more months after surgery, and focus on patient safety by reporting consistent and reliable data on withdrawals due to treatment-related adverse events. Conducting further trials of gabapentinoids for chronic pain prevention should take into consideration their apparent lack of effect for acute postoperative pain,[137] and the diminishing likelihood of effectiveness for preventing chronic postoperative pain. Researchers should consider using detailed standardized outcome measurement tools (*e.g.*, pain intensity on a 0 to 10 numerical rating scale) that can be summarized using dichotomous outcomes (*e.g.*, any pain [more than 0 out of 10] and moderate to severe pain [greater than or equal to 4 of 10]) assessed at multiple and consistent time points (*e.g.*, 3, 6, and 12 months) postsurgery, along with the specific relation of pain to the operated area, and consider stratification of those with and without preoperative pain and analgesic use, as well as implementing better characterization of surgical procedure (nerve damage) and patient characteristics (high pain responders) where appropriate. Studies should focus on drug dosage and duration within the context of the procedure-specific acute pain trajectory in question. There may be little value to repeat studies on single-shot or short-term drug interventions for this multifactorial problem, with a continuous inflammatory response lasting for several days (or weeks). Finally, considering use of the drugs included in this review to prevent chronic postsurgical pain—in light of their apparently uncertain effectiveness—also requires consideration of their safety in the perioperative setting. Given the potential adverse effects of some of these drugs (*e.g.*, COX-2 inhibitors,[138] gabapentinoids[139]), it should be noted that safety assessment and reporting in perioperative clinical trials is sometimes inadequate.[140,141] Therefore, any future research in this area should incorporate more thorough and comprehensive safety assessment and reporting.

Conclusions

Consistent with our original review, and supported by nearly triple the number of studies, this review suggests again the need for larger-scale, high-quality studies to confirm or refute the effectiveness and safety of pharmacologic interventions for the prevention of chronic postsurgical pain. Based on currently available evidence, none of the drugs studied so far can be recommended for clinical use specifically for the indication of preventing chronic pain after surgery.

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Competing Interests

The authors declare no competing interests.

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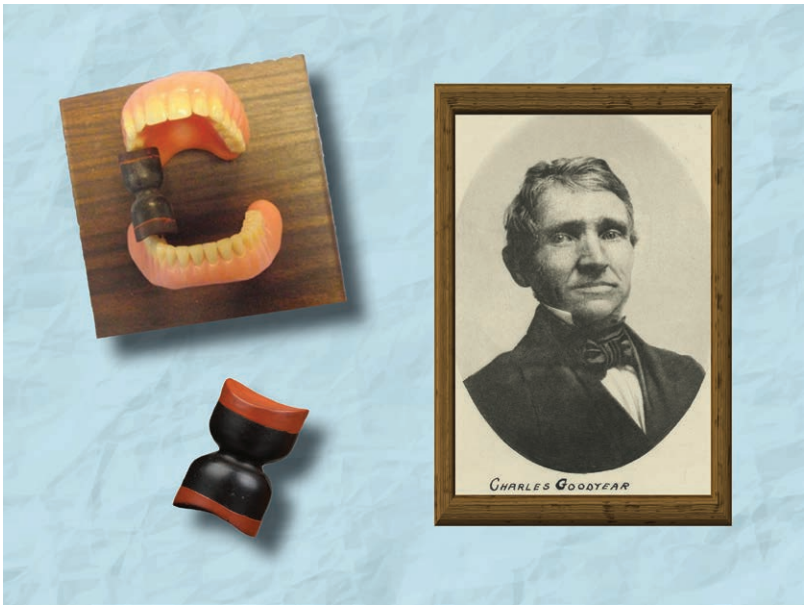
ANESTHESIOLOGY REFLECTIONS FROM THE WOOD LIBRARY-MUSEUM

Mouth Props: Vulcanite Takes a Bite Out of Dental Anesthesia



Unassuming in appearance yet essential for dental anesthetics, the mid-nineteenth century mouth prop (*upper and bottom left)* could not have made its mark without Charles Goodyear (1800 to 1860, *right*) and his creation of vulcanized rubber. Even when expertly placed, early wooden mouth props quickly splintered under the pressure of clenched jaws. A durable alternative was needed. Before the "Good" years of vulcanized rubber, North American rubber products would often melt in the summer and crack in the winter. Determined to develop an enduring material for life preservers, Goodyear heated rubber and sulfur to "vulcanize" the compound. As the popularity of anesthetics for "painless" dental extractions generated significant demand for affordable dentures, dentists became key consumers of vulcanized rubber. "Vulcanite" was easy to implement as bite block material. Eventually, the wealthy Goodyear Dental Vulcanite Company began to enforce patents and collect high royalties. Tensions culminated in the 1879 murder of its financial director by a dentist. Taking the hint, the company did not renew its denture patents. By the turn of the twentieth century, vulcanite dentures and mouth props enjoyed near-ubiquity in dental practices. (Copyright © the American Society of Anesthesiologists' Wood Library-Museum of Anesthesiology, Schaumburg, Illinois.)

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