



# Quality of meta-analyses of non-opioid, pharmacological, perioperative interventions for chronic postsurgical pain: a systematic review

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► Additional supplemental material is published online only. To view, please visit the journal online (<http://dx.doi.org/10.1136/rapm-2021-102981>).

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Received 22 June 2021

Accepted 20 December 2021

Published Online First

13 January 2022

## ABSTRACT

**Background** In an attempt to aggregate observations from clinical trials, several meta-analyses have been published examining the effectiveness of systemic, non-opioid, pharmacological interventions to reduce the incidence of chronic postsurgical pain.

**Objective** To inform the design and reporting of future studies, the purpose of our study was to examine the quality of these meta-analyses.

**Evidence review** We conducted an electronic literature search in Embase, MEDLINE, and the Cochrane Database of Systematic Reviews. Published meta-analyses, from the years 2010 to 2020, examining the effect of perioperative, systemic, non-opioid pharmacological treatments on the incidence of chronic postsurgical pain in adult patients were identified. Data extraction focused on methodological details. Meta-analysis quality was assessed using the A Measurement Tool to Assess Systematic Reviews 2 (AMSTAR 2) critical appraisal tool.

**Findings** Our search yielded 17 published studies conducting 58 meta-analyses for gabapentinoids (gabapentin and pregabalin), ketamine, lidocaine, non-steroidal anti-inflammatory drugs, and mexiletine. According to AMSTAR 2, 88.2% of studies (or 15/17) were low or critically low in quality. The most common critical element missing was an analysis of publication bias. Trends indicated an improvement in quality over time and association with journal impact factor.

**Conclusions** With few individual trials adequately powered to detect treatment effects, meta-analyses play a crucial role in informing the perioperative management of chronic postsurgical pain. In light of this inherent value and despite a number of attempts, high-quality meta-analyses are still needed.

**PROSPERO registration number** CRD42021230941.

## INTRODUCTION

The International Association for the Study of Pain defines chronic postsurgical pain (CPSP) as localized pain arising altered or augmented postsurgery, for a minimum of 3 months, not attributable to other causes.<sup>1</sup> The incidence of CPSP varies between 5% and 85% depending on the operational definition and surgical procedure, with highest estimates arising from amputations, thoracotomies, cardiac surgeries, breast surgeries, inguinal hernia repairs, cholecystectomies, hip replacements, and cesarian

deliveries.<sup>2</sup> Key risk factors for CPSP include longer surgery times, patient demographics (eg, younger, female), perioperative factors (eg, pre-existing pain, nerve injuries, and acute postoperative pain), and psychological characteristics (eg, anxiety and catastrophizing).<sup>3–4</sup> Among the deleterious effects of CPSP are prolonged opioid use, impaired function, decreased quality of life, and increased healthcare costs.<sup>5,6</sup>

The prevention of CPSP is a top priority for research in anesthesiology and perioperative medicine.<sup>7</sup> To this end, a number of clinical trials have examined interventions to reduce the incidence of CPSP.<sup>8–10</sup> A major challenge in interpreting outcomes from individual clinical trials are small sample sizes. Given this limitation, meta-analyses play an important role in developing evidence-based guidelines for the perioperative management of CPSP. The inherent value of meta-analyses lies in the aggregation of outcomes across trials to achieve greater sample sizes and statistical power than the clinical trials. At the top of the evidence-based pyramid, meta-analyses play an important role in informing clinical decision making. A problem emerges, however, when meta-analyses, produced en masse, yield variable and potentially conflicting and misleading outcomes.<sup>11</sup> To aid in evaluating the quality of meta-analyses, a number of critical appraisal tools are now available (eg, A Measurement Tool to Assess Systematic Reviews 2, AMSTAR 2).<sup>12</sup> Applied in a variety of areas of biomedical research, these tools have provided empirical evidence for areas of improvement in future meta-analyses, yet no reviews exist within the context of CPSP.<sup>13–15</sup>

To inform the design and reporting of future studies, our objective was to examine the quality of meta-analyses focused on non-opioid interventions systemically administered during the perioperative period to reduce the incidence of CPSP. Our primary aim was to use the AMSTAR 2 critical appraisal tool to examine the overall quality of meta-analyses and determine the existence of any methodological flaws that might impact the results of these meta-analyses.

## METHODS

### Definitions

From here onward, a ‘trial’ refers to a unique published original research article where a clinical



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**To cite:** McGregor RH, Warner FM, Linde LD, et al. *Reg Anesth Pain Med* 2022;**47**:263–269.

trial was conducted and was later incorporated into a meta-analysis. A ‘meta-analysis’ refers solely to the analytical component of a ‘study,’ where a ‘study’ is a published article which included one or more meta-analysis(es) and met all other inclusion criteria (described below). The search strategy was performed at the study level, as were the quality assessments.

### Search strategy

An electronic literature search in Embase and MEDLINE (Ovid) databases on November 17, 2020, for the years 2010–2020 was conducted by RHM and FMW. This search was updated on July 19, 2021, to include the Cochrane Database of Systematic Reviews. The search was limited by year to capture recent studies, published after reporting guidelines for systematic reviews were made available.<sup>16</sup> Online supplemental table 1 shows the search strategy used in these databases. The reference lists of all eligible articles were further searched for relevant studies. There were no restrictions placed on language (although no non-English articles met the inclusion criteria, the plan for such articles was that they would be translated by researchers or physicians fluent in the relevant language). The protocol for this search and review was registered in the PROSPERO database prior to conducting this review (CRD42021230941). The protocol was not published in a peer-reviewed journal. There were no deviations from the protocol with the exception of a post hoc analysis described in more detail below. The Preferred Reporting Items for Systematic Reviews and Meta-Analyses statement was used as a guideline for the reporting of this study.<sup>16</sup>

### Eligibility criteria

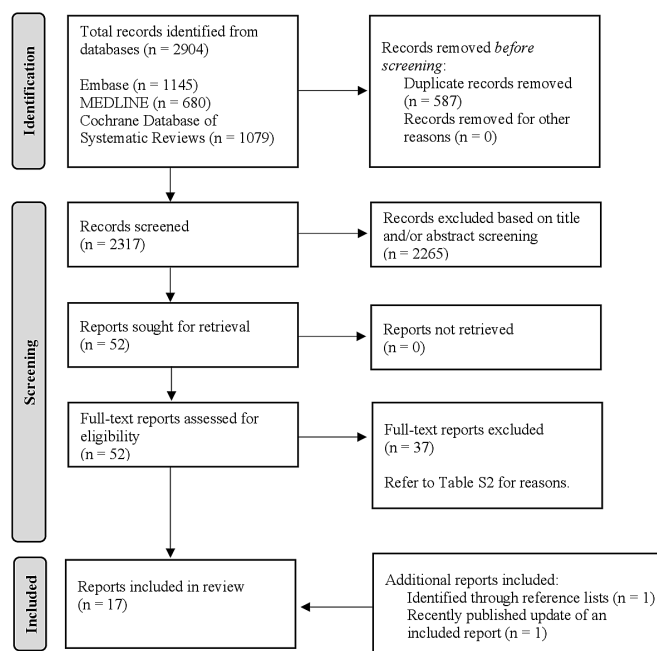
Inclusion criteria were full-text, published studies involving meta-analyses of adult patients (>18 years of age) who underwent a surgical procedure, where the intervention was a systemically delivered non-opioid pharmacological treatment initiated during perioperative management. The outcome of interest was the incidence of CPSP; we broadened the International Association for the Study of Pain definition to include any definition  $\geq 2$  months postsurgery. No restrictions were placed on the control group used in the meta-analyses (eg, comparing two active treatments or an active treatment against placebo or standard of care).

### Article screening and study selection

Study selection was performed in two stages by two independent reviewers (RHM and FMW). Titles and abstracts were screened in the first stage, and full texts were screened in the second stage. Any uncertainty was resolved through discussion with a third author (JLKK).

### Data extraction

Relevant papers were retrieved and entered into reference management software (Mendeley V.2.62). Two reviewers (FMW and JLKK) assessed the included studies using the AMSTAR 2 critical appraisal for systematic reviews tool. In brief, both independently reviewed the study and scored the 16 checklist items, each of which is evaluated on a ‘yes’ or ‘no’ basis, with some items having the option of ‘partial yes’.<sup>12</sup> After scoring, discrepancies were discussed to reach a consensus conclusion regarding each quality item. The final determination and categorization of quality (critically low, low, moderate, high) was determined based on the ‘Rating overall confidence in the results of the review’ provided in Shea *et al*,<sup>12</sup> with ‘high’ indicating no or one non-critical flaw, ‘moderate’ indicating more than



**Figure 1** PRISMA flow diagram for the article screening and selection process. PRISMA, Preferred Reporting Items for Systematic Reviews and Meta-Analyses.

one non-critical flaw, ‘low’ indicating one critical flaw with or without non-critical flaws, and ‘critically low’ indicating more than one critical flaw with or without non-critical flaws.<sup>12</sup> Items 2, 4, 7, 9, 11, 13, and 15 (online supplemental table 3) were considered ‘critical flaws’ based on published guidelines; the remaining items were considered ‘non-critical flaws’.<sup>12</sup>

### Analysis

Our primary analysis addressed the overall quality of meta-analyses based on AMSTAR 2 scoring.<sup>12</sup> The frequency of missing components (ie, questions scored as a ‘no’) was examined to determine the most common elements missing from meta-analyses. For this analysis, ‘partial yes’ scores were counted as ‘yes’. The association between quality and year of publication and journal impact factor (extracted from Web of Science) were examined visually using side-by-side box plots; this was a post hoc analysis that was not included in the original protocol.

## RESULTS

### Search results

After the removal of duplicates, our search yielded 2904 articles. Fifty-two full-text articles were subsequently assessed, 37 of which were ultimately excluded (online supplemental table 2). Following a review of reference lists, one additional eligible study was included. A final study was added during the preparation of our manuscript, reaching a total of 17 (see figure 1).

### Quality assessment and review characteristics

Seventeen published studies conducted 58 meta-analyses addressing the effect of systemic, non-opioid pharmacological interventions for CPSP.<sup>17–33</sup> Analyses were conducted for gabapentinoids (gabapentin and pregabalin), ketamine, lidocaine, non-steroidal anti-inflammatory drugs, and mexiletine, including a total of 81 unique, identifiable trials (tables 1 and 2). One study did not clearly identify trials that were included in the analysis of chronic pain.<sup>19</sup>

**Table 1** Characteristics of mexiletine, non-steroidal anti-inflammatory drugs, lidocaine, and ketamine meta-analyses

Study, year	Drug	Follow-up (months)	No of trials	No of participants	Surgery (no of trials)	Route
Carley, 2021 <sup>33</sup>	Mexiletine	3	2	92	Breast(1) Amputation(1)	Oral
Carley, 2021 <sup>33</sup>	NSAIDs	3, 6, 12	5 3 months Drug >24 hours(2) 6 months Drug>24 hours(2) 12 months Drug ≤24 hours(2) Drug >24 hours(2)	3 months Drug ≤24 hour(171) 6 months Drug ≤24 hours(116) 12 months Drug ≤24 hours(179) Drug >24 hours(157)	Thoracic(1) Breast surgery(4)	Intravenous Oral
Chang, 2017 <sup>32</sup>	Lidocaine	3–6	2	194	Breast surgery(2)	Intravenous
Bailey, 2018 <sup>29</sup>	Lidocaine	3–6	6	420	Nephrectomy(1) Thyroidectomy(1) Breast surgery(4)	Intravenous
Lepot, 2020 <sup>20</sup>	Lidocaine	3–12	3	175	Unknown(1) Breast surgery(2)	Intravenous
Carley, 2021 <sup>33</sup>	Lidocaine	3, 6	6 3 months Drug ≤24 hours(5) 6 months Drug ≤24 hours(2)	3 months Drug ≤24 hours (331) 6 months Drug ≤24 hours(182)	Thyroidectomy(1) Breast surgery(5)	Intravenous
Chaparro, 2013 <sup>30</sup>	Ketamine	3, 6	10 3 months(5) 6 months(8)	3 months(384) 6 months(516)	Mixed(1) Thoracic(1) Hip arthroplasty(1) Amputation(1) Prostatectomy(1) Knee arthroplasty(1) Colorectal(2) Breast surgery(2)	Intravenous
McNicol, 2014 <sup>23</sup>	Ketamine	3, 6, 12	16 IV and epidural:  3 months(11) 6 months(NR) 12 months (NR) IV only 3 months(9) 6 months(8) 12 months(NR)	IV and epidural: 3 months(771) 6 months (NR) 12 months (NR) IV only: 3 months(604) 6 months(492) 12 months (NR)	Breast surgery(1) Hip arthroplasty(1) Prostatectomy(1) Mixed(2) Amputation(2) Cesarian(2) Colorectal(2) Thoracic(5)	Intravenous Epidural Intramuscular
Klatt, 2015 <sup>25</sup>	Ketamine	3, 6, 12	10 At rest: 3 months(8) 6 months(5) 12 months(2) In motion: 3 months(5) 6 months(2)	At rest: 3 months(499) 6 months(309) 12 months(77) In motion: 3 months(297) 6 months(187)	Mixed(1) Breast surgery(1) Hip arthroplasty(1) Amputation(1) Colorectal(2) Thoracic(4)	Intravenous Epidural
Riddell, 2019 <sup>19</sup>	Ketamine	2+	NR	NR	Orthopedic (NR)	Intravenous
Bi, 2020 <sup>28</sup>	Ketamine	3, 6	5 3 months(5) 6 months(2)	3 months(382) 6 months(231)	Breast surgery(5)	Intravenous
Carley, 2021 <sup>33</sup>	Ketamine	3, 6, 12	20 3 months Drug ≤24 hours(4) Drug >24 hours(5) 6 months Drug ≤24 hours(6) Drug >24 hours(10) 12 months Drug ≤24 hours(3) Drug >24 hours(2)	3 months Drug ≤24 hours(298) Drug >24 hours(331) 6 months Drug ≤24 hours(553) Drug >24 hours(591) 12 months Drug ≤24 hours(244) Drug >24 hours (103)	Back(1) Amputation(1) Prostatectomy(1) Hip arthroplasty(1) Cesarian(1) Thyroidectomy(1) Mixed(2) Colorectal(2) Knee arthroplasty(2) Breast surgery(3) Thoracic(5)	Intravenous

NR, not reported.

According to the AMSTAR 2 critical appraisal tool, the quality of the studies performing meta-analyses was predominantly low (n=9) or critically low (n=6) (online supplemental table 4). More than two critical weaknesses were identified in five studies (29%). Moderate/high-quality meta-analyses were limited to lidocaine (n=1)<sup>29</sup> and gabapentinoids (n=1).<sup>18</sup> The

most common AMSTAR 2 non-critical weakness (88%) was that review authors did not 'explain their selection of the study designs for inclusion in the review.' Critical weaknesses included failure to assess the presence and likely impact of publication bias (53%), register a protocol (35%), provide justification for the exclusion of trials (24%), consider the risk of bias in

**Table 2** Characteristics of gabapentinoid meta-analyses

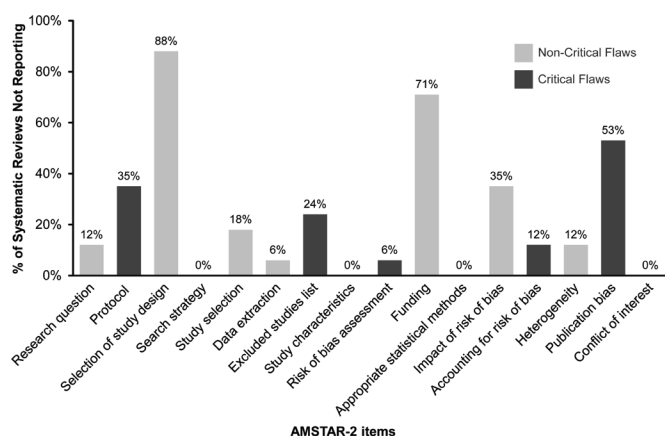
Study, year	Drug	Follow-up (months)	No of trials	No of participants	Surgery (no of trials)	Route
Clarke, 2012 <sup>27</sup>	Pregabalin	3–6	2	641	Knee arthroplasty(1) Thoracic(1)	Oral
Chaparro, 2013 <sup>30</sup>	Pregabalin	3	4	439	Thyroidectomy(1) Back(1) Knee arthroplasty(1) Thoracic(1)	Oral
Mishriky, 2015 <sup>22</sup>	Pregabalin	3, 6, 12	7 3 months(6) 6 months(2) 12 months(2)	3 months(541) 6 months(368) 12 months(200)	Thyroidectomy(1) Knee arthroplasty(1) Thoracic(1) Gynaecologic(2) Back(2)	Oral
Hamilton, 2016 <sup>17</sup>	Pregabalin	3, 6,	3 3 months(3) 6 months(2)	3 months(524) 6 months(413)	Knee arthroplasty(3)	Oral
Martinez, 2017 <sup>24</sup>	Pregabalin	3, 6, 12	16 3 months(15) 6 months(5) 12 months(2)	3 months(1884) 6 months(1360) 12 months(200)	Thyroidectomy(1) Hip arthroplasty(1) Gynaecologic(1) Abdominal(1) Mixed(1) Knee arthroplasty(1) Back(3) Thoracic(5)	Oral
Rai, 2017 <sup>21</sup>	Pregabalin	3	2	91	Breast surgery(2)	Oral
Verret, 2020 <sup>18</sup>	Pregabalin	3+	14	1961	Breast(1) Nephrectomy(1) Knee arthroplasty(1) Thyroidectomy(1) Abdominal(1) Back(1) Mixed(1) Thoracic(3) Unknown(4)	Oral
Chang, 2020 <sup>31</sup>	Pregabalin	3	3	289	Breast surgery(3)	Oral
Carley, 2021 <sup>33</sup>	Pregabalin	3, 6, 12	17 3 months Drug ≤24 hour(2) Drug >24 hours (17) 6 months Drug >24 hours (6) 12 months Drug >24 hours (2)	3 months Drug ≤24 hour(156) Drug >24 hours (2073) 6 months Drug >24 hours (856) 12 months Drug >24 hours (130)	Hip arthroplasty(1) Gynaecologic(1) Nephrectomy(1) Knee arthroplasty(1) Thyroidectomy(1) Mixed(1) Breast(2) Back(3) Thoracic(6)	Oral
Clarke, 2012 <sup>27</sup>	Gabapentin	3–6	6	356	Hip arthroplasty(1) Cesarian(1) Thyroidectomy(1) Breast surgery(3)	Oral
Chaparro, 2013 <sup>30</sup>	Gabapentin	3	5	280	Breast surgery(1) Cesarian(1) Amputation(1) Thoracic(2)	Oral
Rai, 2017 <sup>21</sup>	Gabapentin	3	2	96	Breast surgery(2)	Oral
Jiang, 2018 <sup>26</sup>	Gabapentin	3–12	5	302	Breast surgery(5)	Oral
Verret, 2020 <sup>18</sup>	Gabapentin	3+	13	1237	Cesarian(1) Amputation(1) Hip arthroplasty(1) Mixed(1) Thoracic(3) Breast(3) Unknown(3)	Oral
Carley, 2021 <sup>33</sup>	Gabapentin	3, 6	8 3 months Drug ≤24 hours(2) Drug >24 hours (4) 6 months Drug >24 hours (3)	3 months Drug ≤24 hours (156) Drug >24 hours (200) 6 months Drug >24 hours (511)	Breast surgery(1) Hip arthroplasty(1) Cesarian(1) Amputation(1) Mixed(1) Thoracic(3)	Oral
Lepot, 2020 <sup>20</sup>	Gabapentinoids Gabapentin(1) Pregabalin(1)	3–12	2	246	Breast surgery(2)	Oral

interpretation of results (12%), and assess risk of bias from individual trials included in the review (6%). A breakdown of the AMSTAR 2 scoring is illustrated in [figure 2](#) with further details for each study provided in [table 3](#).

Post hoc analyses revealed trends for better quality meta-analyses in more recent publications, as well as a positive relationship between quality and journal impact factor ([figure 3A,B](#)). There was no clear relationship between quality of reporting and CPSP as a primary or secondary outcome, or if a study was focused solely on CPSP.

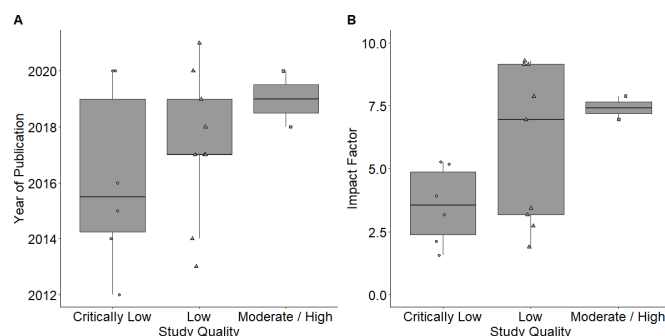
## DISCUSSION

Our assessment using the AMSTAR 2 critical appraisal tool indicates only one ‘high’ quality published study meta-analyzing perioperative management options for CPSP.<sup>18</sup> This is a major concern given the importance of meta-analyses to guide the perioperative management of CPSP, which are primarily informed by underpowered clinical trials. Failure to address publication bias, lack of protocol registration, and the absence of information on excluded studies were the most common critical flaws.



**Figure 2** AMSTAR 2 quality assessment of included studies. The x axis corresponds to the AMSTAR 2 items (16 items total). Each item in AMSTAR 2 is considered as a 'critical flaw' (dark gray) or 'non-critical flaw' (light gray), based on published guidelines. AMSTAR 2, A Measurement Tool to Assess Systematic Reviews 2.

According to AMSTAR 2, excluded studies should be properly accounted for by review authors 'otherwise there is a risk that they remain invisible and the impact of their exclusion from the review is unknown'.<sup>12</sup> The problems that arise from failing to represent excluded trials is exemplified in Clarke and colleagues,<sup>27</sup> Clarke *et al*, who reported an aggregate benefit of pregabalin on the basis of only two trials but provide no justification for the exclusion of Kim *et al*<sup>34</sup>—a seemingly eligible third trial that examined the incidence of CPSP at 3 months after thyroidectomy surgery.<sup>27 34</sup> The exclusion of Kim *et al*<sup>34</sup> is a concern in light of the effect on meta-results, swinging the aggregate estimate for pregabalin reported in Clarke *et al*<sup>27</sup> from



**Figure 3** Relationship between (A) study quality and year of publication and (B) study quality and journal impact factor. Each boxplot shows the median as a horizontal line inside the box and the IQR as the length of the box; the whiskers (lines extending from the top and bottom of the box) represent the minimum and maximum values when they are within 1.5 times the IQR. Study quality was based on the AMSTAR 2. AMSTAR 2, A Measurement Tool to Assess Systematic Reviews 2.

significant to non-significant (OR, 0.25; 95% CI 0.05 to 1.28; unpublished data based on our own calculation). Owing to the seminal nature of Clarke *et al*<sup>27</sup> meta-analysis, Kim *et al*'s<sup>34</sup> study may simply have been overlooked and captured in later studies, which benefited from increased knowledge to generate a more comprehensive search strategy. There are also a number of potential and valid explanations for exclusion to consider that may not be readily apparent, further emphasizing the need for transparency in reporting.

Lack of protocol registration was the second most common critical flaw. The fundamental goal of protocol registration is to reduce the risk of bias through adherence to a prespecified

**Table 3** Summary of quality review

Author, year	IF	AMSTAR 2	Key quality justification	CPSP as primary or secondary outcome	Surgical procedures	Pain outcome
Bailey, 2018 <sup>29</sup>	6.96	Moderate	No explanation of selection for inclusion No report of funding	Primary	Mixed	Chronic only
Bi, 2020 <sup>28</sup>	3.18	Critically low	No justification of excluded trials No predefined criteria Risk of bias not interpreted	Secondary	Surgery specific	Acute and chronic
Carley, 2021 <sup>33</sup>	7.89	Low	Did not examine publication bias	Primary	Mixed	Chronic only
Chang, 2017 <sup>32</sup>	3.18	Low	No predefined criteria	Primary	Surgery specific	Acute and chronic
Chang, 2020 <sup>31</sup>	3.44	Low	Did not examine publication bias	Primary	Surgery specific	Acute and chronic
Chaparro, 2013 <sup>30</sup>	9.29	Low	Did not examine publication bias	Primary	Mixed	Chronic only
Clarke, 2012 <sup>27</sup>	5.18	Critically low	No justification of excluded trials No predefined criteria	Primary	Mixed	Chronic only
Hamilton, 2016 <sup>17</sup>	5.28	Critically low	No justification of excluded trials Did not examine publication bias	Secondary	Surgery specific	Acute and chronic
Jiang, 2018 <sup>26</sup>	1.89	Low	No predefined criteria	Secondary	Surgery specific	Acute and chronic
Klatt, 2015 <sup>25</sup>	1.57	Critically low	No risk of bias Risk of bias not interpreted	Primary	Mixed	Chronic only
Lepot, 2020 <sup>20</sup>	3.93	Critically low	No justification of excluded trials Did not examine publication bias	Secondary	Surgery specific	Acute and chronic
Martinez, 2017 <sup>24</sup>	6.96	Low	Did not examine publication bias	Primary	Mixed	Chronic only
McNicol, 2014 <sup>23</sup>	2.11	Critically low	No predefined criteria Did not examine publication bias	Primary	Mixed	Chronic only
Mishriky, 2015 <sup>22</sup>	9.17	Low	No predefined criteria	Secondary	Mixed	Acute and chronic
Rai, 2017 <sup>21</sup>	2.74	Low	Did not examine publication bias	Primary	Surgery specific	Acute and chronic
Riddell, 2019 <sup>19</sup>	9.17	Low	Did not examine publication bias	Secondary	Mixed	Acute and chronic
Verret, 2020 <sup>18</sup>	7.89	High	—	Secondary	Mixed	Acute and chronic

CPSP, chronic postsurgical pain; IF, impact factor.



analysis plan.<sup>12</sup> The value of a prespecified analysis plan is inherent to all meta-analyses, but particularly important when the outcome of interest is poorly defined or lacks standardization. This issue is well known to the field of CPSP and has been raised by the Initiative on Methods, Measurement, and Pain Assessment in Clinical Trials, who previously advocated for standardization of outcomes to facilitate meta-analyses and systematic reviews.<sup>35</sup> In practice, meta-analyses examined outcomes from clinical trials ranging from three to 12 months and sometimes aggregated across time points (+3 months),<sup>18 31</sup> which lead to differences in effect sizes reported for the same trial<sup>36</sup> ranging from significant<sup>31</sup> to insignificant.<sup>18</sup> Subtler differences in defining CPSP also led to substantial variations in effect size estimates at the individual trial level, including whether the incidence of CPSP was based on pain during movement<sup>18 27 30</sup> or at rest.<sup>24</sup> It is worth noting, however, limitations of protocol registration. For example, a third of systematic review registrations on PROSPERO changed or did not specify the primary outcome,<sup>37</sup> indicating a need to evaluate actual adherence to protocols in the future.

Approximately 50% of studies did not provide an analysis of publication bias. Publication bias is important to consider because an 'underlying tendency to selectively publish small positive studies may be compounded by the effects of lower methodological quality of small studies, a greater tendency to selectively report results, and increased clinical heterogeneity when conducted in patient subgroups'.<sup>12</sup> The lack of attention to publication bias may reflect that a number of studies included in our review analyzed fewer than 10 trials<sup>17 19–21 30 31</sup>—a benchmark to conduct quantitative analyses.<sup>38</sup> However, there are recent examples where more than 10 trials were included and publication bias was still not considered.<sup>23 24 33</sup> To highlight the added value of analyzing publication bias, we reanalyzed data provided in Martinez *et al.*<sup>24</sup> Martinez *et al.*'s meta-analysis was important to the field of CPSP insofar as unreported clinical trial outcomes previously ignored were included. In doing so, benefits of pregabalin were effectively nullified. While highlighting the clinical impact of publication bias, for a variety of reasons (eg, unable to contact author), outcomes from other trials that had addressed CPSP were not accessed and therefore not included. Based on the funnel plot and Doi plot<sup>39</sup> representation of available data (figure 4), publication bias remains a concern. This is consistent with publication bias reported by Verret *et al.*<sup>18</sup> for gabapentinoids and further raises concerns with regards to the efficacy of pregabalin to reduce the incidence of CPSP.

Although not the focus of our review, it was observed that few studies performed individual patient data (IPD) meta-analyses.

IPD represents the gold standard for conducting meta-analyses,<sup>40</sup> with their primary advantage lying in the ability to account for patient-level factors,<sup>40</sup> as well as assess data quality firsthand. Additionally, heterogeneity between trials can be reduced by analyzing outcomes consistently tracked but not necessarily made available in published material. IPD meta-analyses have been conducted to assess acupuncture,<sup>41</sup> spinal manipulative therapy,<sup>42</sup> placebo effects in individuals with chronic pain,<sup>43</sup> and prognostic factors associated with knee pain.<sup>44</sup> In the context of evaluating perioperative interventions for CPSP, an IPD meta-analysis could resolve a number of major challenges, including standardizing outcomes. Notwithstanding the challenges of IPD (eg, greater resources required, risk of selection and availability bias due to barriers in accessing IPD),<sup>45 46</sup> planning IPD meta-analysis is an important future direction of next generation CPSP meta-research.

A descriptive review of factors associated with quality of reporting indicates an improvement over time and a positive association with journal impact factor. This aligns with the timeline for the adoption of reporting guidelines for meta-analyses, endorsement of complete and transparent reporting by higher impact journals, and increased scrutiny regarding quality.<sup>47</sup> Critically low-quality and low-quality studies continue to be published, however, as recently as 2020, thus demonstrating that challenges remain.

Strengths of our study include the first comprehensive quality assessment of non-opioid, pharmacological, perioperative interventions for CPSP. Possible limitations of quality assessments include the subjective nature of screening, data extraction, and scoring, though we attempted to address this with two investigators implementing a validated and reliable quality assessment tool.<sup>48</sup>

## CONCLUSION

Meta-analyses play a pivotal role in informing clinical decisions with regards to perioperative management of CPSP. Based on our systematic review, meta-analyses in the area of CPSP are missing critical methodological details, including an evaluation of publication bias, protocol registration, and the provision of excluded study details. An area for future development is IPD meta-analyses, which is needed to address patient-level factors associated with trial outcomes.

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**Contributors** RHM: Responsible for study design and protocol, screening, data extraction, data interpretation, drafting the manuscript, and final manuscript approval. FMW: Responsible for study design and protocol, screening, data extraction, data interpretation, drafting the manuscript, and final manuscript approval. LDL: Contributed to data interpretation, revising the paper for intellectual content, and final manuscript approval. JJC: Contributed to data interpretation, revising the paper for intellectual content, and final manuscript approval. JAO: Contributed to data interpretation, revising the paper for intellectual content, and final manuscript approval. VPV: Contributed to data interpretation, revising the paper for intellectual content, and final manuscript approval. SKWS: Contributed to data interpretation, revising the paper for intellectual content, and final manuscript approval. JKK: Contributed to study design, data interpretation, drafting the manuscript, revising the paper for intellectual content, and final manuscript approval.

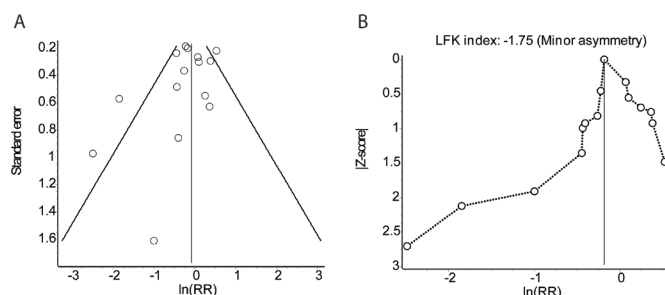
**Funding** The authors have not declared a specific grant for this research from any funding agency in the public, commercial or not-for-profit sectors.

**Competing interests** None declared.

**Patient consent for publication** Not applicable.

**Provenance and peer review** Not commissioned; externally peer reviewed.

**Data availability statement** Data sharing not applicable as no datasets generated and/or analyzed for this study. Not applicable.



**Figure 4** Assessment of publication bias in Martinez *et al.*<sup>24</sup> Funnel plot (A) and Doi plot (B) using the natural logarithm of the relative risk (RR) for the development of CPSP (at 3 months) as the effect measure. The closer the value of the LFK index to zero, the more symmetrical the Doi plot. CPSP, chronic postsurgical pain.

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**Table S1** Literature search criteria

Date	Database	Search Terms
17.11.2020	Embase (Ovid)	1. Pain, Postoperative/ 2. postoperative or post-operative or post-operat* or postoperat* or "after operat*" or "follow* operat*" 3. postsurgical or post-surgical or post-surg* or postsurg* or "after surg*" or "follow* surg*" 4. 2 or 3 5. pain* or discomfort or analgesi* 6. 4 and 5 7. 1 or 6 8. chronic* or constant* or continu* or persist* or longterm or long-term or longstanding or long-standing or long lasting or longlasting 9. 7 and 8 10. 9 and 2010:2020.(sa_year). 11. Meta analysis/ 12. 10 and 11
19.07.2021	MEDLINE (Ovid)	1. Pain, Postoperative/ 2. postoperative or post-operative or post-operat* or postoperat* or "after operat*" or "follow* operat*" 3. postsurgical or post-surgical or post-surg* or postsurg* or "after surg*" or "follow* surg*" 4. 2 or 3 5. (pain* or discomfort or analgesi* 6. 4 and 5 7. 1 or 6 8. chronic* or constant* or continu* or persist* or longterm or long-term or longstanding or long-standing or long lasting or longlasting 9. 7 and 8 10. 9 and 2010:2020.(sa_year). 11. Meta-Analysis/ 12. 10 and 11
19.07.2021	Cochrane Database of Systematic Reviews (Ovid)	1. Pain, Postoperative 2. postoperative or post-operative or post-operat* or postoperat* or "after operat*" or "follow* operat*" 3. postsurgical or post-surgical or post-surg* or postsurg* or "after surg*" or "follow* surg*" 4. 2 or 3 5. (pain* or discomfort or analgesi* 6. 4 and 5 7. 1 or 6 8. chronic* or constant* or continu* or persist* or longterm or long-term or longstanding or long-standing or long lasting or longlasting 9. 7 and 8 10. 9 and 2010:2020.(sa_year). 11. Meta-Analysis/ 12. 10 and 11



**Table S2** Full-text exclusions

Study title	Author, year	Reason for exclusion
Local anaesthetics and regional anaesthesia for preventing chronic pain after surgery.	Andreae, 2012	Wrong intervention
Efficacy of Intraoperative Dexmedetomidine Compared with Placebo for Postoperative Pain Management: A Meta-Analysis of Published Studies	Bellon, 2016	Pediatric population
Effect of perioperative systemic alpha2 agonists on postoperative morphine consumption and pain intensity: systematic review and meta-analysis of randomized controlled trials.	Blaudszun, 2012	Did not examine chronic pain
Pharmacotherapy for the prevention of chronic pain after surgery	Chaparro, 2012	Conference abstract
Effect of Perioperative Vitamin C Supplementation on Postoperative Pain and the Incidence of Chronic Regional Pain Syndrome: A Systematic Review and Meta-Analysis.	Chen, 2016	Wrong outcomes
The efficiency and safety of steroid addition to multimodal cocktail periarticular injection in knee joint arthroplasty: a meta-analysis of randomized controlled trials	Deng, 2019	Did not examine chronic pain
Perioperative single dose systemic dexamethasone for postoperative pain: a meta-analysis of randomized controlled trials.	DeOliveira, 2011	Did not examine chronic pain
Single dose oral celecoxib for acute postoperative pain in adults.	Derry, 2013	Did not examine chronic pain
Preoperative gabapentin for postoperative pain in orthopaedic surgery: Systematic review, meta-analysis and meta-regression	Doleman, 2015	Conference abstract
Pharmacological interventions for the prevention of acute postoperative pain in adults following brain surgery.	Galvin, 2019	Did not examine chronic pain
Single dose oral ketoprofen or dexketoprofen for acute postoperative pain in adults	Gaskell, 2017	Did not examine chronic pain
Intra-articular lidocaine versus intravenous analgesia and sedation for manual closed reduction of acute anterior shoulder dislocation: an updated meta-analysis.	Jiang, 2014	Wrong outcomes
The effects of continuous intravenous infusion of dexmedetomidine and remifentanyl on postoperative pain: A systematic review and meta-analysis	Jin, 2019	Did not examine chronic pain
Interventions to reduce shoulder pain following gynaecological laparoscopic procedures	Kaloo, 2019	Wrong intervention
Continuous intravenous perioperative lidocaine infusion for postoperative pain and recovery.	Kranke, 2015	Did not examine chronic pain
The efficacy and safety of dexamethasone for pain management after total knee arthroplasty: A systematic review and meta-analysis.	Li, 2018	Did not examine chronic pain
The efficiency and safety of dexamethasone for pain control in total joint arthroplasty: A meta-analysis of randomized controlled trials.	Meng, 2017	Did not examine chronic pain

Perioperative adjuvant corticosteroids for post-operative analgesia in elective knee surgery - A systematic review	Mohammad, 2017	Did not examine chronic pain
The efficacy and safety of first-line therapies for preventing chronic post-surgical pain: A network meta-analysis	Ning, 2018	Wrong outcomes
Perioperative Ketamine for Analgesia in Spine Surgery: A Meta-analysis of Randomized Controlled Trials.	Pendi, 2018	Did not examine chronic pain
Peri-operative steroids reduce pain, inflammatory response and hospitalisation length following knee arthroplasty without increased risk of acute complications: a meta-analysis	Previtali, 2019	Did not examine chronic pain
Is intraoperative dexmedetomidine a new option for postoperative pain treatment? A meta-analysis of randomized controlled trials.	Schnabel, 2013	Did not examine chronic pain
Perioperative systemic lidocaine for postoperative analgesia and recovery after abdominal surgery: A meta-analysis of randomized controlled trials	Sun, 2012	Did not examine chronic pain
Lidocaine for preventing postoperative sore throat	Tanaka, 2015	Did not examine chronic pain
Perioperative use of gabapentinoids for the management of postoperative pain: A systematic review & meta-analysis	Verret, 2018	Conference abstract
Efficacy and safety of intravenous lidocaine for postoperative analgesia and recovery after surgery: a systematic review with trial sequential analysis.	Weibel, 2016	Did not examine chronic pain
Continuous intravenous perioperative lidocaine infusion for postoperative pain and recovery in adults	Weibel, 2018	Did not examine chronic pain
The effectiveness of interventions for preventing chronic pain after total knee replacement: Systematic review and meta-analysis	Wylde, 2020	Conference abstract
The efficacy of pregabalin for the management of acute and chronic postoperative pain in thoracotomy: A meta-analysis with trial sequential analysis of randomized-controlled trials	Yu, 2019	Wrong outcomes

**Table S3** Item descriptions for the AMSTAR 2 critical appraisal tool for systematic reviews

Item No.	Item
1.	Did the research questions and inclusion criteria for the review include the components of PICO?
2.	Did the report of the review contain an explicit statement that the review methods were established prior to the conduct of the review and did the report justify any significant deviations from the protocol?
3.	Did the review authors explain their selection of the study designs for inclusion in the review?
4.	Did the review authors use a comprehensive literature search strategy?
5.	Did the review authors perform study selection in duplicate?
6.	Did the review authors perform data extraction in duplicate?
7.	Did the review authors provide a list of excluded studies and justify the exclusions?
8.	Did the review authors describe the included studies in adequate detail?
9.	Did the review authors use a satisfactory technique for assessing the risk of bias (RoB) in individual studies that were included in the review?
10.	Did the review authors report on the sources of funding for the studies included in the review?
11.	If meta-analysis was performed, did the review authors use appropriate methods for statistical combination of results?
12.	If meta-analysis was performed, did the review authors assess the potential impact of RoB in individual studies on the results of the meta-analysis or other evidence synthesis?
13.	Did the review authors account for RoB in primary studies when interpreting/discussing the results of the review?
14.	Did the review authors provide a satisfactory explanation for, and discussion of, any heterogeneity observed in the results of the review?
15.	If they performed quantitative synthesis did the review authors carry out an adequate investigation of publication bias (small study bias) and discuss its likely impact on the results of the review?
16.	Did the review authors report any potential sources of conflict of interest, including any funding they received for conducting the review?

**Table S4** AMSTAR 2 critical appraisal tool for systematic reviews

	Item No.																
Study	1	2	3	4	5	6	7	8	9	10	11	12	13	14	15	16	Quality
Bailey, 2018	Yes	Yes	No	Partial Yes	Yes	Yes	Yes	Yes	Yes	No	Yes	Yes	Yes	Yes	Yes	Yes	Moderate
Bi, 2020	Yes	No	No	Partial Yes	Yes	Yes	No	Yes	Yes	No	Yes	No	No	Yes	Yes	Yes	Critically low
Carley, 2021	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	No	Yes	Low
Chang, 2017	No	No	No	Partial Yes	No	Yes	Partial Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Low
Chang, 2020	Yes	Partial Yes	No	Yes	Yes	Yes	Partial Yes	Yes	Yes	No	Yes	Yes	Yes	Yes	No	Yes	Low
Chaparro, 2013	Yes	Partial Yes	No	Partial Yes	Yes	Yes	Yes	Yes	Yes	No	Yes	Yes	Yes	Yes	No	Yes	Low
Clarke, 2012	Yes	No	No	Partial Yes	Yes	Yes	No	Yes	Yes	No	Yes	No	Yes	Yes	Yes	Yes	Critically low
Hamilton, 2016	Yes	Yes	No	Yes	Yes	Yes	No	Yes	Yes	Yes	Yes	Yes	Yes	No	No	Yes	Critically low
Jiang, 2018	Yes	No	No	Partial Yes	Yes	Yes	Yes	Yes	Yes	No	Yes	Yes	Yes	Yes	Yes	Yes	Low
Klatt, 2015	Yes	Partial Yes	Yes	Partial Yes	No	Yes	Partial Yes	Yes	No	No	Yes	No	No	Yes	Yes	Yes	Critically low
Lepot, 2020	Yes	Yes	No	Partial Yes	Yes	No	No	Partial Yes	Yes	No	Yes	No	Yes	Yes	No	Yes	Critically low
Martinez, 2017	No	Yes	No	Yes	Yes	Yes	Partial Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	No	Yes	Low
McNicol, 2014	Yes	No	No	Partial Yes	No	Yes	Partial Yes	Yes	Yes	No	Yes	No	Yes	Yes	No	Yes	Critically low
Mishriky, 2014	Yes	No	No	Partial Yes	Yes	Yes	Partial Yes	Yes	Yes	No	Yes	Yes	Yes	Yes	Yes	Yes	Low
Rai, 2017	Yes	Yes	No	Partial Yes	Yes	Yes	Partial Yes	Yes	Yes	No	Yes	Yes	Yes	No	No	Yes	Low
Riddell, 2019	Yes	Yes	No	Yes	Yes	Yes	Partial Yes	Yes	Yes	No	Yes	No	Yes	Yes	No	Yes	Low
Verret, 2020	Yes	Yes	No	Yes	Yes	Yes	Partial Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	High