Preventing persistent postsurgical pain: A systematic review and component network meta-analysis

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Abstract
Background and objectives: Evidence for perioperative methods to prevent persistent postsurgical pain (PPP) is uncertain, in part because few treatments have been directly compared.

Databases and data treatment: We searched the Cochrane Central Registry of Controlled Trials, Embase, MEDLINE, ClinicalTrials.gov and the World Health Organization International Clinical Trials Registry up to January 2021 for randomized, double-masked, controlled trials that reported the prevalence of PPP. We assessed trial quality with the Cochrane risk of bias tool (RoB 2.0). We analysed the results with frequentist cNMA models. The primary outcome was the relative risk (RR) of PPP. We assessed efficacy in relation to a clinically important effect size of RR = 0.9, which is a 10% improvement with treatment.

Results: The analysis included 107 trials (13,553 participants) of 13 treatments. The effects of complex interventions were the multiplicative effects of their components. Compared with placebo, serotonin–norepinephrine reuptake inhibitors (SNRIs), neural block alone, or in combination with NMDA receptor blockers or gabapentanoids were effective. Treatments with benefit in the immediate postoperative period predicted a reduced risk of PPP.

Conclusions: Several treatments and treatment combinations effectively reduce PPP prevalence. Pain outcomes in the immediate postoperative period are an important mediator of PPP. Multimodal interventions can be analysed using cNMA.

Significance: Systematic reviews of PPP prevention usually focus on the efficacy of specific treatments in comparison with control interventions. In this study we used component network meta-analysis to compare interventions to each other, including both pharmacological and neural block techniques, and multimodal interventions. Interventions that are not effective alone may improve the efficacy of multimodal interventions that include neural block...
1 | INTRODUCTION

Prevention of persistent postsurgical pain (PPP) is currently a priority for perioperative medicine (Glare et al., 2019; Katz et al., 2015; Kehlet et al., 2006). Evidence from randomized clinical trials (RCTs) suggests that perioperative pharmacological and regional anesthetic interventions may modestly reduce PPP risk (Carley et al., 2021; Weinstein et al., 2018). Since PPP is estimated to affect 10%–50% of the surgical population, even small-to-modest reductions in prevalence have the potential to improve the quality of life for many patients. During the past 20 years, hundreds of RCTs have investigated PPP prevention, often as a ‘follow-up’ outcome in studies of acute postoperative pain management. Most investigations have compared interventions with placebo; few have provided head-to-head comparisons of common treatments. In acute postoperative pain management, the combination of treatments into multimodal analgesia has become a popular means of alleviating pain while reducing reliance on opioids (Mathiesen et al., 2013). In the context of preventing PPP, the clinical choices for components of a multimodal combination are frequently guided by the logic of the pathophysiology models for the transition from acute to chronic pain (Glare et al., 2019; Lavand’homme, 2017).

Meta-analyses of interventions for PPP prevention have often divided the selected studies into subgroups according to types of interventions, timing of outcomes and types of surgery, a so-called ‘splitting strategy’ that aims to define interventions that are effective in specific clinical settings. The results to date have been disappointing (Carley et al., 2021) – ‘extremely little progress has been made since 2013, likely due to study designs being insufficient to address the complexities of this multifactorial problem. 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...’. A large Phase 3/4 trial of ketamine is currently in progress (Schug & Peyton, 2017).

To select which treatments or combinations of treatments have the highest likelihood of success in large clinical trials, it may help to compare and rank the efficacy of current treatments to each other. Network meta-analysis (NMA) allows the synthesis of results across a network of trials that include different treatments, using both direct and indirect evidences (Cipriani et al., 2013; Salanti, 2012). Advantages of NMA include increased precision of effect estimates and comparison of all included treatments. Component NMA (cNMA) is a newly available methodology that extends NMA to include complex interventions that are composed of several components (Higgins et al., 2019; Petticrew et al., 2019). To our knowledge, the only published NMA of pharmacological interventions for PPP prevention was based upon 24 RCTs and included six interventions (Ning et al., 2018).

Our aims for this review and analyses were: 1. to compare the efficacy of pharmacological and neural block interventions, both as monotherapies and as multimodal treatments, on the relative risk of PPP in adults; 2. to identify potential advantages of interventions directed at specific pain pathways, such as N-methyl-D-aspartate (NMDA) receptor blocking drugs or neural block and 3. to evaluate the influence of acute postoperative pain on PPP prevalence.

2 | METHODS

2.1 | Protocol and registration

We pre-registered the study protocol with PROSPERO (number CRD42018085570) in January 2018. We reported the results according to the Preferred Reporting Items for Systematic Reviews and Meta-Analyses guidelines for network meta-analyses (Hutton et al., 2015).

2.2 | Important changes to the registered protocol

Inclusion of non-pharmacological interventions such as physical therapy, splinting and behavioural therapy, which we had initially included in our outcome list, was not possible because most of the trials lacked appropriate control groups or were not masked. Only slightly more than half of the studies reported adverse events, so we could not compare intervention efficacy with tolerability (there were no studies that reported severe adverse events related to the interventions). For the primary analysis, we have used component NMA (cNMA) rather than standard NMA because it allows for the inclusion of complex techniques. Immediate postoperative benefit was an important mediator for reduction of PPP.

Study registration: PROSPERO: CRD42018085570 https://www.crd.york.ac.uk/prospero/.
interventions common in multimodal pain management strategies. cNMA software was not readily available at the time that our initial protocol was written.

2.3 | Inclusion criteria

2.3.1 | Participants

We included randomized double-masked trials involving participants 18 years of age or older of either sex.

2.3.2 | Interventions and comparators – definitions of nodes in the network

We chose at the outset to include all pharmacological and neural block interventions that are or have been in common clinical practice and could be accommodated in the network. When possible, we grouped interventions into nodes or components according to their role in biological models of the transition from acute to chronic pain. Our assumptions in choosing this network structure were that agents that act by similar mechanisms can be grouped together (Glare et al., 2019) and that the effect of components when combined are multiplicative (Higgins et al., 2019) (e.g. the combination of two hypothetical interventions that each reduces the risk of PPP by 50% results in a relative risk of 0.25). We evaluated our choice of network structure by comparing the component model with the standard NMA model using the difference in the Q statistics for each model to test the null hypothesis – that there was no significant difference in heterogeneity between the models (Higgins et al., 2019). We included the following interventions (components): gabapentin and pregabalin (gabapentanoids); nefopam, acetaminophen; non-steroidal anti-inflammatory drugs (anti-inflammatory); steroids; ketamine magnesium, memantine (N-methyl-D-aspartate receptor (NMDA)-blocking drugs); clonidine, dexmedetomidine (alpha-2-receptor agonists); lidocaine infusions, oral mexiletine (systemic local anesthetics); fentanyl, tramadol, morphine (opioids); duloxetine, venlafaxine (selective serotonin–norepinephrine reuptake inhibitors, SNRIs); and neural block with local anesthetics (administered by infiltration, intra-articular injection, topical application or regional/neuraxial anesthesia/analgesia). We included head-to-head trials and trials with inactive comparators (placebo or sham neural block). In dose-finding trials, we selected the study arm with the highest reported dose. We categorized the timing of interventions as ‘before surgical incision’, ‘post-operative’ and ‘throughout the perioperative period’ and evaluated this putative effect modifier with meta-regression. We excluded trials that did not share any intervention or comparator within the network and interventions for which the evidence was limited to one study. We also excluded trials that compared two versions of the same intervention (e.g. two types of neural block) with no other comparator.

2.3.3 | Outcome measures

The primary outcome was the prevalence of pain persisting longer than 3 months after surgery, summarized as the risk ratio (RR) with 95% confidence intervals [95% CI]. When results were reported for multiple time points after surgery, we selected the longest follow-up time. Trials with no events in any study arm were omitted from the analysis. For trials with no events in one arm, we used a continuity correction of 0.5.

Where available, secondary outcomes were all-cause dropouts, withdrawals due to adverse events, the prevalence of adverse events, quality of life, functional assessment, ongoing pharmacological interventions and prevalence of mood disorders.

2.3.4 | Study design

We included only randomized, double-masked, controlled trials. For neural block interventions performed when the participants were aware, we included only trials with sham interventions.

2.4 | Information sources

We searched the following trial registries and electronic databases: Cochrane Central Registry of Controlled Trials (Ovid, to 12 January 2021), MEDLINE (Ovid, 1946 to 12 January 2021); Embase, (Ovid, 1974 to 12 January 2021); ClinicalTrials.gov (to 12 January 2021); and the World Health Organization (WHO) International Clinical Trials Registry Platform (to 12 January 2021). We created a systematic search containing subject headings and keywords for each database. The final search strategies are included in the Supplementary Material, S1. The sensitivity and precision maximizing (2008) version of the randomized controlled trials filter were adapted for use in the searches (Higgins et al., 2021), and retracted trials were excluded. No additional filters or language restrictions were used in the search. We hand searched reference lists of included studies and relevant narrative and systematic reviews. We included published and unpublished trials (trial registries,
meetings abstracts, theses) that reported summary estimates of the prevalence of PPP. When additional information was required, we systematically contacted the authors by e-mail. Trials reported in languages other than English were translated.

2.5 | Study selection

Four investigators in two pairs independently screened titles and abstracts of manuscripts to capture relevant publications. Two investigators independently performed a full-text review of each study for inclusion. A third investigator adjudicated any conflicts in the primary and secondary screens.

2.6 | Data extraction

The following data were extracted pro forma independently by two investigators and independently verified: first author, year of publication and citation, continent of origin, the number of randomized patients, sex, the type of surgery, intervention(s) used (drug dose, technique, and timing of administration – before incision, after surgery, or throughout the perioperative period), the primary, and secondary outcomes. In dose-finding trials, we extracted results for the highest dose. The types of surgery were clustered into the International Classification of Disease (ICD version 11) categories of PPP (Schug et al., 2019).

Features of pain experienced in the immediate postoperative period have been reported to be a risk mediator in the development of PPP (Althaus et al., 2014; Montes et al., 2015); however, the reporting of acute pain severity was inconsistent in the included trials. As a surrogate mediator, we recorded ‘immediate postoperative benefit’, defined as a decrease in pain measured with any validated method, or a decrease in analgesic consumption, both as documented with nominal $p < 0.05$.

2.7 | Outcomes

2.7.1 | Persistent pain

We recorded the prevalence of PPP or when it was not reported, the prevalence of neuropathic pain, at least 3 months after surgery. When PPP was reported at multiple time points, we analysed the results from the longest time from surgery that had data in all treatment arms. When the intensity of PPP was quantified, the prevalence in the moderate-to-severe category was used.

2.8 | Risk of bias assessment

2.8.1 | Within-study bias

Two investigators independently evaluated individual trials for risk of bias (RoB) using the Cochrane risk of bias tool (RoB 2.0) (Sterne et al., 2019). A third investigator adjudicated any differences. For summarizing, RoB assessments of trials were weighted by the random effects weights from a pairwise meta-analysis of comparisons with placebo. The average RoB for direct comparisons in the network was calculated using the CINeMA online application (Papakonstantinou et al., 2020).

2.8.2 | Risk of bias across trials

We explored the data for selective reporting bias or small studies effects using a ‘comparison-adjusted’ funnel plot overlaid with contours for statistical significance (Palmer et al., 2008) and with p-curve analysis (Simonsohn et al., 2014). We evaluated the overall symmetry of the funnel plot with Peters’ regression test for binomial outcomes (Peters et al., 2006). For individual comparisons, we evaluated asymmetry to be potentially related to publication bias if the areas of the funnel plot in which trials are missing were of low statistical significance ($0.01 > p < 0.05$) (Palmer et al., 2008). We performed the p-curve analysis with the online application (Simonsohn et al., 2014).

2.8.3 | Indirectness

Two investigators independently evaluated each study population and outcome for its relevance to our research question.

2.8.4 | Transitivity

Our grouping of interventions according to biological mechanisms meant that they could be jointly randomized – for example, some form of neural block could be implemented in any surgical procedure. In a sensitivity analysis, we compared the risk of PPP among the different types of neural block – neuraxial block, regional nerve block and wound infiltration to confirm that it was reasonable to include them in one category. Since it is possible that regional block interventions may be more prone to technical failure than systemically administered agents, we used network meta-analysis to compare the relative risk of missing outcomes between these two methods.
2.8.5 Potential treatment effect modifiers

Two investigators independently extracted values pro forma for the following risk factors: the timing/duration of interventions – before incision, after surgery, or throughout the perioperative period, sex, and the timing of the PPP assessment in months. We characterized the immediate postoperative response to the treatments as showing ‘benefit’ if the treatment was associated with a reduction in pain scores or analgesic consumption during recovery from surgery with nominative \( p < 0.05 \). We used meta-regression with multimodel inference (Harrer et al., 2019) to evaluate the importance of the potential predictors (sex, timing of outcome, timing of intervention, immediate postoperative benefit and baseline prevalence on placebo by surgical procedure) on the treatment effect.

2.9 Data synthesis

2.9.1 Meta-analyses

We conducted random effects cNMA in a frequentist setting with the netmeta package (version 1.3-0) (Rücker et al., 2021). The summary measure was the relative risk (RR) for PPP. Corrections were made for the correlation of comparisons in multi-arm trials. We evaluated statistical heterogeneity for the network with the \( Q \) statistic for a full design-by-treatment interaction random effects model (Balduzzi et al., 2019) and by comparing the heterogeneity variance parameter \( (\tau^2) \) from the NMA models with the empirical distribution for pharmacological versus placebo/control intervention types (Turner et al., 2015). We assessed goodness-of-fit with the inconsistency between estimates from direct and indirect evidence using \( Z \) scores, with a nominal statistical significance level of \( p < 0.10 \) (Krahn et al., 2014). We expressed uncertainty by the 95% confidence intervals of the estimates. We performed a sensitivity analysis to compare the heterogeneity in the cNMA and standard NMA models. Ranking of outcomes (possible only with the standard NMA model) was by \( P \)-scores (Rücker & Schwarzer, 2015), which are presented without confidence intervals (Veroniki et al., 2018).

We conducted the primary cNMA with participants who completed each trial and we performed a sensitivity analysis including data imputed for missing outcomes according to the ‘reason for missingness’ (Mavridis & White, 2020).

We performed a standard pairwise meta-analysis to evaluate the overall treatment effect of being assigned to ‘intervention’ and to provide random effects weights of individual trials for risk of bias estimation. We used a standard NMA to compare the estimates from wound infiltration, regional nerve block and neuraxial block, which were the individual techniques that were included in the component ‘neural block’.

All analyses were performed in R version 4.0.3 (R Core Team, 2021). We performed the pairwise meta-analysis with the metabin command in the metafor package version 2.4–0 (Viechtbauer, 2015). The baseline prevalence estimates of PPP were calculated from the event rate on placebo using the metaprop command in the meta package (Balduzzi et al, 2019).

2.9.2 Geometry of the network

We visualized the geometry with a network graph constructed from direct comparisons between interventions using a stress majorization algorithm (Schwarzer et al., 2015).

2.9.3 Effects of combining study characteristics

We evaluated the impact of combining (lumping) study characteristics by performing multimodel inference analysis (Harrer et al., 2019) of the associations between the relative risk of PPP and the study characteristics that were ‘lumped’. These characteristics were the predictors in the regression models: timing of the interventions, the baseline risk of PPP by surgical category, sex and the timing of pain outcomes: the immediate postoperative period, at 3 months and at 6 months postoperatively. Models were ranked by model fit using the corrected Akaike information criterion; test statistics and confidence intervals were calculated with the Knapp-Hartung adjustment (Röver et al., 2015). The estimated coefficients of the predictors were then pooled across all the fitted models to estimate the average predictor importance. We conducted the analyses using the MuMIn package version 1.43.17 (Bartoń, 2020) with the multimodel.inference.RDA file from Harrer and colleagues (Harrer et al., 2019).

2.9.4 Subgroup analysis of treatments with ‘immediate postoperative benefit’

To determine whether pain trajectory during recovery from surgery was a mediator in the transition from acute to chronic pain (Althaus et al., 2014) in our dataset, we
performed a post-hoc subgroup analysis comparing treatments with and without immediate postoperative benefit.

2.9.5 | Confidence ratings for network comparisons

We assessed our confidence in the results of the standard NMA using the Confidence in Network Meta-analysis (CINEMA) approach (Nikolakopoulou et al., 2020) using the software available online (Papakonstantinou et al., 2020). This approach evaluates the precision, heterogeneity and incoherence of treatment effects relative to a predefined ‘clinically important effect size’ (Nikolakopoulou et al., 2020). We could not find any published value for a clinically important reduction in the prevalence of PPP. Among surgeons and chronic pain physicians at our institution the consensus was that any reduction PPP prevalence would be important, so we defined a clinically important effect size to be a RR of 0.9. This is consistent with the 10% reduction in the severity of acute pain which has been considered to be clinically relevant (Busse et al., 2015). We performed a sensitivity analysis to evaluate the effect of a larger ‘clinically important effect size’ of RR = 0.5.

3 | RESULTS

3.1 | Trial selection

We conducted the initial literature search in February 2018, supplemented with an updated search from 1 January 2017 to 12 January 2021. The search strategy returned 107 trials, involving a total of 13,553 randomized participants (Figure 1), for whom 11,862 primary outcomes were reported (88%). Overall, 2628 participants reported persistent postsurgical pain (22%). In the results, $k = \text{number of trials}, n = \text{number of treatments}, c = \text{number of active components}, m = \text{number of pairwise comparisons} \text{ and } d = \text{number of designs (neural block versus placebo and neural block versus gabapentanoids are two different designs).}$

3.2 | Geometry of the network

The network is ‘star-shaped’ with many comparisons to placebo (Figure 2). The distribution of studies among the treatments is uneven, and there appear to be ‘preferred’ (gabapentanoids versus placebo) and ‘avoided’ (neural block versus gabapentanoids) comparisons.
3.3 | Synthesis of the results

There were 107 trials with usable information, 11 with 3 or more arms, which compared 13 treatments involving 10 active components in 23 study designs. We selected ‘placebo’ as the inactive component in the cNMA model.

3.3.1 | Reduction of PPP prevalence

Relative to placebo, three monotherapies reduced the risk of persistent pain: SNRIs, systemic local anesthetics and neural block (Figure 3a). Our ‘clinically important difference’ was defined a priori as a reduction in the risk of persistent pain by at least 10% (upper 95% CI of RR <0.9), so by that definition, only SNRIs and neural block were clinically effective as monotherapies. Combinations of neural block with NMDA receptor blockers or gabapentanoids were also clinically effective. The results were not sufficiently precise to identify specific pain pathways that were more important in PPP prevention.

The standard NMA model (Figure 3b) shows that SNRIs, systemic local anesthetics and neural block, alone or with gabapentanoids, reduced PPP relative to placebo. Due to the wider confidence intervals in the standard NMA model, only SNRIs reduced PPP by at least 10%.

The more parsimonious cNMA model explained the data as well as the standard NMA model –there was minimal additional heterogeneity with the cNMA model ($Q_{\text{cNMA}} - Q_{\text{standard NMA}} = 0.79, \text{df} = 2, p = 0.67$). Statistical heterogeneity ($\tau^2 = 0.09$) was similar to the values reported for pharmacological treatment versus placebo/control in Cochrane reviews (Turner et al., 2015). The detailed results for the cNMA and standard NMA models are presented in the Supplementary Material (Section S4).

3.3.2 | Benefit in the immediate postoperative period

‘Immediate postoperative benefit’ was an important predictor of treatment effect (coefficient $= -0.23$ [−0.49 to 0.03], $p = 0.08$, average importance across all models $= 0.89$) (Table S3.4.2). The influence of ‘immediate postoperative benefit’ across interventions is shown in Figure 4. These results suggest that the post-operative pain trajectory is an intervening factor that may mediate the effect of interventions on the PPP prevalence.

3.3.3 | Confidence in the estimates

Confidence in the results could be assessed for the standard NMA model. For the majority of the estimates, confidence judgements by CINeMA were low or very low (Figure 3b), but were high for SNRIs. The most common causes for downgrading confidence were risk of ‘within-study bias’ due to naive per-protocol analyses in the presence of missing outcomes, and imprecision (Tables S4.3 and S4.4) because confidence intervals overlapped the range of clinically important effects.

3.4 | Trial characteristics

Fifty-seven of 107 trials recruited participants from Europe (44% of participants), 18 from North America...
(26%), 18 from Asia (13%), 9 from Africa (8%), 3 from Australia/New Zealand (7%) and 2 from South America (1%). Few trials (6, 6%) received pharmaceutical company sponsorship. The average number of patients per study arm was 52. The distribution of trials by year and continent of origin are shown in Figure S2.1, and the details of included trials are summarized in Tables S2.1 and S2.2, all in the Supplementary Material. The mean [SD] age of participants was 53 [7] years; the majority were female (8268, 61%). The contributions of participants according to the type of surgery they underwent are shown in Figure 5a. Figure 5b shows the baseline prevalence of PPP according to the type of surgery. In a post-hoc subgroup meta-analysis, IASP categories 1–4 had a higher baseline prevalence of PPP (40%, [33%–47%), k = 53) than categories 5–8 (16%, [13%–20%], k = 48; Q between = 36.85, df = 1, p < 0.001). We used these high- and low-risk designations to explore the influence of baseline prevalence on intervention effect size (baseline prevalence could not be calculated for six studies that did not include placebo as a comparator).

For the majority of trials, the longest follow-up period for the diagnosis of PPP was 3 months after surgery (54%), with 36% reporting after 6 months and 10% after 1 year. Sixty-one trials (57%) reported adverse effects that were associated with interventions during the first postoperative week. Due to limited reporting, we were unable to complete analyses on withdrawals due to adverse effects, adverse events, quality of life, functional assessment, ongoing pharmacological interventions and incidence of mood
disorders. Most articles reported two delayed outcomes: the prevalence of PPP either as the presence of pain or neuropathic pain, and the disposition of patients initially entered into each study; a minority of trials (33/107) reported more than three items from the six core outcome measures for chronic pain clinical trials (Dworkin et al., 2005).

### 3.5 Risk of bias

We rated the within-study risk of bias as low in 58 trials, some concerns in 40 and high in 9. As shown in Figure 6, the most frequent contributor was ‘deviations from intended interventions’ which occurred when naïve per-protocol analyses were performed on datasets with missing outcomes (RoB 2.0, attrition bias, item 2.6 (Sterne et al., 2019)). Across all interventions, the average paired difference in RR estimates between imputed and available case analyses was $-0.005 \ [\text{from } -0.02 \text{ to } 0.015] \ (p = 0.58)$, indicating that the bias introduced by naïve per-protocol analysis was minimal (SI, Figure S3.1). The evidence for ‘small studies effects’, publication bias and selective reporting was weak (SI, Section 3.3). The linear regression test result for overall asymmetry was $t = 0.09$, $df = 132$, $p = 0.93$, and the results with low statistical significance were evenly distributed in the funnel plot (SI, Figure S3.2). The p-curve of trial results with $p < 0.05$ were consistent with evidential value in the findings ($p = 0.011$), with 2/16 studies being of concern for selective reporting (SI, Section S3.2.2).

#### FIGURE 4  Confidence interval plot comparing estimates derived from trials with benefit in the immediate postoperative period (reduced pain scores or analgesic consumption postoperatively, green symbols) with trials that did not (red symbols)

| Treatment                                      | RR     | 95%-CI  |
|-----------------------------------------------|--------|---------|
| acetaminophen                                  | 0.96   | [0.45; 2.03] |
| Postop Benefit                                 |        |         |
| No Postop Benefit                              | 0.33   | [0.14; 0.81] |
| alpha-2 agonist                                | 0.85   | [0.36; 1.99] |
| Postop Benefit                                 |        |         |
| No Postop Benefit                              | 0.57   | [0.07; 4.93] |
| anti-inflammatory                              | 0.30   | [0.12; 0.78] |
| Postop Benefit                                 |        |         |
| No Postop Benefit                              | 1.27   | [0.81; 2.00] |
| gabapentanoid                                  | 0.65   | [0.49; 0.86] |
| Postop Benefit                                 |        |         |
| No Postop Benefit                              | 1.08   | [0.85; 1.37] |
| nefopam                                        | 0.56   | [0.27; 1.14] |
| Postop Benefit                                 |        |         |
| neural block                                   | 0.69   | [0.55; 0.85] |
| Postop Benefit                                 |        |         |
| No Postop Benefit                              | 0.87   | [0.64; 1.19] |
| neural block + gabapentanoid                   | 0.38   | [0.17; 0.85] |
| Postop Benefit                                 |        |         |
| No Postop Benefit                              | 0.79   | [0.39; 1.58] |
| NMDA blocker                                   | 0.73   | [0.52; 1.02] |
| Postop Benefit                                 |        |         |
| No Postop Benefit                              | 0.94   | [0.73; 1.21] |
| SNRI                                           | 0.31   | [0.17; 0.56] |
| Postop Benefit                                 |        |         |
| steroid                                        | 0.90   | [0.43; 1.87] |
| Postop Benefit                                 |        |         |
| No Postop Benefit                              | 1.01   | [0.70; 1.47] |
| systemic local anesthetic                      | 0.63   | [0.42; 0.93] |
| Postop Benefit                                 |        |         |
| No Postop Benefit                              | 0.77   | [0.42; 1.43] |
| neural block + NMDA blocker                    | 0.68   | [0.33; 1.43] |
Transitivity in the network is necessary to enable valid indirect comparisons between interventions; indirect comparisons are not valid when the interventions being compared differ in a characteristic that influences the effect being studied (Salanti, 2012). However, ‘valid indirect comparisons can be obtained even when trials are dissimilar in characteristics which are not effect modifiers’ (Salanti, 2012). The multimodel regression results showed that none of the dissimilar characteristics – timing of the intervention, timing of outcome measurements, prevalence of persistent pain in patients without interventions, or sex were significant or important predictors of treatment effects (Table S3.2). We judged the ‘lumped’ characteristics not to be effect modifiers in this network. The component ‘neural block’ included pain relief achieved by neuraxial, regional and wound application techniques. Compared with placebo, the treatment effects (RR, 95% CI) of neuraxial block \((k = 4)\), regional block \((k = 13)\) and wound infiltration \((k = 14)\) were 0.38 [0.17–0.85], 0.69 [0.53–0.90] and 0.70
[0.54–0.91], respectively. We judged that the transitivity assumption is valid for this network.

3.7 Block failure

As part of our transitivity assessment, we performed a standard NMA to examine whether treatments requiring neural block were more likely to have treatment failure with missing outcomes (‘dropouts’). Overall there were 1420/12,460 (11%) ‘dropouts’ in 70 studies, involving 9 treatments. The relative risk of ‘dropout’ according to treatment can be explained by chance alone ($I^2 = 0\%$, $Q$ between designs $= 7.67$, with 7 degrees of freedom; $p = 0.94$).

4 DISCUSSION AND CONCLUSIONS

In this cNMA of 107 randomized trials of patients at least 3 months after surgery, two monotherapies, serotonin–norepinephrine antagonists and neural block were associated with reduction in the prevalence of persistent postsurgical pain by at least 10%. Complex interventions – neural block + gabapentanoids or NMDA receptor blockers – were also effective. Our results are consistent with the assumption that multimodal interventions can be analysed using the cNMA model without increasing heterogeneity and with improved precision of the estimates compared with the standard NMA model (Figure 3). Our findings support the assumption that treatment effects for prevention of persistent postsurgical pain are multiplicative. For example, the RR values for neural block (0.73 [0.61–0.87], $p < 0.001$) and gabapentanoids (0.84 [0.70–1.00], $p = 0.06$) when combined have a RR of 0.61 [0.48–0.78], $p < 0.001$. These findings suggest that interventions evaluated as ‘ineffective’ as monotherapies, for example gabapentanoids (Verret et al., 2020), may add value when used in multimodal combinations; further adequately powered studies are required to assess these possibilities.

There was little evidence for attrition bias, small studies effects, selective reporting or inconsistency in the networks. Heterogeneity for the models was within the predicted range (Turner et al., 2015).

The outcome of pain management in the immediate postoperative period, categorized broadly as treatments with or without benefit, was an intervening outcome predictor in these analyses. This result is consistent with the previous findings (Althaus et al., 2014; Gilron et al., 2017). Since the acute pain trajectory intervenes between the treatment and the PPP outcome, it may mediate the effect of the intervention (Kraemer, 2016) on the PPP prevalence. A randomized trial comparing a subgroup of patients with a treatment + ‘good’ acute pain control to patients with the treatment + ‘poor’ control would support causality, but requires the analysis of individual patient data (Thompson & Higgins, 2002), and for an intervening predictor, randomization does not guarantee independence (Kraemer, 2016). A further complexity is suggested by the SNRI results – even if SNRI treatment does not result in lower pain scores, it may lower the prevalence of PPP by allowing the patient to better cope with the postoperative experience.

The CINeMA approach to the confidence of the estimates relates precision, heterogeneity and incoherence to the clinically important effect size. With the clinically important effect size set at $RR = 0.90$, relative effect estimates below 0.90 and above 1.11 were considered clinically important. This narrow range meant that it was common for the 95% CI values to extend both into effective and harmful ranges (Figure 3b), resulting in downgrading of confidence by two levels due to ‘major concerns’ for precision. For example, the estimate for anti-inflammatory drugs (0.94 [0.61–1.45]) is doubly imprecise because the confidence intervals overlap both the ‘effective’ and the ‘harmful’ range of effects. If the clinically important effect size is chosen to be 0.5, then relative effect estimates below 0.5 and above 2 are considered clinically important. The estimate for anti-inflammatory drugs is now ‘precise’ because it is unambiguously neither effective nor harmful. Changing the clinically important effect size does not change the estimate or its confidence intervals; it alters the confidence in the precision of the estimate relative to the clinically important effect. The comparison of CINeMA ratings with clinically important effect sizes of $RR = 0.5$ and $RR = 0.9$ is shown in the Supplementary Material (S4, Tables S4.3 and S4.4).

There was an overall attrition rate of 12% in the included trials. Our risk of bias assessment was conservative – we assigned ‘some concerns’ to any trial in which the investigators performed a naïve per-protocol analysis that omitted missing outcomes $>10\%$ of the randomized sample (Section 2.6, RoB 2.0 [Sterne et al., 2019]). Since the sensitivity analysis showed minimal differences between the RR estimates from available and imputed case analyses, these judgments, which are subjective (Babic et al., 2019), may have been too harsh.

The present study combines and extends the results of Chaparro, Carley and colleagues (Carley et al., 2021) and Weinstein and colleagues (Weinstein et al., 2018) with comparisons for pharmacological and neural block treatments. Previous systematic reviews have often analysed the efficacy of monotherapies such as ketamine or gabapentin on the prevalence of PPP; even when
updated over time, the results have been disappointing because few large studies of individual drugs have been reported (Carley et al., 2021). The goal of identifying an ‘intervention of choice’ for prevention of PPP in specific clinical settings has remained elusive because the effect size of single interventions is typically small, in the order of RR = 0.3 or less. The pilot study upon which the ROCKet trial of the efficacy of perioperative ketamine for preventing PPP (Schug & Peyton, 2017) estimated an enrollment target of 4884 participants at a cost of AU$4,823,395.

In the present study, we have taken a ‘broad’ approach (Gotzsche, 2000), assigning studies that likely act by similar biological mechanisms into single categories, combining outcome times and including different types of surgery. We are unaware of any empirical evidence that these categories are effect modifiers for PPP prevention and the exploratory meta-regression does not contradict this view. Our ‘broad’ approach and the use of network meta-analysis increase the amount of evidence that can be usefully applied to mono- and multi-modal interventions.

For three interventions in our study there was enough evidence to make comparisons with previous investigations: gabapentanoids, NMDA receptor antagonists and local anesthetic infusions. In the present study, the network estimate of the efficacy versus placebo of gabapentanoids was RR = 0.84 [0.70–1.00]; the findings of Verret and colleagues were: pregabalin: RR = 0.77 [−0.52 to 1.15], gabapentin RR = 0.94 [0.77–1.14] (Verret et al., 2020). For NMDA receptor blockers, the result of the present study was RR = 0.84 [0.68–1.04]. For ketamine, McNicol and colleagues reported RR = 0.84 [0.70–1.01] (McNicol et al., 2014). Our estimate for the efficacy of systemic local anesthetics, based on 11 trials, was RR = 0.69 [0.50–0.96]. Based on seven trials, Bailey and colleagues reported an odds ratio of 0.29 [0.18–0.48], equivalent to RR = 0.40 [0.27–0.59] (Bailey et al., 2018). The ketamine and gabapentanoid results reported by Carley and colleagues (Carley et al., 2021) were sub-grouped according to type of surgery, making comparison with our findings difficult. Differences between the results of Ning et al. (2018) and the present findings probably relate to different numbers of included studies (24 versus 107) due to the fact that Ning et al. only evaluated first-line pharmacological interventions. To our knowledge, this is the first NMA on PPP that includes combination therapies and explores the impact of potential moderating factors on treatment effects.

The primary outcome, simple presence or absence of pain more than 3 months after surgery, may overestimate the prevalence of PPP (Macrae, 2008). Only 10% of the included studies reported the IMMPACT core outcome measures (Dworkin et al., 2005) and the reporting of pain severity was very inconsistent. The main limitations of the analysis are the small size (low power) of many trials, small numbers of trials contributing to several interventions and the lack of diversity and presence of preferred comparisons in the network.

The results were pooled from studies from many continents including participants with wide genetic and environmental diversity. These factors influence the availability and cost of interventions and the disposition and responses to drugs (Wood, 1998), so results identified as potentially beneficial in the present study need to be confirmed in specific patient populations.

Meta-analysis, by combining the results of many studies, is vulnerable to high false positive results, particularly if the false positive rates in the component studies are enhanced by selective reporting (Vosgerau et al., 2019). The studies in the present review were usually designed to obtain a single, subject-reported outcome at a pre-specified follow-up time. This design limits the ‘investigator-controlled variables’ (stopping data collection when p < 0.05, analysing many outcome measures and analysing subgroups such that p < 0.05). From the design features and the results of the p-curve analysis, we conclude that the risk of bias from selective reporting is low.

While we were able to evaluate some potential modifiers of PPP, we were unable to investigate other important psychological and social factors associated with the development of PPP (prior opioid use, pre-existing chronic pain and pain catastrophizing, for example) which were not generally reported by studies.

The results from this exploratory network meta-analysis suggest that irrespective of the interventions used, outcomes of acute postoperative pain management were a mediator for the transition to persistent pain. For future studies, investigators may consider including individual participant data for immediate postoperative pain outcomes to evaluate associations with PPP, because aggregate data are of limited usefulness for subgroup analysis involving patient responses (Thompson & Higgins, 2002). The preventive effects of interventions were multiplicative, and no intervention was identified as being both required and sufficient for prevention of PPP. Component NMA methods were effective for exploring multimodal interventions. It appears to us premature to abandon interventions for prevention of persistent postoperative pain unless a lack of efficacy has been demonstrated in clinically appropriate multimodal combinations.

CONFLICTS OF INTEREST

None declared.
AUTHOR CONTRIBUTIONS
All authors contributed substantially to the project, discussed the results, and approved the final version of the manuscript. Claire Allen, Andrew Walker, David Archer: conception, design, data acquisition, analysis of data, drafting, revision and final approval of the article. Zahra Premji: design of search strategies, acquisition of studies, update of searches, drafting and final approval of the article. Jenny Wong: acquisition of data, revision and final approval of the article. Sonya Soh: analysis of data, drafting and final approval of the article. Marie-Eve Beauchemin-Turcotte, Geoffrey Hawbولد, Kelly Shinkaruk: conception and design of the study, revision for critical intellectual content and final approval of the article.

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**How to cite this article:** Allen, C., Walker, A. M., Premji, Z. A., Beauchemin-Turcotte, M.-E., Wong, J., Soh, S., Hawboldt, G. S., Shinkaruk, K. S., & Archer, D. P. (2022). Preventing persistent postsurgical pain: A systematic review and component network meta-analysis. *European Journal of Pain, 26*, 771–785. https://doi.org/10.1002/ejp.1915