Cochrane Library

Cochrane Database of Systematic Reviews

Preventive opioids for postoperative pain (Protocol)

Doleman B, Leonardi-Bee J, Heinink TP, Lund J, Williams JP

Doleman B, Leonardi-Bee J, Heinink TP, Lund J, Williams JP.
Preventive opioids for postoperative pain.
Cochrane Database of Systematic Reviews 2017, Issue 4. Art. No.: CD012624.
DOI: 10.1002/14651858.CD012624.

www.cochranelibrary.com

WILEY

TABLE OF CONTENTS

[Intervention Protocol]

Preventive opioids for postoperative pain

Brett Doleman[1], Jo Leonardi-Bee[2], Thomas P Heinink[3], Jon Lund[4], John P Williams[1]

[1]Department of Surgery and Anaesthesia, Division of Medical Sciences and Graduate Entry Medicine, School of Medicine, University of Nottingham, Derby, UK. [2]Division of Epidemiology and Public Health, The University of Nottingham, Nottingham, UK. [3]Department of Anaesthesia, Frimley Health NHS Foundation Trust, Frimley Park Hospital, Frimley, UK. [4]Division of Health Sciences, School of Medicine, University of Nottingham, Derby, UK

Contact address: Brett Doleman, Department of Surgery and Anaesthesia, Division of Medical Sciences and Graduate Entry Medicine, School of Medicine, University of Nottingham, Uttoxeter New Road, Derby, DE22 3DT, UK. dr.doleman@gmail.com.

Editorial group: Cochrane Anaesthesia, Critical and Emergency Care Group.
Publication status and date: New, published in Issue 4, 2017.

Citation: Doleman B, Leonardi-Bee J, Heinink TP, Lund J, Williams JP. Preventive opioids for postoperative pain. *Cochrane Database of Systematic Reviews* 2017, Issue 4. Art. No.: CD012624. DOI: 10.1002/14651858.CD012624.

ABSTRACT

This is a protocol for a Cochrane Review (Intervention). The objectives are as follows:

To assess the effects of preventive and pre-emptive opioids for reducing postoperative pain in patients undergoing surgery.

BACKGROUND

Description of the condition

Postoperative pain is a common consequence of surgery that affects around 80% of patients. The severity of postoperative pain is variable, with 18% of patients suffering extreme pain (Apfelbaum 2003). Pain can have deleterious effects during the postoperative period, including patient dissatisfaction (Myles 2000), interference with daily activities (Strassels 2002), pulmonary complications (Desai 1999), increases in the stress response to surgery (Desborough 2000), and an increased risk of chronic post-surgical pain (Kehlet 2006). Risk factors for severe postoperative pain include the presence of pre-operative pain, pre-operative anxiety and the type of surgery (Ip 2009). Intravenous opioids are commonly used to treat pain in the postoperative period (Benhamou 2008), however their use is associated with many side effects such as vomiting, pruritus (itching), sedation (drowsiness) and patient concerns over addiction (Apfelbaum 2003). Therefore, alternative strategies to manage both postoperative pain and reduce postoperative opioid consumption may have important benefits for patients undergoing surgery.

Description of the intervention

Multimodal or balanced analgesia is the gold standard for perioperative pain. However, opioids are still used in the majority of patients undergoing surgery (Benhamou 2008), despite an association between higher opioid use and lower patient satisfaction (Mhuircheartaigh 2009). The mechanism of action of opioids involves binding to mu opioid receptors within the central nervous system, which produces analgesia (Pathan 2012). Although the efficacy of opioids is well established, recent studies have highlighted concerns over the administration of opioids around the peri-operative period (Fletcher 2014). Opioid use is associated with a range of adverse effects such as hypotension, bradycardia, vomiting, constipation, respiratory depression and suppression of immune function (Wheeler 2002; Williams 2007). Furthermore,

opioid use may be associated with a paradoxical increase in postoperative pain, a phenomenon termed opioid-induced hyperalgesia. One meta-analysis found that higher intra-operative doses of opioids resulted in both higher postoperative pain scores and opioid consumption (Fletcher 2014).

Pre-emptive analgesia involves the initiation of an analgesic agent (painkiller) prior to surgical incision (before the surgeon cuts the skin). It is thought that by initiating analgesic interventions before surgical injury, the analgesic can provide reductions in intra-operative nociception to the central nervous system and therefore provide superior pain relief compared with the same analgesic given post-incision (after the surgeon has cut the skin) (Kissin 2000). Preventive analgesia extends this definition to include increasing the intensity and duration of pre-emptive analgesic interventions until final wound healing (Dahl 2011). The first review to examine the clinical effects of pre-emptive analgesia showed that pre-emptive opioids increased postoperative pain scores when compared to post-incision opioids (Møiniche 2002). A second review published a few years later also showed a possible increase in postoperative pain with pre-emptive opioids when compared to post-incision opioids (Ong 2005). However, as these reviews were performed over a decade ago, new evidence published since then may have changed these conclusions. Furthermore, these reviews did not evaluate reductions in postoperative opioid side effects and potential adverse events.

How the intervention might work

Surgical incision promotes changes in both the central and peripheral nervous system called sensitization. Such sensitization can cause biochemical changes that manifest as hyperalgesia (the same pain stimulus causing increased pain) and allodynia (normal sensations causing pain). It is thought that by initiating analgesia before surgical incision, both peripheral and central sensitization can be reduced, resulting in reductions in intra-operative nociception and later both acute and chronic postoperative pain. Preventive analgesia extends this reduction in sensitization to include the postoperative period. This enhanced definition came from an increased understanding of the development of persistent post-surgical pain, which is associated with postoperative sensitization and may only be reduced by continuing analgesia longer into the postoperative period (Dahl 2011). As opioids are commonly used to treat pain postoperatively (Benhamou 2008), any reductions in opioid use may also result in a reduction in opioid adverse events and improve the patient experience. Opioids are known to induce analgesia by binding to mu opioid receptors within the central nervous system, therefore if these are initiated before surgical incision, this may reduce sensitization and thus lead to lower postoperative pain when compared to post-incision administration. Conversely, the use of intra-operative opioids has been associated with the phenomenon of opioid-induced hyperalgesia, which may paradoxically increase postoperative pain (Fletcher 2014; Ong 2005). Exposure to opioids is thought to increase sensitivity to pain via the glutaminergic system, which may manifest as increased pain scores following surgery (Lee 2011).

Why it is important to do this review

Due to both its common occurrence (Apfelbaum 2003), and potential deleterious effects during the postoperative period, reducing postoperative pain is an important clinical issue. A simple change in clinical practice, such as changing the timing of administration of analgesics, could have important implications for postoperative pain management. Moreover, such a change is cost-neutral and therefore may benefit both anaesthetists in low-income countries and those working within healthcare systems with finite resources (such as the National Health Service (NHS) in the UK). A previous review has highlighted an increase in postoperative pain with pre-emptive opioids (Ong 2005), although most of the data were published over a decade ago, which mandates an updated review of the evidence.

OBJECTIVES

To assess the effects of preventive and pre-emptive opioids for reducing postoperative pain in patients undergoing surgery.

METHODS

Criteria for considering studies for this review

Types of studies

We will include parallel-group randomized controlled trials only. We will consider studies that did not use a double dummy placebo (for example, intervention group receives active drug before incision and placebo after incision; control group receives placebo before incision and active drug after incision). We will exclude studies that include paediatric participants and pharmacokinetic studies not reporting any clinical outcomes.

Types of participants

We will include adults (aged 15 years and older) undergoing any type of surgery.

We will not include studies that include both participants aged over 15 years and paediatric participants.

Types of interventions

We will compare both preventive opioids and pre-emptive opioids (intervention groups) with post-incision opioids (control group). We define:

1. preventive opioids as opioids initiated before surgical incision and continued postoperatively;
2. pre-emptive opioids as opioids initiated before incision but not continued postoperatively; and
3. post-incision opioids as the same analgesic intervention initiated after surgical incision, whether single dose (as comparator with pre-emptive analgesia) or continued postoperatively (as comparator with preventive analgesia) (control group). However, we acknowledge that most studies including opioids will be preventive by definition (with opioids continued postoperatively).

We will only compare interventions if identical analgesics with identical dosages are used. In addition, we will only include studies if concurrent use of other multimodal analgesic agents during the peri-operative period is identical to avoid confounding. If the studies report multiple intervention subgroups that have comparable control groups (identical interventions), we will combine these into one group using recommended methods (Higgins 2011a). We will include all types of opioid, at any dose, via any route of administration (oral and parenteral) and all types of regimen (pre-emptive or preventive) in the analysis.

Types of outcome measures

Primary outcomes

1. Early acute postoperative pain (measured within six hours postoperatively using a validated pain scale, converted to a 0 to 10 scale where a 0 to 100 scale is used, and where multiple time points are reported we will include the earliest time point reported).
2. Adverse events (respiratory depression (defined as SaO_2 < 92%; yes/no), intra-operative bradycardia (yes/no and mean dose of chronotrope in mg to assess severity) and intra-operative hypotension (yes/no and mean dose of inotrope/vasopressor in mg to assess severity).

Secondary outcomes

1. Nausea and vomiting (yes/no).
2. Late acute postoperative pain (measured at 24 to 48 hours postoperatively using a validated pain scale, converted to a 0 to 10 scale where a 0 to 100 scale is used, and where multiple time points are reported we will include the earliest time point reported).
3. 24-hour morphine consumption (mg) (if alternative opioids are used, we will convert these to morphine-equivalents using standard conversion factors).
4. Time to first analgesic request (minutes).
5. Pruritus (yes/no).
6. Sedation (measured on a continuous scale such as the Ramsay Sedation Scale).
7. Patient satisfaction (converted to a 0 to 10 scale where a 0 to 100 scale is used).
8. Chronic pain (yes/no, measured three to six months postoperatively, and we will include the earliest time point closest to three months).
9. Time to first bowel movement (hours).

For the secondary outcomes where time points are not specified, we will use the end point closest to two hours (one to six hours) to assess immediate short-term effects, and the end point closest to 24 hours (six to 48 hours) to assess longer-term effects. We will consider a reduction in pain score of 1.5 (on a 0 to 10 scale) (Gallagher 2001), a reduction in the time to first analgesic request of one hour, a time to first bowel movement of 12 hours, a 10 mg reduction in morphine consumption and a number needed to treat for an additional beneficial/harmful outcome (NNTB/NNTH) of 10 as clinically significant (Doleman 2015a).

Outcomes will not form part of the study eligibility assessment so studies that meet the participant, intervention and comparison criteria will be included in the review even if they report no relevant outcomes.

Search methods for identification of studies

Electronic searches

We will not apply any restrictions on the basis of language or publication status of the studies. If necessary, we will translate non-English language studies. We will search the following electronic databases: the Cochrane Central Register of Controlled Trials (CENTRAL) (the *Cochrane Library*, latest issue); Ovid MEDLINE (1946 to date) (Appendix 1); Ovid MEDLINE (In-Process & Other Non-Indexed Citations); Ovid EMBASE (1974 to date); EBSCO Cumulative Index to Nursing and Allied Health Literature (CINAHL) (1982 to date).

We will use the Cochrane Highly Sensitive Search Strategy (sensitivity maximizing version) for identifying randomized controlled trials in MEDLINE (Lefebvre 2011). For the EMBASE search, we will utilize the EMBASE filter developed by Cochrane (Lefebvre 2011). We will search the following databases for unpublished clinical trials:

1. ClinicalTrials.gov (https://www.clinicaltrials.gov);
2. World Health Organization International Clinical Trials Registry Platform (http://apps.who.int/trialsearch/Default.aspx);
3. European Union Clinical Trials Registry (https://www.clinicaltrialsregister.eu/).

Searching other resources

We will conduct a search of the OpenSIGLE database to identify grey literature sources. We will search reference lists of identified studies and reviews for further studies. We will utilize Google Scholar to identify studies that have cited those included. In addition, we will search the following conference proceedings to identify further unpublished studies (all years considered):

1. World Congress on Pain (International Association for the Study of Pain);
2. Anaesthetic Research Society Meetings;
3. Association of Anaesthetists of Great Britain and Ireland Winter Symposium and Annual Congress;
4. American Society of Anesthesiologists Annual Meeting;
5. European Society of Anaesthesiologists Euroanaesthesia Conference.

Data collection and analysis

Selection of studies

We will use two review authors (BD and JPW) to independently screen the identified studies using the inclusion criteria to assess eligibility. BD and JPW will resolve any disagreements by consensus. If disagreement still exists following discussion, we will consult a third author (JLB). BD and JPW will use the information from the retrieved reports to help identify any duplicate publications, such as author name, study centre, type and dose of interventions used and study dates. We will link any duplicate publications.

Data extraction and management

We will extract data into an electronic database using standardized data extraction forms (Appendix 2; Appendix 3). We will perform this independently using two study authors (BD and TH) and any disagreements will be resolved by consensus. If disagreement still exists, we will consult a third author (JPW). We will perform the analysis using one author (BD). We will translate non-English language studies and extract data following translation. If data are not contained within the original research report, we will contact the corresponding author irrespective of the age of publication. We will extract the following information:

1. bibliographic data including date of completion/ publication;
2. country;
3. publication status;
4. source of funding;
5. trial design, e.g. parallel;
6. study setting;
7. number of participants randomized to each trial arm and number included in final analysis;
8. eligibility criteria and key baseline participant data including sex and age;
9. details of treatment regimen received by each group;
10. details of any co-interventions;
11. primary and secondary outcome(s) (with definitions and, where applicable, time points);
12. outcome data for primary and secondary outcomes (by group);
13. duration of follow-up;
14. number of withdrawals (by group) and number of withdrawals (by group) due to adverse events;
15. adverse events.

Assessment of risk of bias in included studies

We will assess risk of bias in the included studies using the Cochrane tool for assessing risk of bias (Higgins 2011b). Two study authors (BD and JPW) will independently undertake assessment of risk of bias and reach agreement by consensus. We will assess risk of bias in the domains of sequence generation, allocation concealment, blinding of participants, study personnel and outcome assessors, incomplete outcome data, selective outcome reporting and other sources of bias (Appendix 2). We will assess each domain as low, unclear or high risk of bias (Higgins 2011b). We will present the results in both a 'Risk of bias' summary and a 'Risk of bias' graph. We will interpret risk of bias across studies by reducing the quality of evidence if there is potential risk of bias in the studies included in each analysis.

Measures of treatment effect

We will present dichotomous outcomes as risk ratios (RR) and NNTB/NNTH. We will calculate NNTB/NNTH from the reciprocal of the risk difference. For continuous outcomes, we will present these as mean differences (MD), or if non-comparable scales are used across studies but still presented as continuous data, we will present these as standardized mean differences (SMD). We will present the outcomes of time to first analgesic and time to first bowel movement as hazard ratios (HR) where reported. We will aggregate reported log hazard ratios and their associated standard errors using the generic inverse variance method. We will present the precision of effect estimates using 95% confidence intervals (CI).

Unit of analysis issues

As we will include parallel-group randomized controlled trials only, unit of analysis issues are not expected (Higgins 2011c). For the main results, we will combine different dose subgroups into one treatment group as suggested in the *Cochrane Handbook for Systematic Reviews of Interventions* (Higgins 2011a). When conducting meta-regression, if a study reports multiple treatment groups for each covariate, we will treat these as separate studies and distribute

the control group participants between these treatment groups to avoid analysing them twice (Higgins 2011c).

Dealing with missing data

We will contact corresponding authors for any data missing from the original publication irrespective of publication date. If no response is received, we will extract data from published graphs. If standard deviations are not reported, we will attempt to calculate these from other reported statistics. If this is not possible, we will estimate standard deviations from other studies within the meta-analysis (Higgins 2011c). We will not attempt to calculate standard deviations from other measures of dispersion such as the interquartile range.

Assessment of heterogeneity

We will assess clinical heterogeneity by examining study characteristics such as the type of population, type of surgery and intervention used and consider when pooling of results is clinically appropriate. We will assess statistical heterogeneity using the I^2 statistic. We will use the following recommended cut-off values in the interpretation of the I^2 statistic (Deeks 2011):

1. 0% to 40% might not be important;
2. 30% to 60% may represent moderate heterogeneity;
3. 50% to 90% may represent substantial heterogeneity;
4. 75% to 100% considerable heterogeneity.

For analyses with substantial or considerable statistical heterogeneity, we will consider investigating that heterogeneity by using meta-regression.

Assessment of reporting biases

We will assess selective outcome reporting by examining the original study protocol or methods section and comparing these with the reported results. We will report this as part of the Cochrane tool for assessing risk of bias (Higgins 2011b). If 10 or more studies are included in the meta-analysis, we will assess publication bias graphically using funnel plots and quantitatively using Egger's linear regression test (Egger 1997). Due to the low power of this test, we will regard $P < 0.1$ as evidence of imprecise study effects and possible publication bias.

Data synthesis

We will use Review Manager 5.3 to aggregate study data (RevMan 5). We will conduct separate analyses for pre-emptive and preventive interventions. We will aggregate data using a DerSimonian and Laird random-effects model. This is because we expect the treatment effect to vary with respect to the different populations within each study and therefore there is no single underlying effect to estimate, making the random-effects model more appropriate. We will input mean, standard deviation and sample size data from the individual studies and combine these using the generic inverse variance method. Where raw data cannot be extracted from the studies (and authors do not reply to requests for data), but mean differences are reported, we will use the generic inverse variance method to combine effect measures from studies. We will combine dichotomous outcomes using the Mantel-Haenszel method.

Subgroup analysis and investigation of heterogeneity

We will consider conducting subgroup analysis for the type of opioid (remifentanil, rapidly short-acting, short-acting, intermediate-acting and long-acting). If 10 studies or more are included in a meta-analysis, we will explore reasons for heterogeneity by performing a restricted maximum likelihood, random-effects meta-regression using the covariates type of opioid, dose of opioid (different opioids will be converted to morphine equivalents), type of anaesthesia and type of surgery (Thompson 2002). For dummy variables, we will use the least effective subgroup as the reference category. We will present the R^2 analogue with a corresponding P value for each covariate. Due to the expected low number of studies, we will only perform univariate analysis for each covariate. We will use the Knapp-Hartung method to calculate P values (as this method more appropriately uses the t distribution for the between-study variance). We will perform this analysis using the software STATA Version 14.

Sensitivity analysis

We will perform sensitivity analysis by including studies at low risk of bias (defined as low risk for randomization, allocation concealment, blinding and incomplete outcome data and not judged high risk for any other domain). As studies that did not use a double dummy design will be judged high risk of bias for blinding, we will assess the impact of excluding these from the analysis. We will also perform further sensitivity analysis by excluding studies where standard deviations were estimated. Furthermore, for dichotomous outcomes, if it is unclear if all randomized participants were analysed using intention-to-treat, we will assume that any missing participants did not suffer an event in the main analysis (best case scenario). During sensitivity analysis, we will also assume missing participants did suffer an event (worst case scenario). We will not use any other forms of imputation for missing values. For continuous outcomes, we will analyse only the participants whose outcomes were measured (available case analysis).

'Summary of findings' table and GRADE

We will present outcomes in a 'Summary of findings' table. We will produce two 'Summary of findings' tables, one for each comparison:

1. Pre-emptive opioids versus post-incision opioids
2. Preventive opioids versus post-incision opioids

The outcomes for each comparison will include early and late acute postoperative pain, nausea and vomiting, 24-hour morphine consumption, time to first analgesic request, chronic pain and adverse events. We will present these using the GRADE approach (Schünemann 2011). We will downgrade the quality of evidence from high quality to moderate, low or very low quality. Downgrading will be undertaken independently by two study authors (BD and JPW) and agreement reached by consensus. Characteristics of the evidence that will cause downgrading include:

1. limitations in the design and implementation of available studies suggesting a high likelihood of bias (for example, studies not using a double dummy placebo design);
2. indirectness of evidence (indirect population, intervention, control or outcomes);
3. unexplained heterogeneity (I^2 > 50%) or inconsistency of results not explained through meta-regression or sensitivity analyses;
4. imprecision of results (wide confidence intervals);
5. evidence of publication bias (P < 0.1 on Egger's linear regression test).

ACKNOWLEDGEMENTS

We would like to acknowledge the editorial comments of Marialena Trivella, Anna Lee, Arash Afshari, Bronagh Blackwood, Asieh Golozar, Nathan Pace, Jane Cracknell and Nuala Livingstone (Editorial Screening). We would also like to thank Mike Bennett (content editor), Asieh Golozar (statistical editor) and Liz Bickerdike (Cochrane Editorial Unit), and David Dickerson and R Andrew Moore (peer referees) for their help and editorial advice during the preparation of this protocol for the systematic review.

REFERENCES

Additional references

Apfelbaum 2003
Apfelbaum JL, Chen C, Mehta SS, Gan TJ. Postoperative pain experience: results from a national survey suggest postoperative pain continues to be undermanaged. *Anesthesia and Analgesia* 2003;**97**:534–40. [PUBMED: 12873949]

Benhamou 2008
Benhamou D, Berti M, Brodner G, Andres JD, Draisci G, Moreno-Azcoita M. Postoperative Analgesic THerapy Observational Survey (PATHOS): a practice pattern study in 7 central/southern European countries. *Pain* 2008;**136**:134–41. [PUBMED: 17703887]

Dahl 2011
Dahl JB, Kehlet H. Preventive analgesia. *Current Opinion in Anesthesiology* 2011;**24**:331–8. [PUBMED: 21478742]

Deeks 2011
Deeks JJ, Higgins JPT, Altman DG (editors). Chapter 9: Analysing data and undertaking meta-analyses. In: Higgins JPT,Green S (editors). Cochrane Handbook for Systematic Reviews of Interventions Version 5.1.0 [updated March 2011]. The Cochrane Collaboration, 2011. Available from www.cochrane-handbook.org.

Desai 1999
Desai PM. Pain management and pulmonary dysfunction. *Critical Care Clinics* 1999;**15**:151–66. [PUBMED: 9929792]

Desborough 2000
Desborough JP. The stress response to trauma and surgery. *British Journal of Anaesthesia* 2000;**85**:109–17. [PUBMED: 10927999]

Doleman 2015a
Doleman B, Heinink TP, Read DJ, Faleiro RJ, Lund JN, Williams JP. A systematic review and meta-regression analysis of prophylactic gabapentin for postoperative pain. *Anaesthesia* 2015;**70**:1186–204. [PUBMED: 26300519]

Doleman 2015b
Doleman B, Read D, Lund JN, Williams JP. Preventive acetaminophen reduces postoperative opioid consumption, vomiting, and pain scores after surgery: systematic review and meta-analysis. *Regional Anesthesia and Pain Medicine* 2015;**40**:706–12. [PUBMED: 26469366]

Egger 1997
Egger M, Smith GD, Schneider M, Minder C. Bias in meta-analysis detected by a simple, graphical test. *BMJ* 1997;**315**:629–34. [PUBMED: 9310563]

Fletcher 2014
Fletcher D, Martinez V. Opioid-induced hyperalgesia in patients after surgery: a systematic review and a meta-analysis. *British Journal of Anaesthesia* 2014;**112**:991–1004. [PUBMED: 24829420]

Gallagher 2001
Gallagher EJ, Liebman M, Bijur PE. Prospective validation of clinically important changes in pain severity measured on a visual analog scale. *Annals of Emergency Medicine* 2001;**38**:633–8. [PUBMED: 11719741]

Higgins 2011a
Higgins JPT, Deeks JJ (editors). Chapter 7: Selecting studies and collecting data. In: Higgins JPT, Green S (editors). Cochrane Handbook for Systematic Reviews of Interventions Version 5.1.0 [updated March 2011]. The Cochrane Collaboration, 2011. Available from www.cochrane-handbook.org.

Higgins 2011b
Higgins JPT, Altman DG, Sterne JAC (editors). Chapter 8: Assessing risk of bias in included studies. In: Higgins JPT, Green S (editors). Cochrane Handbook for Systematic Reviews of Interventions Version 5.1.0 [updated March 2011]. The Cochrane Collaboration, 2011. Available from www.cochrane-handbook.org.

Higgins 2011c
Higgins JPT, Deeks JJ, Altman DG (editors). Chapter 16: Special topics in statistics. In: Higgins JPT, Green S (editors). Cochrane Handbook for Systematic Reviews of Interventions Version 5.1.0 [updated March 2011]. The Cochrane Collaboration, 2011. Available from www.cochrane-handbook.org.

Ip 2009
Ip HYV, Abrishami A, Peng PW, Wong J, Chung F. Predictors of postoperative pain and analgesic consumption: a qualitative systematic review. *Anesthesiology* 2009;**111**: 657–77. [PUBMED: 19672167]

Kehlet 2006
Kehlet H, Jensen TS, Woolf CJ. Persistent postsurgical pain: risk factors and prevention. *Lancet* 2006;**367**:1618–25. [PUBMED: 16698416]

Kissin 2000
Kissin I. Preemptive analgesia. *Anesthesiology* 2000;**93**: 1138–43. [PUBMED: 20336442]

Lee 2011
Lee M, Silverman S, Hansen H, Patel V. A comprehensive review of opioid-induced hyperalgesia. *Pain Physician* 2011; **14**:145–61. [PUBMED: 21412369]

Lefebvre 2011
Lefebvre C, Manheimer E, Glanville J. Chapter 6: Searching for studies. In: Higgins JPT, Green S (editors). Cochrane Handbook for Systematic Reviews of Interventions Version 5.1.0 [updated March 2011]. The Cochrane Collaboration, 2011. Available from www.cochrane-handbook.org.

Mhuircheartaigh 2009
Mhuircheartaigh RN, Moore RA, McQuay HJ. Analysis of individual patient data from clinical trials: epidural morphine for postoperative pain. *British Journal of Anaesthesia* 2009;**103**:874–81. [PUBMED: 19889750]

Myles 2000
Myles PS, Williams DL, Hendrata M, Anderson H, Weeks AM. Patient satisfaction after anaesthesia and surgery: results of a prospective survey of 10,811 patients. *British Journal of Anaesthesia* 2000;**84**:6–10. [PUBMED: 10740539]

Møiniche 2002
Møiniche S, Kehlet H, Dahl JB. A qualitative and quantitative systematic review of preemptive analgesia for postoperative pain relief: the role of timing of analgesia. *Anesthesiology* 2002;**96**:725–41. [PUBMED: 11873051]

Ong 2005
Ong CKS, Lirk P, Seymour RA, Jenkins BJ. The efficacy of preemptive analgesia for acute postoperative pain management: a meta-analysis. *Anesthesia and Analgesia* 2005;**100**:757–73. [PUBMED: 15728066]

Pathan 2012
Pathan H, Williams J. Basic opioid pharmacology: an update. *British Journal of Pain* 2012;**6**:11–6. [PUBMED: 26516461]

RevMan 5 [Computer program]
The Nordic Cochrane Centre, The Cochrane Collaboration. Review Manager (RevMan). Version 5.3. Copenhagen: The Nordic Cochrane Centre, The Cochrane Collaboration, 2014.

Schünemann 2011
Schünemann HJ, Oxman AD, Vist GE, Higgins JPT, Deeks JJ, Glasziou P, Guyatt GH. Chapter 12: Interpreting results and drawing conclusions. In: Higgins JPT, Green S (editors). Cochrane Handbook for Systematic Reviews of Interventions Version 5.1.0 [updated March 2011]. The Cochrane Collaboration, 2011. Available from www.cochrane-handbook.org.

Strassels 2002
Strassels SA, Chen C, Carr DB. Postoperative analgesia: economics, resource use, and patient satisfaction in an urban teaching hospital. *Anesthesia and Analgesia* 2002;**94**: 130–7. [PUBMED: 11772815]

Thompson 2002
Thompson SG, Higgins JP. How should meta-regression analyses be undertaken and interpreted?. *Statistics in Medicine* 2002;**21**:1559–73. [PUBMED: 12111920]

Wheeler 2002
Wheeler M, Oderda GM, Ashburn MA, Lipman AG. Adverse events associated with postoperative opioid analgesia: a systematic review. *Journal of Pain* 2002;**3**: 159–80. [PUBMED: 14622770]

Williams 2007
Williams JP, Thompson JP, McDonald J, Barnes TA, Cote T, Rowbotham DJ, et al. Human peripheral blood mononuclear cells express nociceptin/orphanin FQ, but not μ, δ, or κ opioid receptors. *Anesthesia and Analgesia* 2007; **105**:998–1005. [PUBMED: 17898379]

* *Indicates the major publication for the study*

APPENDICES

Appendix 1. MEDLINE search strategy

1. preemptive analgesia [ti.ab]

2. postoperative pain [ti.ab]

3. preventive analgesia [ti.ab]

4. preincision* [ti.ab]
5. exp PAIN, POSTOPERATIVE/

6. 1 OR 2 OR 3 OR 4 OR 5

7. opioid* or opiate* [ti.ab]

8. morphine OR diamorphine OR fentanyl OR remifentanil OR alfentanil OR meperidine OR pethidine OR tramadol OR ketobemidone [ti.ab]

9. 7 OR 8

10. 6 AND 9

11. randomi?ed controlled trial [pt]

12. controlled clinical trial [pt]

13. randomi?ed [ti.ab]

14. placebo [ti.ab]

15. drug therapy [sh]

17. randomly [ti.ab]

18. trial [ti.ab]

19. groups [ti.ab]

20. 11 OR 12 OR 13 OR 14 OR 15 OR 16 OR 17 OR 18

21. 10 AND 20

22. 21 [Limit to: (Age group Young Adult or Adult or Middle aged or Aged or Aged, 80 and over) and Humans]

Appendix 2. 'Risk of bias' tool

Random sequence generation

Selection bias (biased allocation to interventions) due to inadequate generation of a randomized sequence.
Criteria for a judgement of 'low risk' of bias.
The investigators describe a random component in the sequence generation process such as:

- referring to a random number table;
- using a computer random number generator;
- coin tossing;
- shuffling cards or envelopes;
- throwing dice;
- drawing of lots;
- minimization*.

*Minimization may be implemented without a random element and this is considered to be equivalent to being random.
Criteria for the judgement of 'high risk' of bias.
The investigators describe a non-random component in the sequence generation process. Usually, the description would involve some systematic, non-random approach, for example:

- sequence generated by odd or even date of birth;
- sequence generated by some rule based on date (or day) of admission;
- sequence generated by some rule based on hospital or clinic record number.

Other non-random approaches happen much less frequently than the systematic approaches mentioned above and tend to be obvious. They usually involve judgement or some method of non-random categorization of participants, for example:

- allocation by judgement of the clinician;
- allocation by preference of the participant;
- allocation based on the results of a laboratory test or a series of tests;
- allocation by availability of the intervention.

Criteria for the judgement of 'unclear risk' of bias.

- Insufficient information about the sequence generation process to permit judgement of 'low risk' or 'high risk'.

Allocation concealment

Selection bias (biased allocation to interventions) due to inadequate concealment of allocations prior to assignment.
Criteria for a judgement of 'low risk' of bias. Participants and investigators enrolling participants could not foresee assignment because one of the following, or an equivalent method, was used to conceal allocation:

- central allocation (including telephone, web-based and pharmacy-controlled randomization);
- sequentially numbered drug containers of identical appearance;
- sequentially numbered, opaque, sealed envelopes.

Criteria for the judgement of 'high risk' of bias. Participants or investigators enrolling participants could possibly foresee assignments and thus introduce selection bias, such as allocation based on:

- using an open random allocation schedule (e.g. a list of random numbers);
- assignment envelopes used without appropriate safeguards (e.g. if envelopes were unsealed or nonopaque or not sequentially numbered);
- alternation or rotation;
- date of birth;
- case record number;
- any other explicitly unconcealed procedure.

Criteria for the judgement of 'unclear risk' of bias. Insufficient information to permit judgement of 'low risk' or 'high risk'. This is usually the case if the method of concealment is not described or not described in sufficient detail to allow a definite judgement - for

example if the use of assignment envelopes is described, but it remains unclear whether envelopes were sequentially numbered, opaque and sealed.

Blinding of participants and personnel

Performance bias due to knowledge of the allocated interventions by participants and personnel during the study.
Criteria for a judgement of 'low risk' of bias. Any one of the following:

- no blinding or incomplete blinding, but the review authors judge that the outcome is not likely to be influenced by lack of blinding;
- blinding of participants and key study personnel ensured, and unlikely that the blinding could have been broken.

Criteria for the judgement of 'high risk' of bias. Any one of the following:

- no blinding or incomplete blinding, and the outcome is likely to be influenced by lack of blinding;
- blinding of key study participants and personnel attempted, but likely that the blinding could have been broken, and the outcome is likely to be influenced by lack of blinding.

Criteria for the judgement of 'unclear risk' of bias. Any one of the following:

- insufficient information to permit judgement of 'low risk' or 'high risk';
- the study did not address this outcome.

Blinding of outcome assessment

Detection bias due to knowledge of the allocated interventions by outcome assessors.
Criteria for a judgement of 'low risk' of bias. Any one of the following:

- no blinding of outcome assessment, but the review authors judge that the outcome measurement is not likely to be influenced by lack of blinding;
- blinding of outcome assessment ensured, and unlikely that the blinding could have been broken.

Criteria for the judgement of 'high risk' of bias. Any one of the following:

- no blinding of outcome assessment, and the outcome measurement is likely to be influenced by lack of blinding;
- blinding of outcome assessment, but likely that the blinding could have been broken, and the outcome measurement is likely to be influenced by lack of blinding.

Criteria for the judgement of 'unclear risk' of bias. Any one of the following:

- insufficient information to permit judgement of 'low risk' or 'high risk';
- the study did not address this outcome.

Incomplete outcome data

Attrition bias due to the amount, nature or handling of incomplete outcome data.
Criteria for a judgement of 'low risk' of bias. Any one of the following:

- no missing outcome data;
- reasons for missing outcome data unlikely to be related to true outcome (for survival data, censoring unlikely to be introducing bias);
- missing outcome data balanced in numbers across intervention groups, with similar reasons for missing data across groups;
- for dichotomous outcome data, the proportion of missing outcomes compared with observed event risk not enough to have a clinically relevant impact on the intervention effect estimate;
- for continuous outcome data, plausible effect size (difference in means or standardized difference in means) among missing outcomes not enough to have a clinically relevant impact on observed effect size;
- missing data have been imputed using appropriate methods.

Criteria for the judgement of 'high risk' of bias. Any one of the following:

- reason for missing outcome data likely to be related to true outcome, with either imbalance in numbers or reasons for missing data across intervention groups;
- for dichotomous outcome data, the proportion of missing outcomes compared with observed event risk enough to induce clinically relevant bias in intervention effect estimate;

- for continuous outcome data, plausible effect size (difference in means or standardized difference in means) among missing outcomes enough to induce clinically relevant bias in observed effect size;
- 'as-treated' analysis done with substantial departure of the intervention received from that assigned at randomization;
- potentially inappropriate application of simple imputation.

Criteria for the judgement of 'unclear risk' of bias. Any one of the following:
- insufficient reporting of attrition/exclusions to permit judgement of 'low risk' or 'high risk' (e.g. number randomized not stated, no reasons for missing data provided);
- the study did not address this outcome.

Selective reporting

Reporting bias due to selective outcome reporting.
Criteria for a judgement of 'low risk' of bias. Any of the following:
- the study protocol is available and all of the study's pre-specified (primary and secondary) outcomes that are of interest in the review have been reported in the pre-specified way;
- the study protocol is not available but it is clear that the published reports include all expected outcomes, including those that were pre-specified (convincing text of this nature may be uncommon).

Criteria for the judgement of 'high risk' of bias. Any one of the following:
- not all of the study's pre-specified primary outcomes have been reported;
- one or more primary outcomes is reported using measurements, analysis methods or subsets of the data (e.g. subscales) that were not pre-specified;
- one or more reported primary outcomes were not pre-specified (unless clear justification for their reporting is provided, such as an unexpected adverse effect);
- one or more outcomes of interest in the review are reported incompletely so that they cannot be entered in a meta-analysis;
- the study report fails to include results for a key outcome that would be expected to have been reported for such a study.

Criteria for the judgement of 'unclear risk' of bias.
- Insufficient information to permit judgement of 'low risk' or 'high risk'. It is likely that the majority of studies will fall into this category.

Other bias

Bias due to problems not covered elsewhere in the table.
Criteria for a judgement of 'low risk' of bias.
- The study appears to be free of other sources of bias.

Criteria for the judgement of 'high risk' of bias. There is at least one important risk of bias. For example, the study:
- had a potential source of bias related to the specific study design used; or
- has been claimed to have been fraudulent; or
- had some other problem.

Criteria for the judgement of 'unclear risk' of bias. There may be a risk of bias, but there is either:
- insufficient information to assess whether an important risk of bias exists; or
- insufficient rationale or evidence that an identified problem will introduce bias.

Appendix 3. Data extraction form

Review title or ID

Study ID *(surname of first author and year first full report of study was published e.g. Smith 2001)*

Report IDs of other reports of this study *(e.g. duplicate publications, follow-up studies)*

Notes:

1. General information

Date form completed *(dd/mm/yyyy)*	
Name/ID of person extracting data	
Report title *(title of paper/abstract/report that data are extracted from)*	
Report ID *(ID for this paper/abstract/report)*	
Reference details	
Report author contact details	
Publication type *(e.g. full report, abstract, letter)*	
Study funding sources *(including role of funders)*	

(*Continued*)

Possible conflicts of interest *(for study authors)*	
Notes:	**Notes:**

2. Study eligibility

Study characteristics	**Eligibility criteria** *(Insert eligibility criteria for each characteristic as defined in the Protocol)*	Yes	No	Unclear	**Location in text** *(pg & ¶/fig/table)*
Type of study	Randomized controlled trial				
	Controlled clinical trial *(quasi-randomized trial)*				
Participants					
Types of intervention					
Types of outcome measures					

INCLUDE	**EXCLUDE**
Reason for exclusion	

Notes:	**Notes:**

DO NOT PROCEED IF STUDY EXCLUDED FROM REVIEW

3. Population and setting

	Description *Include comparative information for each group (i.e. intervention and controls) if available*	Location in text *(pg & ¶/fig/table)*
Population description *(from which study participants are drawn)*		
Setting *(including location and social context)*		
Inclusion criteria		
Exclusion criteria		
Method/s of recruitment of participants		
Informed consent obtained	Yes No Unclear	
Notes:		**Notes:**

4. Methods

	Descriptions as stated in report/ paper	Location in text *(pg & ¶/fig/table)*
Aim of study		
Design *(e.g. parallel, cross-over, cluster)*		
Unit of allocation *(by individuals, cluster/groups or body parts)*		
Start date		
End date		
Total study duration		

(*Continued*)

Ethical approval needed/obtained for study	Yes No Unclear		
Notes:			**Notes:**

5. 'Risk of bias' assessment

See Chapter 8 of the Cochrane Handbook

Domain	**Risk of bias**			**Support for judgement**	**Location in text** *(pg & ¶/fig/table)*
	Low risk	High risk	Unclear		
Random sequence generation *(selection bias)*					
Allocation concealment *(selection bias)*					
Blinding of participants and personnel *(performance bias)*				**Outcome group: All/**	
(if required)				**Outcome group:**	
Blinding of outcome assessment *(detection bias)*				**Outcome group: All/**	
(if required)				**Outcome group:**	
Incomplete outcome data *(attrition bias)*					
Selective outcome reporting? *(reporting bias)*					
Other bias					

(*Continued*)

Notes:	Notes:

6. Participants

Provide overall data and, if available, comparative data for each intervention or comparison group.

	Description as stated in report/paper	Location in text (pg & ¶/fig/table)
Total no. randomized		
Baseline imbalances		
Withdrawals and exclusions *(if not provided below by outcome)*		
Age		
Sex		
Other treatment received *(additional to study intervention)*		
Subgroups measured		
Subgroups reported		

Notes:	Notes:

7. Intervention groups

Copy and paste table for each intervention and comparison group
Intervention Group 1

	Description as stated in report/paper	Location in text *(pg & ¶/fig/table)*
Group name		
No. randomized to group		

(*Continued*)

Description *(include sufficient detail for replication, e.g. content, dose, components)*		
Duration of treatment period		
Timing *(e.g. how long before surgery?)*		
Delivery *(e.g. intravenous, oral or intramuscular)*		
Co-interventions		
Notes:		**Notes:**

8. Outcomes

Copy and paste table for each outcome.
Outcome 1

	Description as stated in report/ paper	**Location in text** *(pg & ¶/fig/table)*
Outcome name		
Time points measured		
Time points reported		
Outcome definition *(with diagnostic criteria if relevant)*		
Person measuring/reporting		
Unit of measurement *(if relevant)*		
Is outcome/tool validated?	Yes No Unclear	
Notes:		**Notes:**

9. Results

Copy and paste the appropriate table for each outcome, including additional tables for each time point and subgroup as required.
Dichotomous outcome

	Description as stated in report/paper				Location in text *(pg & ¶/fig/table)*
Comparison					
Outcome					
Subgroup					
Time point *(specify whether from start or end of intervention)*					
Results	**Intervention**		**Comparison**		
	No. events	No. participants	No. events	No. participants	
No. missing participants and reasons					
No. participants moved from other group and reasons					
Any other results reported					
Reanalysis required? *(specify)*	Yes No Unclear				
Reanalysis possible?	Yes No Unclear				
Reanalysed results					
Notes:					**Notes:**

Continuous outcome

	Description as stated in report/paper						Location in text *(pg & ¶/fig/table)*
Comparison							
Outcome							
Subgroup							
Time point *(specify whether from start or end of intervention)*							
Post-intervention or change from baseline?							
Results	**Intervention**			**Comparison**			
	Mean	SD (or other variance)	No. participants	Mean	SD (or other variance)	No. participants	
No. missing participants and reasons							
No. participants moved from other group and reasons							
Any other results reported							
Reanalysis required? *(specify)*	Yes No Unclear						
Reanalysis possible?	Yes No Unclear						
Reanalysed results							
Notes:							

10. Applicability

Have important populations been excluded from the study? *(consider disadvantaged populations, and possible differences in the intervention effect)*	Yes No Unclear
Is the intervention likely to be aimed at disadvantaged groups? *(e.g. lower socioeconomic groups)*	Yes No Unclear
Does the study directly address the review question? *(any issues of partial or indirect applicability)*	Yes No Unclear
Notes:	**Notes:**

11. Other information

	Description as stated in report/paper	**Location in text** *(pg & ¶/fig/table)*
Key conclusions of study authors		
References to other relevant studies		
Correspondence required for further study information *(from whom, what and when)*		
Notes:		**Notes:**

CONTRIBUTIONS OF AUTHORS

Brett Doleman (BD), John P Williams (JPW), Jon Lund (JL), Jo Leonardi-Bee (JLB), Thomas Heinink (TH)

Conceiving the review: BD, JPW

Co-ordinating the review: BD, JPW, JL, JLB, TH

Undertaking manual searches: BD

Screening search results: BD

Organizing retrieval of papers: BD

Screening retrieved papers against inclusion criteria: BD, JPW, TH, JLB

Appraising quality of papers: BD, JPW, TH, JLB

Abstracting data from papers: BD, JPW, TH

Writing to authors of papers for additional information: BD

Providing additional data about papers: BD

Obtaining and screening data on unpublished studies: BD

Data management for the review: BD, JPW

Entering data into Review Manager (RevMan 5): BD, JPW

RevMan statistical data: BD, JPW

Other statistical analysis not using RevMan: BD

Interpretation of data: BD, JPW, JLB

Statistical inferences: BD, JPW, JLB

Writing the review: BD, JPW

Securing funding for the review: N/A

Performing previous work that was the foundation of the present study: BD, JPW, JL, TH

Guarantor for the review (one author): BD

Person responsible for reading and checking review before submission: BD, JL, JPW, JLB, TH

DECLARATIONS OF INTEREST

Brett Doleman: received a grant in 2015 from the Association of Anaesthetists of Great Britain and Ireland (AAGBI) (free from industry support) for a RCT of preventive paracetamol and has previously undertaken a meta-analysis of preventive paracetamol and gabapentin (Doleman 2015a; Doleman 2015b).

John P Williams: received a grant in 2015 from AAGBI (free from industry support) for a RCT of preventive paracetamol and has previously undertaken a meta-analysis of preventive paracetamol and gabapentin (Doleman 2015a; Doleman 2015b).

Jon Lund: received a grant in 2015 from AAGBI (free from industry support) for a RCT of preventive paracetamol and has previously undertaken a meta-analysis of preventive paracetamol and gabapentin (Doleman 2015a; Doleman 2015b).

Jo Leonardi-Bee: is a co-applicant on an Educational Grant from Roche to carry out further research in the area of pandemic influenza. Dr. Leonardi-Bee will be using this to carry out a systematic review and individual patient meta-analysis of the evidence (published and unpublished) of the impact of antiviral use on public health outcomes for 2009 pandemic influenza A/H1N1. This systematic review has been registered with PROSPERO (international prospective register of systematic reviews).

Thomas Heinink: no declarations of interest.