



Cochrane
Library

Cochrane Database of Systematic Reviews

Liposomal bupivacaine peripheral nerve block for the management of postoperative pain (Review)

Hamilton TW, Athanassoglou V, Trivella M, Strickland LH, Mellon S, Murray D, Pandit HG

Hamilton TW, Athanassoglou V, Trivella M, Strickland LH, Mellon S, Murray D, Pandit HG.
Liposomal bupivacaine peripheral nerve block for the management of postoperative pain.
Cochrane Database of Systematic Reviews 2016, Issue 8. Art. No.: CD011476.
DOI: 10.1002/14651858.CD011476.pub2.

www.cochranelibrary.com

TABLE OF CONTENTS

HEADER	1
ABSTRACT	1
PLAIN LANGUAGE SUMMARY	2
SUMMARY OF FINDINGS FOR THE MAIN COMPARISON	4
BACKGROUND	6
OBJECTIVES	7
METHODS	7
Figure 1.	9
RESULTS	11
Figure 2.	13
Figure 3.	14
DISCUSSION	17
AUTHORS' CONCLUSIONS	18
ACKNOWLEDGEMENTS	19
REFERENCES	19
CHARACTERISTICS OF STUDIES	22
DATA AND ANALYSES	42
APPENDICES	42
FEEDBACK	44
WHAT'S NEW	45
HISTORY	45
CONTRIBUTIONS OF AUTHORS	46
DECLARATIONS OF INTEREST	46
SOURCES OF SUPPORT	46
DIFFERENCES BETWEEN PROTOCOL AND REVIEW	47
INDEX TERMS	47

Liposomal bupivacaine peripheral nerve block for the management of postoperative pain

Thomas W Hamilton¹, Vassilis Athanassoglou², Marialena Trivella³, Louise H Strickland¹, Stephen Mellon¹, David Murray¹, Hemant G Pandit¹

¹Nuffield Department of Orthopaedics, Rheumatology and Musculoskeletal Sciences (NDORMS), University of Oxford, Oxford, UK. ²Nuffield Department of Anaesthetics, Oxford University Hospitals NHS Foundation Trust, Oxford, UK. ³Centre for Statistics in Medicine, University of Oxford, Oxford, UK

Contact address: Thomas W Hamilton, Nuffield Department of Orthopaedics, Rheumatology and Musculoskeletal Sciences (NDORMS), University of Oxford, Oxford, UK. thomas.hamilton@ndorms.ox.ac.uk, thomas.hamilton@sbs.ox.ac.uk.

Editorial group: Cochrane Pain, Palliative and Supportive Care Group.

Publication status and date: Edited (no change to conclusions), published in Issue 2, 2017.

Review content assessed as up-to-date: 15 January 2016.

Citation: Hamilton TW, Athanassoglou V, Trivella M, Strickland LH, Mellon S, Murray D, Pandit HG. Liposomal bupivacaine peripheral nerve block for the management of postoperative pain. *Cochrane Database of Systematic Reviews* 2016, Issue 8. Art. No.: CD011476. DOI: 10.1002/14651858.CD011476.pub2.

Copyright © 2017 The Cochrane Collaboration. Published by John Wiley & Sons, Ltd.

ABSTRACT

Background

Postoperative pain remains a significant issue with poor perioperative pain management associated with an increased risk of morbidity and mortality. Liposomal bupivacaine is an analgesic consisting of bupivacaine hydrochloride encapsulated within multiple, non-concentric lipid bi-layers offering a novel method of sustained release.

Objectives

To assess the analgesic efficacy and adverse effects of liposomal bupivacaine infiltration peripheral nerve block for the management of postoperative pain.

Search methods

We identified randomised trials of liposomal bupivacaine peripheral nerve block for the management of postoperative pain. We searched the Cochrane Central Register of Controlled Trials (CENTRAL) (2016, Issue 1), Ovid MEDLINE (1946 to January Week 1 2016), Ovid MEDLINE In-Process (14 January 2016), EMBASE (1974 to 13 January 2016), ISI Web of Science (1945 to 14 January 2016), and reference lists of retrieved articles. We sought unpublished studies from Internet sources, and searched clinical trials databases for ongoing trials. The date of the most recent search was 15 January 2016.

Selection criteria

Randomised, double-blind, placebo- or active-controlled clinical trials of a single dose of liposomal bupivacaine administered as a peripheral nerve block in adults aged 18 years or over undergoing elective surgery at any surgical site. We included trials if they had at least two comparison groups for liposomal bupivacaine peripheral nerve block compared with placebo or other types of analgesia.

Data collection and analysis

Two review authors independently considered trials for inclusion in the review, assessed risk of bias, and extracted data. We performed analyses using standard statistical techniques as described in the *Cochrane Handbook for Systematic Reviews of Interventions*, using Review Manager 5. We planned to perform a meta-analysis, however there were insufficient data to ensure a clinically meaningful answer; as such we have produced a 'Summary of findings' table in a narrative format, and where possible we assessed the evidence using GRADE (Grading of Recommendations Assessment, Development and Evaluation).

Main results

We identified seven studies that met inclusion criteria for this review. Three were recorded as completed (or terminated) but no results were published. Of the remaining four studies (299 participants): two investigated liposomal bupivacaine transversus abdominis plane (TAP) block, one liposomal bupivacaine dorsal penile nerve block, and one ankle block. The study investigating liposomal bupivacaine ankle block was a Phase II dose-escalating/de-escalating trial presenting pooled data that we could not use in our analysis.

The studies did not report our primary outcome, cumulative pain score between 0 and 72 hours, and secondary outcomes, mean pain score at 12, 24, 48, 72, or 96 hours. One study reported no difference in mean pain score during the first, second, and third postoperative 24-hour periods in participants receiving liposomal bupivacaine TAP block compared to no TAP block. Two studies, both in people undergoing laparoscopic surgery under TAP block, investigated cumulative postoperative opioid dose, reported opposing findings. One found a lower cumulative opioid consumption between 0 and 72 hours compared to bupivacaine hydrochloride TAP block and one found no difference during the first, second, and third postoperative 24-hour periods compared to no TAP block. No studies reported time to first postoperative opioid or percentage not requiring opioids over the initial 72 hours. No studies reported a health economic analysis or patient-reported outcome measures (outside of pain). The review authors sought data regarding adverse events but none were available, however there were no withdrawals reported to be due to adverse events.

Using GRADE, we considered the quality of evidence to be very low with any estimate of effect very uncertain and further research very likely to have an important impact on our confidence in the estimate of effect. All studies were at high risk of bias due to their small sample size (fewer than 50 participants per arm) leading to uncertainty around effect estimates. Additionally, inconsistency of results and sparseness of data resulted in further downgrading of the quality of the data.

Authors' conclusions

A lack of evidence has prevented an assessment of the efficacy of liposomal bupivacaine administered as a peripheral nerve block. At present there is a lack of data to support or refute the use of liposomal bupivacaine administered as a peripheral nerve block for the management of postoperative pain. Further research is very likely to have an important impact on our confidence in the estimate of effect and is likely to change the estimate.

PLAIN LANGUAGE SUMMARY

Liposomal bupivacaine as a nerve block to treat pain after surgery

Authors' conclusions

There is currently a lack of evidence around the use of liposomal bupivacaine as a nerve block to treat pain after surgery. Further large studies are required to see if there is a role for liposomal bupivacaine to treat pain after surgery.

Background and objectives

Pain after surgery is a significant concern, with poor pain management linked to an increased risk of complications. One method to treat pain is to inject a painkiller around the nerves that transmit pain (sensory nerves) from the surgical site; this is called a nerve block. A new drug called liposomal bupivacaine has been developed consisting of multiple small parcels of bupivacaine (a commonly used painkiller), and it has been designed to release the painkiller over a long time. This review assessed how good liposomal bupivacaine sensory nerve blocks are at treating pain after surgery, and whether there are any risks associated with their use.

Study characteristics and key results

In January 2016, we found seven studies that assessed liposomal bupivacaine nerve block. Three studies were listed as completed but had not reported results. This left four studies involving 299 participants for this review. Two studies investigated liposomal bupivacaine

given between two of the layers of abdominal muscles to block the nerves supplying sensation to that area (known as a transversus abdominus plane (TAP) block); one study investigated liposomal bupivacaine given around the nerves that supply sensation to the penis (dorsal penile nerve block); and one study investigated the ankle (ankle block).

We did not identify any studies that reported our primary outcome cumulative pain score between 0 and 72 hours or pain-centred secondary outcomes. Two studies reported cumulative opioid (a strong painkiller) use with inconsistent results. We looked for results about side effects but none were reported, however no participants dropped out of the studies due to side effects. Overall, the lack of evidence, due to the small number of trials each reporting different outcomes, prevented a full assessment of the role of liposomal bupivacaine administered as a nerve block for the management of pain after surgery in adults.

Quality of the evidence

Due to the small number of trials, and small number of participants in these trials, the quality of evidence was very low. As such, further research is required to evaluate the role of liposomal bupivacaine as a nerve block to treat pain after surgery.

SUMMARY OF FINDINGS FOR THE MAIN COMPARISON [\[Explanation\]](#)

Liposomal bupivacaine infiltration at the surgical site for the management of postoperative pain			
Patient or population: adults aged ≥ 18 years undergoing elective surgery at any surgical site Settings: inpatient Intervention: liposomal bupivacaine peripheral nerve block (TAP block or nerve block) Comparison: placebo or other types of analgesia delivered systemically, via local infiltration, perineural injection or epidural routes			
Outcomes	Impact	No of participants (studies)	Quality of the evidence (GRADE)
Cumulative pain score from the end of operation (0 hours) to 72 hours	No data reported	-	-
	vs. no TAP block No serious adverse events reported. No withdrawals reported to be due to drug-related serious adverse events	50 participants (1 study)	
	vs. bupivacaine hydrochloride TAP block No serious adverse events reported. No withdrawals reported to be due to drug-related serious adverse events	60 participants (1 studies)	
	Nerve block		
	vs. no nerve block No serious adverse events reported. No withdrawals reported to be due to drug-related serious adverse events	131 participants (1 study; 44 no nerve block, 47 ropivacaine hydrochloride nerve block, 40 liposomal bupivacaine nerve block)	
	vs. ropivacaine hydrochloride nerve block No serious adverse events reported. No withdrawals reported to be due to drug-related serious adverse events		
Mean pain score at 12, 24, 48, 72, and 96 hours following surgery	TAP block		⊕○○○ very low ¹

	<p>vs. no TAP block 50 participants 1 study reported no difference in mean pain score between liposomal bupivacaine TAP block and control (no TAP block) during the first, second, and third 24-hour periods postoperatively (1 study)</p>	
	<p>vs. bupivacaine hydrochloride TAP block - No data reported</p>	
	<p>Nerve block</p>	
	<p>No data reported -</p>	
Time to first postoperative opioid dose	<p>No data reported -</p>	-
Total postoperative opioid consumption over first 72 hours	<p>TAP block</p> <p>vs. no TAP block 50 participants 1 study reported no difference in cumulative opioid consumption over the first 72 hours between liposomal bupivacaine TAP block and control (no TAP block) (1 study)</p> <p>vs. bupivacaine hydrochloride TAP block 60 participants 1 study found a significant reduction in cumulative opioid consumption over the first 72 hours associated with the use of liposomal bupivacaine TAP block compared to bupivacaine hydrochloride TAP block (1 study)</p> <p>Nerve block</p> <p>No data reported -</p>	<p>⊕○○○ very low²</p>
Percentage of participants not requiring postoperative opioids over initial 72 hours	<p>No data reported -</p>	-
Health economic assessment	<p>No data reported -</p>	-

Incidence of adverse events within 30 days of surgery	No data reported	-	-
Patient-reported outcomes	No data (outside of pain) reported	-	-

GRADE Working Group grades of evidence

High quality: Further research is very unlikely to change our confidence in the estimate of effect.

Moderate quality: Further research is likely to have an important impact on our confidence in the estimate of effect and may change the estimate.

Low quality: Further research is very likely to have an important impact on our confidence in the estimate of effect and is likely to change the estimate.

Very low quality: We are very uncertain about the estimate.

TAP: transversus abdominis plane

GRADE evidence:

¹ Downgraded one level due to high risk of bias due to small sample size (< 50 participants/arm), one level due to sparseness of data, and one level due to the limitations in interpreting data from a small number of trials that included a small number of participants.

² Downgraded one level due to high risk of bias due to small sample size (< 50 participants/arm), one level due to inconsistency in results, and one level due to sparseness of data.

BACKGROUND

Description of the condition

Up to three-quarters of people undergoing surgery receive inadequate pain relief, with poor perioperative pain management being associated with an increased risk of postoperative morbidity and mortality (Apfelbaum 2003; Nimmaanrat 2007; Lorentzen 2012; Gan 2014). Whilst uncontrolled postoperative pain is more common following certain procedures, in particular abdominal, thoracic and joint replacement operations, it can affect all people undergoing surgery. Postoperative pain can be reduced using multi-modal analgesia, providing significant benefits to both people undergoing surgery as well as healthcare systems through enhanced patient satisfaction and reduced healthcare costs. Furthermore, there is increasing evidence that optimising peri- and postoperative analgesia reduces the incidence of chronic postsurgical pain resulting in enhanced patient outcomes; both in the short-term as well as the long-term (Kehlet 2006).

Description of the intervention

Multi-modal analgesia employs a range of drugs, with local as well as systemic effects, that inhibit nociceptive stimuli along their path from the site of surgical injury to the brain. The concept of multi-modal analgesia was introduced by Kehlet et al in the 1990s and its use has expanded to many surgical specialities (Kehlet 1993). The use of paracetamol, non-steroidal anti-inflammatory drugs (NSAIDs), gabapentinoids, as well as local and regional anaesthetic techniques, reduce the need for oral or parenteral opioids in the postoperative period, and as a consequence the adverse effects seen with opioids are reduced.

In local anaesthetic peripheral nerve blocks local anaesthetic is infiltrated, often under ultrasound guidance or nerve stimulation, around a nerve proximal to the site of surgical injury. In local anaesthetic incisional infiltration, local anaesthetic is infiltrated at the site of the surgical incision at the time of surgery. Both of these are commonly used either as intraoperative anaesthesia or as part of a postoperative multi-modal analgesic regimen. The view is that modification of pain stimuli at their origin will reduce the transmission of nociceptive stimuli, thereby reducing downstream organ dysfunction, pain, and stress responses, including centrally mediated changes in the spinal cord or cerebral cortex, or both (Kehlet 2006). The use of liposomal bupivacaine surgical site infiltration is the subject of a separate review (Hamilton 2017).

Local anaesthetic peripheral nerve blocks are used in a wide range of operations. The local anaesthetic nerve blocks, used either as peri- or postoperative analgesia, are typically administered prior to surgical incision, but they can be performed at any time for the management of postoperative pain. Bupivacaine is the most commonly used local anaesthetic for peripheral nerve blocks, however its duration of action is a major limiting factor which, despite the addition of drugs such as adrenaline (epinephrine), clonidine, and dexamethasone to enhance its duration of action, results in many people reporting significant rebound pain when the effect of the local anaesthetic wears off (Apfelbaum 2003). As such there has been a great deal of interest in sustained release local anaesthetics such as liposomal bupivacaine, which are administered in the same manner but have been reported to have an effect that lasts significantly longer (Grant 2004).

Whilst there is a low incidence of adverse effects following local anaesthetics, peripheral nerve block complications can occur due to nerve injury or high plasma levels of the drug. High plasma levels can occur secondary to overdosage, rapid absorption from the injection site, diminished tolerance, accidental intravascular injection, or slow metabolic degradation. The most common adverse effects that require immediate countermeasures are related to the central nervous system and cardiovascular toxicity.

How the intervention might work

Liposomal bupivacaine consists of bupivacaine hydrochloride encapsulated within multiple, non-concentric lipid bi-layers. This encapsulation technique produces vesicles with a diameter of 10 to 20 μm containing the active drug, which offers a novel method of sustained release (Spector 1996). Release of the active drug from these multi-vesicular liposomes is via three mechanisms, membrane breakdown, membrane reorganisation, and diffusion (Mantripragada 2002). The relative importance of each mechanism is unknown.

Following its release from the liposome vesicles, the active component bupivacaine, an amide local anaesthetic, acts by binding the intracellular portion of voltage-gated sodium channels, therefore preventing depolarisation of the nerve cell, propagation of action potentials, and thus conduction of nociceptive stimuli. Bupivacaine hydrochloride is subsequently metabolised, primarily in the liver via a microsomal cytochrome P450 3A4-mediated pathway, to pipercolylxylidine, with 5% undergoing renal excretion and around 15% being excreted unchanged (Gantenbein 2000). The multi-vesicular liposome component of liposome bupivacaine undergoes a slow process of lipid degradation and clearance; studies have demonstrated that a significant proportion of the liposome component is detectable at the injection site at periods exceeding 21 days following administration (Mantripragada 2002).

Why it is important to do this review

Regional anaesthetic techniques for intraoperative anaesthesia and postoperative analgesia, especially with the development of ultrasound-guided techniques, are gaining popularity and have an increasing role as part of a multi-modal analgesic technique across a wide range of surgical specialities. Currently their duration of action is a major limiting factor with people reporting rebound pain. Liposomal bupivacaine is a new therapy, utilising a novel mechanism, to provide sustained release of local anaesthetic at the origin of the pain that has the potential to address this limitation. This independent review was designed to critically appraise the current literature on liposomal bupivacaine peripheral nerve block in people undergoing elective surgery to evaluate its effectiveness at managing postoperative pain.

OBJECTIVES

To assess the analgesic efficacy and adverse effects of liposomal bupivacaine infiltration peripheral nerve block for the management of postoperative pain.

METHODS

Criteria for considering studies for this review

Types of studies

We included prospective randomised controlled trials (RCTs) and quasi-randomised controlled trials (including cluster randomised trials) if they had at least two comparisons groups for liposomal bupivacaine peripheral nerve block compared to placebo or other types of analgesia. We included data from clinical trials registries and clinical trials records in the review. We included studies irrespective of publication status and language.

Types of participants

We included all trials with participants aged 18 years and older undergoing elective surgery at any surgical site, without restriction of any comorbidities.

Types of interventions

We included all double-blind RCTs that compared the effects of liposomal bupivacaine peripheral nerve block to placebo or other types of analgesia delivered systemically, via local infiltration, perineural injection, and epidural routes. Due to potential differences

in the mechanism of action between techniques, we have considered the results of studies investigating field blocks (transversus abdominis plane (TAP)) and where the local anaesthetic was infiltrated directly around a nerve or set of nerves separately.

Types of outcome measures

We included patient-reported outcome measures of pain, use of supplementary opiate analgesia (incidence of supplementary analgesia, time to supplementary analgesia, mean and total opiate consumption, opiate or other analgesia-related adverse events) and measures of cost effectiveness. We also included withdrawals from the trial and adverse events.

Primary outcomes

- Cumulative pain intensity (area under curve) assessed on a 100-mm visual analogue scale (VAS) over the initial 72 hours following surgery, at rest or with activity. However, we considered all types of pain scales with standardisation of pain intensity data described by other means than a 100-mm VAS, where possible.
- Serious adverse events, specifically incidence of cardiac events and peripheral nerve block injection site complications.

Secondary outcomes

- Mean pain score, at rest or with activity, assessed on a 100-mm VAS at 12, 24, 48, 72, and 96 hours following surgery. We considered all pain scores with standardisation of pain intensity data described by other means than a 100-mm VAS, where possible.
- Time to first postoperative opioid dose over initial 72 hours.
- Total postoperative opioid consumption over first 72 hours.
- Percentage of participants not requiring postoperative opioids over initial 72 hours.
- Health economics assessed using a recognised health economic technique.
- Incidence of adverse events within 30 days of surgery.
- Patient-reported outcomes, using validated outcome scores, at any time point following surgery.

Search methods for identification of studies

Electronic searches

We searched the following electronic databases:

- the Cochrane Central Register of Controlled Trials (CENTRAL) 2016, Issue 1;
- MEDLINE and MEDLINE in Process (Ovid), 1946 to 14 January 2016;
- EMBASE (Ovid) 1974 to 13 January 2016;
- Web of Science (ISI) 1945 to 14 January 2016.

We used medical subject headings (MeSH) or equivalent and text word terms. There were no language restrictions. We tailored the searches to individual databases. [Appendix 1](#) shows the search strategies.

Searching other resources

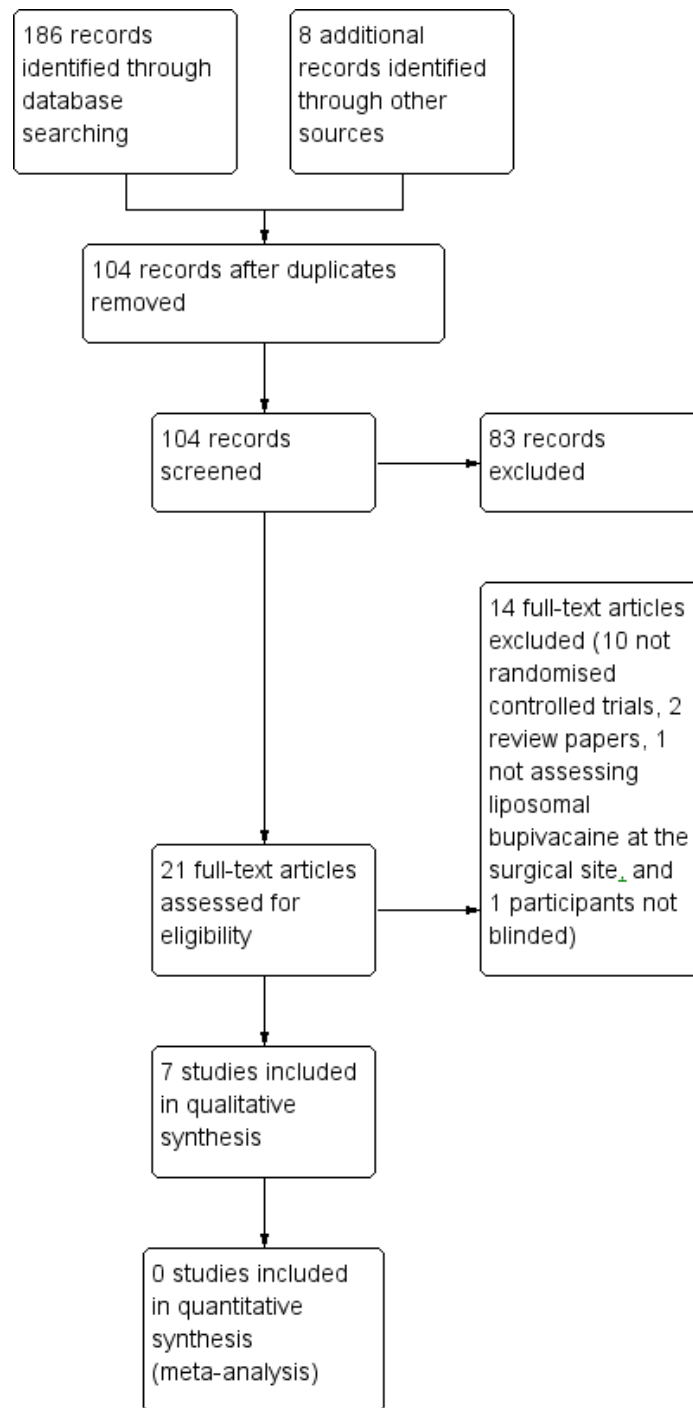
We searched the metaRegister of controlled trials (mRCT) (www.controlled-trials.com/mrct), clinicaltrials.gov (www.clinicaltrials.gov), and the World Health Organization (WHO) International Clinical Trials Registry Platform (ICTRP) (apps.who.int/trialsearch/) for ongoing trials. In addition, we checked reference lists of reviews and retrieved articles for additional studies and performed citation searches on key articles. We contacted experts in the field for unpublished and ongoing trials. We contacted study authors, where necessary, for additional information.

Data collection and analysis

Selection of studies

Two review authors (TWH, VA) assessed studies independently and in duplicate for eligibility. In the first instance, we selected studies from titles and abstracts. For those deemed relevant, we obtained the full texts. Different pairs of two review authors (TWH, VA, LHS) assessed the full text according to the eligibility criteria. We resolved disagreement by consensus following consultation with the senior review author (HP). [Figure 1](#) presents a summary of the search strategy and study selection as a PRISMA flowchart ([Liberati 2009](#)). We retrieved the full texts of eligible studies with collating of data from multiple publications of individual studies and removal of duplicate data.

Figure 1. Study flow diagram.



Data extraction and management

Two review authors independently in duplicate (TWH, VA) extracted data onto a pre-tested, standardised, electronic data collection pro forma. We resolved inconsistency in data collection by discussion and with the input of a third review author (LS). If necessary, we sought additional information from the study authors and sponsors.

Assessment of risk of bias in included studies

We used the Oxford Quality Score (Jadad 1996) as the basis for inclusion, limiting inclusion to studies that were randomised and double-blind as a minimum.

Two review authors (TWH, LS) independently assessed the risk of bias for each study, using the criteria outlined in the *Cochrane Handbook for Systematic Reviews of Interventions* (Higgins 2011), and adapted from those used by the Cochrane Pregnancy and Childbirth Group, and resolved any disagreements by discussion. We assessed the following for each study.

- Random sequence generation (checking for possible selection bias). We assessed the method used to generate the allocation sequence as: low risk of bias (any truly random process, e.g. random number table, computer random number generator); unclear risk of bias (method used to generate sequence not clearly stated). We excluded studies using a non-random process (e.g. odd or even date of birth, hospital or clinic record number).

- Allocation concealment (checking for possible selection bias). The method used to conceal allocation to interventions prior to assignment determines whether intervention allocation could have been foreseen in advance of, or during, recruitment or changed after assignment. We assessed the methods as: low risk of bias (e.g. telephone or central randomisation, consecutively numbered sealed opaque envelopes); unclear risk of bias (method not clearly stated). We excluded studies that did not conceal allocation (e.g. open list).

- Blinding of outcome assessment (checking for possible detection bias). We assessed the methods used to blind study participants and outcome assessors from knowledge of which intervention a participant received. We assessed the methods as: low risk of bias (study stated that it was blinded and described the method used to achieve blinding, e.g. identical tablets, matched in appearance and smell); unclear risk of bias (study stated that it was blinded but did not provide an adequate description of how it was achieved). We excluded studies that were not double-blind.

- Incomplete outcome data (checking for possible attrition bias due to the amount, nature, and handling of incomplete outcome data). We assessed the methods used to deal with

incomplete data as: low risk (less than 10% of participants did not complete the study or used 'baseline observation carried forward' analysis, or both); unclear risk of bias (used 'last observation carried forward' analysis); high risk of bias (used 'completer' analysis).

- Size of study (checking for possible biases confounded by small size). We assessed studies as being at low risk of bias (200 or more participants per treatment arm); unclear risk of bias (50 to 199 participants per treatment arm); high risk of bias (fewer than 50 participants per treatment arm).

Measures of treatment effect

A lack of data prevented a quantitative assessment of the efficacy of liposomal bupivacaine administered as a peripheral nerve block. For dichotomous data, we planned to calculate the risk ratio (RR) and for continuous data the standardised mean difference (SMD), along with 95% confidence intervals (CI). We planned to calculate the incidence rates of opioid-related adverse effects and, where possible, for efficacy outcomes the numbers needed to treat for a beneficial outcome (NNTB) and harmful outcome (NNTH) for adverse events.

Unit of analysis issues

We assessed outcomes at the participant level and proposed to analyse studies involving multiple treatment arms by dividing the sample size of the control group into the appropriate number depending on the number of arms the trial had.

Dealing with missing data

We contacted study authors and sponsors to request further information in the event of missing data. Care was taken to explore the reasons for missing data, with no data imputation performed because of the controversies associated with imputing data from multiple scoring schemes, especially with possible small sample sizes per scoring scale.

Assessment of heterogeneity

We planned to examine the heterogeneity of included studies using the I^2 statistic as described in the *Cochrane Handbook for Systematic Reviews of Interventions* (Higgins 2011), and if there was substantial heterogeneity (i.e. I^2 greater than 85%), we would not have attempted pooled analysis. As we expected a level of variability among the eligible studies, in terms of measurement scale used and subjectivity of the outcome, we proposed using the random-effects model in all meta-analyses in this review.

Assessment of reporting biases

To assess for publication bias, due to non-reporting of negative studies, we contacted the principal investigator of unpublished relevant trials registered as completed on trial registries to determine the study outcome. As the review included were fewer than 10 studies, we did not perform an assessment of publication bias.

Data synthesis

A lack of data prevented a quantitative assessment of the efficacy of liposomal bupivacaine administered as a peripheral nerve block and as such we did not perform a meta-analysis. In future updates of this review, where outcome data are of sufficient quality, and participants, interventions, comparisons, and outcomes are judged to be sufficiently similar to ensure an answer that is clinically meaningful, we will perform analyses using standard statistical techniques as described in the *Cochrane Handbook for Systematic Reviews of Interventions*, using Review Manager 5 software (Higgins 2011; RevMan 2014). For continuous data, we will calculate the pooled SMD using the inverse variance method for meta-analysis, and 95% CI. We will reverse standardised results to the original scale format in order to relate to the pooled result. For dichotomous outcomes, we will estimate the pooled RR and 95% CI using the Mantel-Haenszel method.

Quality of the evidence

Two review authors (TH, LS) planned to assess the quality of the evidence for each of the primary and secondary outcomes independently in duplicate using the GRADE system for all of the primary and secondary outcomes assessed. However, this was not possible for all outcomes due to the lack of data available. The GRADE approach uses five considerations (study limitations, consistency of effect, imprecision, indirectness, and publication bias) to assess the quality of the body of evidence for each outcome. The GRADE system uses the following criteria for assigning grade of evidence:

- high = further research is very unlikely to change our confidence in the estimate of effect;
- moderate = further research is likely to have an important impact on our confidence in the estimate of effect and may change the estimate;
- low = further research is very likely to have an important impact on our confidence in the estimate of effect and is likely to change the estimate;
- very low = any estimate of effect is very uncertain.

The grade is decreased if there is:

- serious (-1) or very serious (-2) limitation to study quality;
- important inconsistency (-1);
- some (-1) or major (-2) uncertainty about directness;
- imprecise or sparse data (-1);
- high probability of reporting bias (-1).

Chapter 12.2 of the *Cochrane Handbook for Systematic Reviews of Interventions* (Higgins 2011) provides further information on the use of the GRADE System and GRADEprofiler Guideline Development Tool software (GRADEpro 2015).

'Summary of findings' table

We have produced [Summary of findings for the main comparison](#) as a narrative to present the main findings in a transparent and simple tabular format. In further updates, data permitting, we plan to include key information concerning the magnitude of effect of the interventions examined, and the sum of available data on the outcomes.

Subgroup analysis and investigation of heterogeneity

We did not perform subgroup analyses, however in future reviews, subject to data availability, we plan to carry out subgroup analysis for the different doses (based on the licensed recommendations for dosage) of liposomal bupivacaine administered and different surgical procedures. The indications for these subgroup analyses are the following. Basic science studies have demonstrated that there is a dose-response curve and, as such, the dose of liposomal bupivacaine may have an effect on outcome. Furthermore, different surgeries will have different pain profiles and, in addition, the release pattern of bupivacaine hydrochloride from liposomal bupivacaine may be altered by local environment such that different efficacies may be observed for different surgical procedures.

Sensitivity analysis

If there had been enough data, we planned to perform sensitivity analyses based on the following domains from the risk of bias tool: blinding of outcome assessment and incomplete outcome data.

RESULTS

Description of studies

Results of the search

Using electronic searches, we identified 186 possible studies for inclusion. We identified an additional eight possible studies, six by searches of clinical trials registers and two by searching reference lists of included studies. After removal of duplicates, we screened the titles of 104 records and judged 83 studies to be irrelevant. We explored the full text of 21 studies. We excluded 14 studies (see [Excluded studies](#); [Characteristics of excluded studies](#) table) leaving seven studies for inclusion in the review (see [Characteristics](#)

of included studies table). For a flowchart of the study selection process, see Figure 1.

Included studies

We identified seven studies that met our inclusion criteria. Two of these studies were reported as having been completed, however the results of these studies have not been published, nor have results been made available via clinical trials registry websites (NCT01683071; NCT01802411). One study was reported as terminated after reaching a pre-determined interim analysis time point, however the results of this study have not been published, nor have results been made available via clinical trials registry websites (NCT01919190).

The remaining four studies that met inclusion criteria for this review involved 299 participants with 133 participants randomised to receive liposomal bupivacaine via peripheral nerve block either administered via either by field block (subcostal TAP block; 55 participants) or directly around a nerve or set of nerves (78 participants) for the management of postoperative pain (Nicholson 2014; Hutchins 2015a; Jrebi 2015; NCT01206595).

All studies were conducted in the hospital setting with control or liposomal bupivacaine administered up to 60 minutes prior to the operation. In the control group, one study administered no TAP block in participants undergoing laparoscopic colectomy (Jrebi 2015). Two studies used bupivacaine hydrochloride as an active control (one TAP block 150 mg (Hutchins 2015a) and one ankle block 125 mg (NCT01206595)). One study investigating dorsal penile nerve block for people undergoing inflatable penile prosthesis used both placebo (normal saline 0.9%) and active comparator control arms (ropivacaine hydrochloride) (Nicholson 2014).

Studies used three sites for anaesthesia:

- TAP block for laparoscopic robot-assisted hysterectomy and laparoscopic colectomy; 2 studies, 110 participants (Hutchins 2015a; Jrebi 2015);

- ankle block for bunionectomy, 1 study, 58 participants (NCT01206595);
- dorsal penile nerve block for inflatable penile prosthesis implantation, 1 study, 131 participants (Nicholson 2014).

The dose of liposomal bupivacaine in included studies ranged from 155 mg to 310 mg. One of the included studies was a Phase II adaptive design trial (NCT01206595). In adaptive design trials that are often used to assess the efficacy or safety of new drugs during their development, sequential cohorts of participants are randomised to control or intervention arms with the dose of the intervention arm, in this case liposomal bupivacaine, increased or decreased conditional on the efficacy and safety of the previous cohort. Details of randomisation schedule and interventions, together with details of all eligible studies are given in the Characteristics of included studies table. Outcomes of interest were not investigated in all studies or not reported (reporting bias), or reported in an idiosyncratic manner in the adaptive design trial. As such we were unable to include data from every study in all analyses.

Excluded studies

We excluded 14 studies as 10 were not RCTs, two were review papers, one did not assess liposomal bupivacaine as a peripheral nerve block, and one, unblinded, study was terminated after three participants were enrolled and as such was excluded. The Characteristics of excluded studies table gives details the excluded studies.

We identified 16 ongoing studies, details of which are in the Characteristics of ongoing studies table.

Risk of bias in included studies

Figure 2 and Figure 3 show the summaries of the risk of bias assessment.

Figure 2. Risk of bias graph: review authors' judgements about each risk of bias item presented as percentages across all included studies.

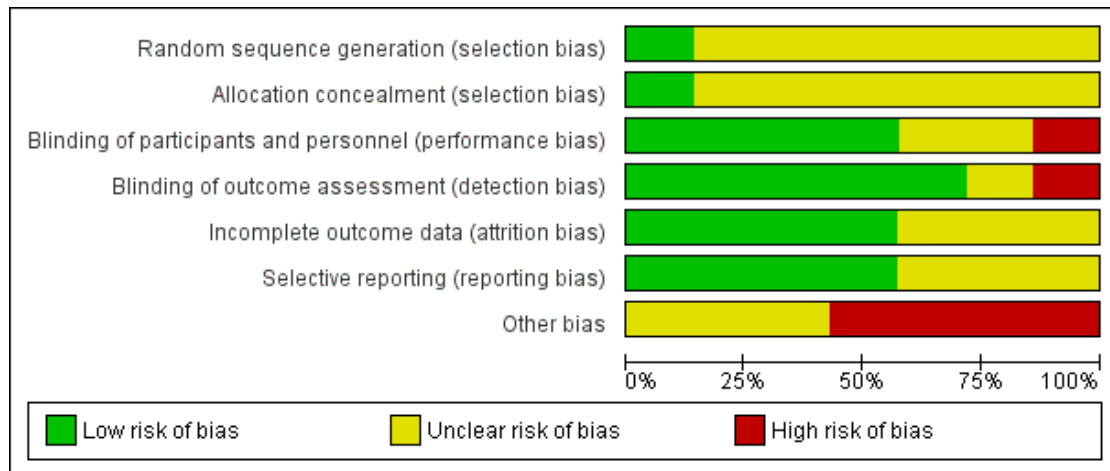


Figure 3. Risk of bias summary: review authors' judgements about each risk of bias item for each included study.

	Random sequence generation (selection bias)	Allocation concealment (selection bias)	Blinding of participants and personnel (performance bias)	Blinding of outcome assessment (detection bias)	Incomplete outcome data (attrition bias)	Selective reporting (reporting bias)	Other bias
Hutchins 2015a	+	+	+	+	+	+	-
Jrebi 2015	?	?	?	+	+	+	-
NCT01206595	?	?	+	+	+	+	-
NCT01683071	?	?	+	+	?	?	?
NCT01802411	?	?	+	+	?	?	?
NCT01919190	?	?	-	-	?	?	?
Nicholson 2014	?	?	?	?	+	+	-

The reporting quality of trials was variable. On the five-point Oxford Scale addressing randomisation, blinding, and withdrawals (Jadad 1996), one study scored five points (Hutchins 2015b), three studies scored three points (NCT01206595; Nicholson 2014; Jrebi 2015), two studies scored two points (NCT01683071; NCT01802411), and one study scored one point (NCT01919190). The three studies that scored fewer than three points were clinical trials registry records that did not describe the method of randomisation or blinding and, while they were marked as completed, we found no published results and as such could not make an assessment of drop-outs and withdrawals. Outside of these three studies, all other studies scored three points or greater and as such would be considered unlikely to be subject to major systematic bias (Khan 1996).

Allocation

One study clearly described the method of randomisation (random sequence generation) and allocation concealment and we assigned it a low risk of bias for selection bias (Hutchins 2015a).

Six studies, which included two conference abstracts (Jrebi 2015; Nicholson 2014) and four clinical trials registry entries (NCT01206595; NCT01683071; NCT01802411; NCT01919190), did not describe the method of random sequence generation or allocation concealment and as such presented an unclear risk of selection bias.

Blinding

Liposomal bupivacaine is a cloudy liquid and has a different visual appearance to both normal saline and bupivacaine hydrochloride. Furthermore, liposomal bupivacaine is more viscous than both normal saline and bupivacaine hydrochloride. As such there is a risk of performance bias by the surgeon or anaesthetist who administered the drug at the time of surgery.

To reduce the risk of performance bias, five trials standardised the injection technique (Hutchins 2015a; NCT01206595; NCT01683071; NCT01802411; NCT01919190), which presented a low risk of performance bias. However, in one of these studies, while the trial standardised the injection technique, the participants were not blinded and the study did not describe the use of placebos and so presented a high risk of performance bias (NCT01919190). Two studies, both conference abstracts, did not specify the injection technique so presented an unclear risk of performance bias (Nicholson 2014; Jrebi 2015).

Five studies blinded participants and staff involved in assessment of outcome measures to the treatment allocation presenting a low risk of detection bias (Hutchins 2015a; Jrebi 2015; NCT01206595; NCT01683071; NCT01802411). One study, a conference abstract, did not state whether the participants and staff were blinded presenting an unclear risk of bias (Nicholson 2014). One study

did not blind participants and did not describe the use of placebos presenting a high risk of detection bias (NCT01919190).

Incomplete outcome data

Three studies were at unclear risk of attrition bias as the study sponsor reported the trial as complete, or terminated after predetermined interim analysis, however we found no results (NCT01683071; NCT01802411; NCT01919190). Four studies were at low risk of attrition bias with greater than 95% follow-up of randomised participants (NCT01206595; Nicholson 2014; Hutchins 2015a; Jrebi 2015).

Selective reporting

Three studies were at unclear risk of reporting bias as the study sponsor reported them as completed, or terminated after predetermined interim analysis, however we found no results (NCT01683071; NCT01802411; NCT01919190). All other studies were at low risk, with all outcome measures assessed reported (NCT01206595; Nicholson 2014; Hutchins 2015a; Jrebi 2015).

Other potential sources of bias

As the majority of trials were drug development trials, Phase II and Phase III, the sample sizes of the treatment and control groups were small. Of the seven studies, three studies did not report their results or sample size (NCT01683071; NCT01802411; NCT01919190), and four presented a high risk of bias as they involved fewer than 50 participants per treatment arm (NCT01206595; Nicholson 2014; Hutchins 2015a; Jrebi 2015). In addition, Pacira Pharmaceuticals Incorporated, manufacturer of liposomal bupivacaine, sponsored four studies (NCT01206595; NCT01683071; NCT01802411; NCT01919190), and a consultant of Pacira Pharmaceuticals Incorporated conducted one study (Hutchins 2015a), presenting an unclear risk of bias.

Effects of interventions

See: [Summary of findings for the main comparison](#) Liposomal bupivacaine infiltration at the surgical site for the management of postoperative pain

Results of adaptive design trials

Dose-escalating/de-escalating studies are used during drug development to evaluate efficacy and safety. This review identified two Phase II adaptive design studies (NCT01206595; NCT01683071), of which only one study had published results

(NCT01206595), with neither investigating any of our outcomes of interest. The NCT01206595 study reported the results of the control groups of all dose-escalating steps in the randomisation process were collectively as single population. Data from adaptive design trials cannot be included in meta-analysis for a number of reasons, for example:

- the decision to escalate or de-escalate a dose is conditional on the failure of the previous dose on the efficacy, safety, or cost-effectiveness of the intervention, introducing bias in any pooled analysis;
- the randomisation ratio is altered with each escalation/de-escalation while the control group population is typically reported cumulatively for all dose levels.

In hindsight, due to the role of adaptive design trials in identifying an efficient and safe dose for further exploration of the intervention in larger-scale trials, and the limitations imposed in including such data in meta-analyses, in future updates of this review, we may consider excluding trials of this design from the definition of the 'types of studies'.

Results of simultaneous parallel arm studies (not adaptive design trials)

Primary outcomes

Cumulative pain intensity over initial 72 hours following surgery

None of the studies reported the cumulative pain intensity over 72 hours following surgery.

Serious adverse events

None of the studies reported the incidence of cardiac events and wound complications within 30 days of surgery.

Three studies posted results on withdrawals (Nicholson 2014 (dorsal penile nerve block); Hutchins 2015a (TAP block); Jrebi 2015 (TAP block); 241 participants) and reported no withdrawals due to adverse events.

Using GRADE, we downgraded the quality of this evidence one level due to a high risk of bias due to the small sample size (fewer than 50 participants per arm) in all studies, one level due to sparseness of data, and by a further level due to the limitations in interpreting data from a small number of small studies. Overall, we judged the evidence to be very low quality, meaning that any estimate of effect is very uncertain with further research highly likely to have an important impact on our confidence in the estimate of effect and is likely to change the estimate.

Secondary outcomes

Mean pain score at 12, 24, 48, 72, and 96 hours following surgery

None of the studies reported the mean pain score at 12, 24, 48, 72, or 96 hours. However, Jrebi 2015 reported no difference in mean pain score measured on a scale of 1 to 10 between 0 and 24 hours (4.2 with liposomal bupivacaine TAP block versus 4.5 with control, $P = 0.14$), 24 and 48 hours (3.2 with liposomal bupivacaine TAP block versus 3.0 with control, $P = 0.44$), and 48 and 72 hours (1.8 with liposomal bupivacaine TAP block versus 2.3 with control, $P = 0.25$) between liposomal bupivacaine TAP block ($n = 25$) or control (no TAP block $n = 25$).

Using GRADE, we downgraded the quality of this evidence one level due to Jrebi 2015 being subject to a high risk of bias due to the small sample size (fewer than 50 participants per arm) as well as unclear risk of selection, and performance bias. We downgraded the evidence further due to the sparseness of reported data and by a further level due to the limitations in interpreting data from a small number of small studies. Due to there being no other data it was not possible to assess the consistency of this result. Overall, we judged the evidence to be of very low quality, meaning that any estimate of effect is very uncertain with further research highly likely to have an important impact on our confidence in the estimate of effect and is likely to change the estimate.

Time to first postoperative opioid dose over initial 72 hours

None of the studies reported time to first postoperative dose.

Total postoperative opioid consumption over first 72 hours

One study reported total postoperative opioid consumption over the first 72 hours (Hutchins 2015a), which found a greater than 50% reduction in cumulative opioid consumption over the first 72 hours postoperatively in participants ($n = 60$) undergoing robot-assisted hysterectomy under TAP block with liposomal bupivacaine compared to TAP block with bupivacaine hydrochloride (median: 24.9 mg, range 0 mg to 86.7 mg IV morphine equivalent dose with liposomal bupivacaine versus 51.7 mg, range 0 mg to 249.7 mg IV morphine equivalent dose with bupivacaine hydrochloride; $P = 0.002$).

Jrebi 2015 reported no difference in cumulative opioid usage between 0 and 24 hours ($P = 0.49$), 24 and 48 hours ($P = 0.16$), and 48 and 72 hours ($P = 0.69$) between those participants receiving liposomal bupivacaine TAP block ($n = 25$) or control (no TAP block, $n = 25$).

Using GRADE, we downgraded the quality of this evidence one level due to Hutchins 2015a and Jrebi 2015 being subject to a high risk of bias due to the small sample size (fewer than 50 participants per arm). We further downgraded the evidence due to

inconsistency in results between studies and due to sparseness of data. Overall, we judged the evidence to be of very low quality, meaning that any estimate of effect is very uncertain with further research highly likely to have an important impact on our confidence in the estimate of effect and is likely to change the estimate.

Percentage of participants not requiring postoperative opioids over initial 72 hours

None of the studies reported percentage of participants not requiring postoperative opioids over initial 72 hours.

Health economics assessment

None of the studies presented a health economic assessment.

Incidence of adverse events within 30 days of surgery

None of the studies reported the incidence of adverse events within 30 days of surgery.

Participant-reported outcomes

None of the included studies posted patient-reported outcomes, using a validated outcome scores, at any time point following surgery.

DISCUSSION

Summary of main results

We identified seven trials meeting inclusion criteria for this review. However, three studies were recorded as completed, or terminated after interim analysis, but no results were published (NCT01683071; NCT01802411; NCT01919190), and one study was a Phase II dose-escalating/de-escalating trial (NCT01206595), designed to evaluate and demonstrate efficacy and safety. These data could not be used in this analysis leaving three trials for analysis. Of the remaining three studies, two investigated liposomal bupivacaine administered as a TAP block and one investigated liposomal bupivacaine administered as a dorsal penile nerve block in people undergoing inflatable penile prostheses (Nicholson 2014). Of the two studies investigating TAP blocks, one was in participants undergoing laparoscopic robot-assisted hysterectomy and had an active comparator (bupivacaine hydrochloride; Hutchins 2015a); the other was in participants undergoing laparoscopic colectomy and had no active control (Jrebi 2015).

None of the studies reported our primary outcome, cumulative pain score 0 to 72 hours, or our secondary outcomes mean pain

score at 12, 24, 48, 72, or 96 hours; however, one study reported no difference in mean pain score during the first, second, and third 24-hour block postoperatively in participants receiving liposomal bupivacaine TAP block for laparoscopic colectomy compared to participants receiving no TAP block (Jrebi 2015). The quality of this evidence was very low using GRADE indicating uncertainty over any estimate of effect and meaning that further research is highly likely to have an important impact on our confidence in the estimate of effect.

Two studies reported cumulative opioid consumption in the first 72 hours postoperatively finding conflicting results. One study reported significantly lower cumulative opioid consumption in the first 72 hours postoperatively in participants receiving liposomal bupivacaine TAP block for laparoscopic robot-assisted hysterectomy compared to participants receiving bupivacaine hydrochloride TAP block (Hutchins 2015a). However, this was not supported by Jrebi 2015 who found no difference in cumulative opioid use during the first, second, and third 24-hour block postoperatively in participants receiving liposomal bupivacaine TAP block for laparoscopic colectomy compared to participants receiving no TAP block. The quality of this evidence was very low using GRADE indicating uncertainty over any estimate of effect and meaning that further research is highly likely to have an important impact on our confidence in the estimate of effect.

No studies reported: time to first postoperative opioid dose, percentage of participants not requiring postoperative opioids over the initial 72 hours, health economic assessment, or participant-reported outcomes, aside from pain, using a validated outcome score following surgery. Of the three studies posting results, 241 participants, there were no withdrawals due to adverse effects reported (Nicholson 2014; Hutchins 2015a; Jrebi 2015). Overall, we judged this evidence to be very low indicating meaning that further research is likely to have an important impact on our confidence in the estimate of effect.

At present the lack of data, as well as the low quality (predominantly due to low sample sizes), does not support or refute the use of liposomal bupivacaine administered as a peripheral nerve block for the management of postoperative pain.

Overall completeness and applicability of evidence

The main limitations of this review were the small number of trials and heterogeneity of outcome data reporting limiting comparative analysis between trials. Furthermore, the range of different surgical models (bunionectomy, knee replacement, laparoscopic colectomy, laparoscopic hysterectomy, penile prosthesis, shoulder arthroscopy, thoracotomy) and methods of administration of nerve block (ankle block, femoral nerve block, interscalene block, TAP block, dorsal penile nerve block) must be considered and may present significant heterogeneity that may limit statistical analysis.

Quality of the evidence

The quality of evidence was very low across the different outcomes. The major limitation in quality was that all studies were at high risk of bias due to their small sample size (fewer than 50 participants/arm). In addition, due to the small number of included studies presenting results for inclusion in this review, the uncertainty around effect estimates for some outcomes, and inconsistency of results for other outcomes, resulted in further downgrading of the quality of the data.

Potential biases in the review process

Liposomal bupivacaine is a relatively new drug and it is not currently licensed (March 2016) for peripheral nerve block. As such, studies investigating its efficacy and safety are ongoing. While we attempted to minimise bias in this review, new evidence will continue to emerge in this field that may impact on the conclusions drawn. Methods used to minimise the possibility of bias in this review included the use of a comprehensive broad search strategy based on previous Cochrane reviews for RCTs in postoperative pain such that we could identify all relevant studies. In addition, we searched reference lists of potentially relevant studies and reviews, and searched trial registries.

Agreements and disagreements with other studies or reviews

We are not aware of any previous reviews evaluating the efficacy of liposomal bupivacaine administered as a nerve block. Ilfeld has published two reviews evaluating the pharmacokinetics and safety of liposomal bupivacaine administered as a nerve block and, like this review, found no evidence of an increased risk of adverse events or withdrawals associated with its use (Ilfeld 2013; Ilfeld 2015).

AUTHORS' CONCLUSIONS

Implications for practice

A lack of evidence has prevented a quantitative assessment of the efficacy of liposomal bupivacaine administered as a peripheral nerve block. At present there is a lack of data to support or refute the use of liposomal bupivacaine administered as a peripheral nerve block for the management of postoperative pain. Further research is very likely to have an important impact on our confidence in the estimate of effect and is likely to change the estimate.

For people with postoperative pain

The current data cannot support or refute the use of liposomal bupivacaine administered as a peripheral nerve block to reduce postoperative pain. Further evidence is required.

For clinicians

The current data cannot support or refute the use of liposomal bupivacaine administered as a peripheral nerve block to reduce postoperative pain. Further evidence is required.

For policy makers

The current data cannot support or refute the use of liposomal bupivacaine administered as a peripheral nerve block to reduce postoperative pain. Further evidence of clinical, as well as cost effectiveness, is required.

For funders

This review has highlighted the need for further evidence to establish if there is a role for liposomal bupivacaine administered as a peripheral nerve block for the management of postoperative pain. Currently (March 2016) liposomal bupivacaine is not licensed for administration as a peripheral nerve block, and several ongoing studies have yet to report (see [Characteristics of ongoing studies](#) table). It is likely that the results of these ongoing studies will provide further evidence as to the clinical and cost effectiveness of liposomal bupivacaine and that this evidence will highlight areas for further research.

Implications for research

General implications

Further trials are required to establish the clinical and cost effectiveness of liposomal bupivacaine as a peripheral nerve block in the management of acute postoperative pain. Trials should be conducted across a range of surgical sites, with a range of block types, with the results stratified and interpreted in a block and procedure-specific manner. Trials should be focused on surgeries that are known to be associated with significant postoperative pain, particularly surgeries where inadequate pain control may be associated with increased morbidity (i.e. pneumonia following thoracotomy) or delayed hospital discharge (i.e. total knee replacement). Prior to conducting large-scale pragmatic trials, further work is required to establish the optimum dose of liposomal bupivacaine for administration as a peripheral nerve block.

Design

Future trials should be parallel arm, active comparator RCTs. Trials should be well designed and adequately powered, involving more than 200 participants per arm, to reduce the risk of bias. Inclusion criteria for future trials should be broad such that results are applicable to the general population.

Measurement (endpoints)

The gold standard outcome measure for postoperative recovery following surgery has yet to be established. In addition to the absence of pain, people also value the absence of nausea and sedation as well the ability to mobilise and perform self care highly. In addition to the clinical outcome measures of pain scores, opioid usage, and cost-effectiveness outcome measures, future studies should also evaluate patient-reported functional outcome measures, which are likely to be surgery specific, as these outcome measures will provide further informational about the effectiveness of any intervention from the person's perspective.

ACKNOWLEDGEMENTS

The authors wish to thank Joanne Abbott, Information Specialist, for her assistance with developing the search strategy.

TWH funding acknowledgement: supported by the National Institute for Health Research (NIHR) Biomedical Research Centre, based at Oxford University Hospitals Foundation Trust, Oxford. The views expressed are those of the authors and not necessarily those of the National Health Service (NHS), the NIHR, or the Department of Health.

CRG funding acknowledgement: the NIHR is the largest single funder of the Cochrane Pain, Palliative and Supportive Care (Pa-PaS) Review Group. Disclaimer: the views and opinions expressed therein are those of the authors and do not necessarily reflect those of the NIHR, NHS, or the Department of Health.

REFERENCES

References to studies included in this review

Hutchins 2015a {published data only}

Hutchins J, Delaney D, Vogel RI, Ghebre RG, Downs LS Jr, Carson L, et al. Ultrasound guided subcostal transversus abdominis plane (TAP) infiltration with liposomal bupivacaine for patients undergoing robotic assisted hysterectomy: a prospective randomized controlled study. *Gynecologic Oncology* 2015; Vol. 138, issue 3: 609–13. [4356997]

Jrebi 2015 {published data only}

Jrebi N, Ogilvie J, Jaluta T, Figg R, Dujovny N, Luchtefeld M, et al. The transversus abdominis plane block: a prospective randomized controlled trial using Exparel. *Diseases of the colon and rectum* 2015:e299–300. [4356999]

NCT01206595 {published data only}

NCT01206595. Safety, efficacy, and pharmacokinetics of SKY0402 administered as a nerve block in subjects undergoing bunionectomy, 2006. clinicaltrials.gov/ct2/show/NCT01206595 (accessed 24 March 2016). [4357001]

NCT01683071 {published data only}

NCT01683071. Femoral nerve block with liposome bupivacaine for postsurgical analgesia following total knee arthroplasty, 2014. clinicaltrials.gov/ct2/show/NCT01683071 (accessed 24 March 2016). [4357003]

NCT01802411 {published data only}

NCT01802411. Intercostal nerve block with liposome bupivacaine in subjects undergoing posterolateral

thoracotomy, 2013. clinicaltrials.gov/ct2/show/NCT01802411 (accessed 24 March 2016). [4357005]

NCT001919190 {published data only}

NCT001919190. EXPAREL administered by infiltration into the TAP for prolonged postsurgical analgesia in lower abdominal surgeries (TRANSCEND), 2013. clinicaltrials.gov/ct2/show/study/NCT001919190 (accessed 24 March 2016). [4357007]

Nicholson 2014 {published data only}

Nicholson M, Bianco F, Perito P, Perez A, Kislinger I, Gheiler E. Effect of operative local anesthesia on postoperative pain outcomes of inflatable penile prosthesis: prospective comparison of two medications. *Journal of Sexual Medicine* 2014;138–204. [4357009]

References to studies excluded from this review

Boogaerts 1994 {published data only}

Boogaerts JG, Lafont ND, Declercq AG, Luo HC, Gravet ET, Bianchi JA, et al. Epidural administration of liposome-associated bupivacaine for the management of postsurgical pain: a first study. *Journal of Clinical Anesthesia* 1994;6(4): 315–20. [4357011]

Feierman 2014 {published data only}

Feierman DE, Kronenfeld M, Gupta PM, Younger N, Logvinskiy E. Liposomal bupivacaine infiltration into the transversus abdominis plane for postsurgical analgesia in open abdominal umbilical hernia repair: results from a cohort of 13 patients. *Journal of Pain Research* 2014;16: 477–82. [4357013]

Gasanova 2015 {published data only}

Gasanova I, Alexander JC, Ogunnaike B, Hamid C, Rogers D, Minhajuddin A, et al. Transversus abdominis plane block versus surgical site infiltration for pain management after open total abdominal hysterectomy. *Anesthesia and Analgesia* 2015;**121**(5):1383–8. [4357015]

Hutchins 2015b {published data only}

Hutchins J, Vogel RI, Ghebre R, McNally A, Downs LS Jr, Gryzmala E, et al. Ultrasound-guided subcostal transversus abdominis plane infiltration with liposomal bupivacaine for patients undergoing robotic-assisted hysterectomy: a retrospective study. *International Journal of Gynecological Cancer* 2015;**25**(5):937–41. [4357017]

Ilfeld 2013 {published data only}

Ilfeld BM. Liposome bupivacaine in peripheral nerve blocks and epidural injections to manage postoperative pain. *Expert Opinion on Pharmacotherapy* 2013;**14**(17):2421–31. [4357019]

Ilfeld 2015 {published data only}

Ilfeld BM, Viscusi ER, Hadzic A, Minkowitz HA, Morren MD, Lookabaugh J, et al. Safety and side effect profile of liposome bupivacaine (Exparel) in peripheral nerve blocks. *Regional Anaesthesia and Pain Medicine* 2015;**40**(5):572–82. [4357021]

Jrebi 2014 {published data only}

Jrebi N, Szeto P, Hoedema R, Slay H, Figg R, Ogilvie J, et al. TAP block with Exparel decreases postoperative pain and narcotic use in elective colorectal patients. *Diseases of the colon and rectum* 2014;**57**(5):e350. [4357023]

Khalil 2015 {published data only}

Khalil KG, Boutrous ML, Irani AD, Miller CC, Pawelek TR, Estrera AL, et al. Operative intercostal nerve blocks with long-acting bupivacaine liposome for pain control after thoracotomy. *Annals of Thoracic Surgery* 2015;**100**(6): 2013–8. [4357025]

Lagergren 2015 {published data only}

Lagergren E, Boureau C, Reynolds J, Jaffe J, Russell G, Waters G, et al. Effect of Exparel TAP infiltration on postoperative outcomes after laparoscopic colectomy. *Diseases of the Colon and Rectum* 2015;**58**(5):e292. [4357027]

Morales 2013 {published data only}

Morales R Jr, Mentz H 3rd, Newall G, Patronella C, Masters O 3rd. Use of abdominal field block injections with liposomal bupivacaine to control postoperative pain after abdominoplasty. *Aesthetic Surgery Journal* 2013; Vol. 33, issue 8:1148–53. [4357029]

NCT00807209 {published data only}

NCT00807209. Dose finding posterolateral thoracotomy study, 2012. clinicaltrials.gov/ct2/show/NCT00807209 (accessed 24 March 2016). [4357031]

NCT01801124 {published data only}

NCT01801124. EXPAREL infiltrated into the TAP for postoperative analgesia in unilateral abdominal hernia repair (702), 20132. clinicaltrials.gov/ct2/show/NCT01801124 (accessed 24 March 2016). [4357033]

Oppenheimer 2016 {published data only}

Oppenheimer AJ, Fiala TG, Oppenheimer DC. Direct transversus abdominis plane blocks with Exparel during abdominoplasty. *Annals of Plastic Surgery* 2016 Aug 15 [Epub ahead of print]. [4357035]

Sternlicht 2014 {published data only}

Sternlicht A, Shapiro M, Robelen G, Vellayappan U, Tuerk IA. Infiltration of liposome bupivacaine into the transversus abdominis plane for postsurgical analgesia in robotic laparoscopic prostatectomy: a pilot study. *Local and Regional Anesthesia* 2014;**7**:69–74. [4357037]

References to ongoing studies

NCT01826851 {published data only}

NCT01826851. Parasternal nerve block in cardiac patients, 2013. clinicaltrials.gov/ct2/show/NCT01826851 (accessed 24 March 2016). [4357039]

NCT01977352 {published data only}

NCT01977352. Efficacy of interscalene brachial plexus block with liposomal bupivacaine for arthroscopic shoulder surgery, 2013. clinicaltrials.gov/ct2/show/study/NCT01977352 (accessed 24 March 2016). [4357041]

NCT02058303 {published data only}

NCT02058303. Study of a long lasting local anesthetic for hand, wrist or finger surgery, 2014. clinicaltrials.gov/ct2/show/NCT02058303 (accessed 24 March 2016). [4357043]

NCT02178553 {published data only}

NCT02178553. Study of Exparel versus epidural for pain control after thoracotomy, 2014. clinicaltrials.gov/ct2/show/NCT02178553 (accessed 24 March 2016). [4357045]

NCT02179892 {published data only}

NCT02179892. Comparison of Exparel to bupivacaine with dexamethasone in TAP block, 2014. clinicaltrials.gov/ct2/show/NCT02179892 (accessed 24 March 2016). [4357047]

NCT02197273 {published data only}

NCT02197273. Liposomal bupivacaine versus standard analgesia in TJA, 2014. clinicaltrials.gov/ct2/show/NCT02197273 (accessed 24 March 2016). [4357049]

NCT02197988 {published data only}

NCT02197988. TAP versus thoracic epidural in major abdominal resections, 2014. clinicaltrials.gov/ct2/show/NCT02197988 (accessed 24 March 2016). [4357051]

NCT02274077 {published data only}

NCT02274077. Transverse abdominal plane anesthesia for abdominal wall reconstruction, 2014. clinicaltrials.gov/ct2/show/NCT02274077 (accessed 24 March 2016). [4357053]

NCT02356198 {published data only}

NCT02356198. Exparel transversus abdominis plane block vs intrathecal analgesia in colorectal surgery, 2015. clinicaltrials.gov/ct2/show/NCT02356198 (accessed 24 March 2016). [4357055]

NCT02519023 {published data only}

NCT02519023. TAP vs surgical infiltration of local anesthetic in laparoscopic and robotic hysterectomy. clinicaltrials.gov/ct2/show/NCT02519023 (accessed 24 March 2016). [4357057]

NCT02554357 {published data only}

NCT02554357. Quality of analgesia after interscalene block after arthroscopic shoulder surgery, 2015. clinicaltrials.gov/ct2/show/NCT02554357 (accessed 24 March 2016). [4357059]

NCT02591407 {published data only}

NCT02591407. Trial comparing transversus abdominis plane block versus epidural anesthesia for pain management in colorectal surgery, 2015. clinicaltrials.gov/ct2/show/NCT02591407 (accessed 24 March 2016). [4357061]

NCT02607579 {published data only}

NCT02607579. Comparing Exparel & ropivacaine for pain relief in total knee arthroplasty, 2015. clinicaltrials.gov/ct2/show/NCT02607579 (accessed 24 March 2016). [4357063]

NCT02624856 {published data only}

NCT02624856. Liposomal bupivacaine versus standard bupivacaine plus dexamethasone in quadriceps sparing femoral nerve block and wound infiltration for total knee arthroplasty, 2015. clinicaltrials.gov/ct2/show/NCT02624856 (accessed 24 March 2016). [4357065]

NCT02652156 {published data only}

NCT02652156. TAP block for postoperative pain control, 2015. clinicaltrials.gov/ct2/show/NCT02652156 (accessed 24 March 2016). [4357067]

NCT02662036 {published data only}

NCT02662036. Analgesic efficacy of liposomal bupivacaine vs. bupivacaine HCL as a TAP block after abdominally based autologous breast reconstruction, 2016. clinicaltrials.gov/ct2/show/NCT02662036 (accessed 24 March 2016). [4357069]

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**(2):534–40.

Gan 2014

Gan TJ, Habib AS, Miller TE, White W, Apfelbaum JL. Incidence, patient satisfaction, and perceptions of post-surgical pain: results from a US national survey. *Current Medical Research Opinion* 2014;**30**(1):149–60.

Gantenbein 2000

Gantenbein M, Attolini L, Bruguerolle B, Villard PH, Puyou F, Durand A, et al. Oxidative metabolism of bupivacaine into pipercolylxylylidine in humans is mainly catalyzed by CYP3A. *Drug Metabolism and Disposition* 2000;**28**(4):383–5.

GRADEpro 2015 [Computer program]

McMaster University (developed by Evidence Prime, Inc.). GRADEpro Guideline Development Tool. McMaster University (developed by Evidence Prime, Inc.), 2015.

Grant 2004

Grant GJ, Barenholz Y, Bolotin EM, Bansinath M, Turndorf H, Piskoun B, et al. A novel liposomal bupivacaine formulation to produce ultralong-acting analgesia. *Anesthesiology* 2004;**101**(1):133–7.

Hamilton 2017

Hamilton TW, Athanassoglou V, Mellon S, Trivella M, Murray D, Pandit HG. Liposomal bupivacaine infiltration at the surgical site for the management of postoperative pain. *Cochrane Database of Systematic Reviews* 2017, Issue 2. [DOI: 10.1002/14651858.CD011419.pub2]

Higgins 2011

Higgins J, 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.

Jadad 1996

Jadad AR, Moore RA, Carroll D, Jenkinson C, Reynolds DJ, Gavaghan DJ, et al. Assessing the quality of reports of randomized clinical trials: is blinding necessary?. *Controlled Clinical Trials* 1996;**17**(1):1–12.

Kehlet 1993

Kehlet H, Dahl JB. The value of “multimodal” or “balanced analgesia” in postoperative pain treatment. *Anesthesia and Analgesia* 1993;**77**(5):1048–56.

Kehlet 2006

Kehlet H, Jensen TS, Woolf CJ. Persistent postsurgical pain: risk factors and prevention. *Lancet* 2006;**367**(9522):1618–25.

Khan 1996

Khan KS, Daya S, Jadad A. The importance of quality of primary studies in producing unbiased systematic reviews. *Archives of Internal Medicine* 1996;**156**(6):661–6.

Liberati 2009

Liberati A, Altman DG, Tetzlaff J, Mulrow C, Gotzsche PC, Ioannidis JP, et al. The PRISMA statement for reporting systematic reviews and meta-analyses of studies that evaluate health care interventions: explanation and elaboration. *Journal of Clinical Epidemiology* 2009;**62**(10):e1–34.

Lorentzen 2012

Lorentzen V, Hermansen IL, Botti M. A prospective analysis of pain experience, beliefs and attitudes, and pain management of a cohort of Danish surgical patients. *European Journal of Pain* 2012;**16**(2):278–88.

Mantripragada 2002

Mantripragada S. A lipid based depot (DepoFoam((R)) technology) for sustained release drug delivery. *Progress in Lipid Research* 2002;**41**(5):392–406.

Nimmaanrat 2007

Nimmaanrat S, Liabsuetrakul T, Uakritdathikarn T, Wasinwong W. Attitudes, beliefs, and expectations of

gynecological patients toward postoperative pain and its management. *Journal of the Medical Association of Thailand* 2007;**90**(11):2344–51.

RevMan 2014 [Computer program]

The Cochrane Collaboration. Review Manager. Version 5.3. Copenhagen: The Nordic Cochrane Centre: The Cochrane Collaboration, 2014.

Spector 1996

Spector MS, Zasadzinski JA, Sankaram MB. Topology of multivesicular liposomes, a model biliquid foam. *Langmuir*

1996;**12**(20):4704–8.

References to other published versions of this review

Hamilton 2015

Hamilton TW, Athanassoglou V, Trivella M, Mellon S, Murray D, Pandit HG. Liposomal bupivacaine peripheral nerve block for the management of postoperative pain. *Cochrane Database of Systematic Reviews* 2015, Issue 1. [DOI: 10.1002/14651858.CD011476]

* Indicates the major publication for the study

CHARACTERISTICS OF STUDIES

Characteristics of included studies [ordered by study ID]

Hutchins 2015a

Methods	Phase III parallel arm blinded RCT in people undergoing laparoscopic robot-assisted hysterectomy under bilateral subcostal TAP block	
Participants	People undergoing laparoscopic robot-assisted hysterectomy (n = 60) Age ≥ 18 years Location: 1 centre Dates: October 2013 to October 2014	
Interventions	Control or intervention drug administered under ultrasound guidance bilaterally into TAP using standardised technique 30 to 60 minutes prior to operation Control: <ul style="list-style-type: none">● Arm 1: bupivacaine hydrochloride 150 mg with adrenaline 1:200,000 (n = 30) Intervention: <ul style="list-style-type: none">● Arm 2: liposomal bupivacaine 266 mg (n = 30)	
Outcomes	Primary outcomes: <ul style="list-style-type: none">● Cumulative opioid consumption (mg) 0 to 72 hours Secondary outcomes: <ul style="list-style-type: none">● Length of surgery● Estimated blood loss● Intraoperative opioid requirement● Total time in PACU● Total opioid requirement in PACU● Pain score 11-point NRS (0 to 11). Maximum and minimum at 0 to 24, 24 to 48, 48 to 72 hours● Pain medication use● Length of hospital stay● Nausea/vomiting● Participant satisfaction with analgesia	
Notes	Clinical trials reference: NCT02289079 Lead author is consultant for, and has received funding from, Pacira Pharmaceuticals Incorporated	
<i>Risk of bias</i>		
Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Randomisation performed using a random number generator
Allocation concealment (selection bias)	Low risk	Randomisation performed on day of surgery

Hutchins 2015a (Continued)

Blinding of participants and personnel (performance bias) All outcomes	Low risk	TAP blocks performed by 1 of 4 anaesthesiologists who were not blinded to the treatment allocation; however, used a standardised technique to minimise risk of bias
Blinding of outcome assessment (detection bias) All outcomes	Low risk	All surgical, nursing, and research personnel blinded to treatment assignment
Incomplete outcome data (attrition bias) All outcomes	Low risk	1 participant (1.7%) lost to follow-up. 2 participants excluded as operations converted to open procedures
Selective reporting (reporting bias)	Low risk	Reported all outcome measures recorded
Other bias	High risk	High risk of bias - sample size < 50 participants/arm Unclear risk of bias - lead author is consultant for, and has received grant funding from, the manufacturer of liposomal bupivacaine

Jrebi 2015

Methods	Phase III parallel arm blinded RCT in people undergoing elective laparoscopic colectomy under bilateral TAP block
Participants	People undergoing elective laparoscopic colectomy (n = 50) Age ≥ 18 years ASA 1 or 2 Location: 1 centre Dates: not specified
Interventions	Single dose of the control or intervention drug administered after induction of general anaesthesia Control: <ul style="list-style-type: none"> Arm 1: no TAP block (n = 25) Intervention: <ul style="list-style-type: none"> Arm 2: liposomal bupivacaine, dose not specified (n = 25)
Outcomes	Outcomes: <ul style="list-style-type: none"> Cumulative opioid consumption (mg) 0 to 72 hours Mean pain score 0 to 24, 24 to 48, and 48 to 72 hours Incidence of postoperative ileus Length of stay
Notes	Clinical trials reference: NCT02263963

<i>Risk of bias</i>		
Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Not reported
Allocation concealment (selection bias)	Unclear risk	Not reported
Blinding of participants and personnel (performance bias) All outcomes	Unclear risk	Not reported
Blinding of outcome assessment (detection bias) All outcomes	Low risk	Participants and postoperative care team blinded to treatment allocation
Incomplete outcome data (attrition bias) All outcomes	Low risk	No withdrawals or loss to follow-up reported
Selective reporting (reporting bias)	Low risk	Reported all outcome measures recorded
Other bias	High risk	High risk of bias - sample size < 50 participants/arm

NCT01206595

Methods	Adaptive design. Phase II dose-ranging blinded RCT in participants undergoing bunionectomy under ankle block. 4 parallel groups Dose-escalating/de-escalating trial with participants enrolled in consecutive cohorts based on efficacy and safety results of previous cohort
Participants	Participants undergoing bunionectomy (n = 58) Age ≥ 18 years ASA 1 or 2 Location: multicentre (Australia, Belgium, UK, Netherlands) Dates: March 2005 to March 2006
Interventions	Single dose of the control or intervention drug administered as an ankle block, with or without a tourniquet, between 1 hour before the induction of general anaesthesia and 20 minutes before the end of general anaesthesia. The ankle block procedure consisted of 5 injections via 3 skin entries targeting the posterior tibial, sural, deep peroneal, superficial peroneal, and saphenous nerves Control: <ul style="list-style-type: none"> • Arm 1: bupivacaine hydrochloride 125 mg with adrenaline 1:200,000 (n = 20) Intervention: <ul style="list-style-type: none"> • Arm 2: liposomal bupivacaine 155 mg (n = 12) • Arm 3: liposomal bupivacaine 199 mg (n = 12)

	● Arm 4: liposomal bupivacaine 310 mg (n = 14)	
Outcomes	Primary outcome: <ul style="list-style-type: none">● Time to first supplemental pain medication (opioid or non-opioid) within 96 hours Secondary outcomes: <ul style="list-style-type: none">● Adverse events day 0 to day 8● Serious adverse events day 0 to day 30	
Notes	Clinical trials reference: NCT01206595 Sponsor: Pacira Pharmaceuticals Incorporated	
<i>Risk of bias</i>		
Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Not reported
Allocation concealment (selection bias)	Unclear risk	Not reported
Blinding of participants and personnel (performance bias) All outcomes	Low risk	Method of ankle block was standardised and consisted of 5 injections via 3 skin entries targeting the posterior tibial, sural, deep peroneal, superficial peroneal, and saphenous nerves
Blinding of outcome assessment (detection bias) All outcomes	Low risk	Double-blind study with both the participant and investigator blind to treatment allocation
Incomplete outcome data (attrition bias) All outcomes	Low risk	No withdrawals or loss to follow-up reported
Selective reporting (reporting bias)	Low risk	Reported all outcome measures recorded
Other bias	High risk	High risk of bias - sample size < 50 participants/arm Unclear risk of bias - trial conducted by the manufacturer of liposomal bupivacaine. Adaptive design trial with conditional escalation/de-escalation of drug dose

Methods	<p>Phase II/III parallel arm blinded RCT in people undergoing primary unilateral total knee arthroplasty under femoral nerve block. 2 study phases</p> <p>Phase 1: adaptive design. Dose-escalating/de-escalating trial. Participants randomised 1:1:1:1 to receive a femoral nerve block with placebo or 67 mg, 133 mg, or 266 mg liposomal bupivacaine</p> <p>Phase 2: parallel arm study. Participants randomised 1:1 to receive a femoral nerve block with placebo vs. optimum dose from Phase 1</p> <p>Study recorded as completed but results not reported</p>
Participants	<p>People undergoing primary unilateral total knee arthroplasty (sample size not reported)</p> <p>Age \geq 18 years</p> <p>ASA 1 to 3</p> <p>Location: 30 centres (USA)</p> <p>Dates: September 2012 to January 2014</p>
Interventions	<p>Single dose of control or intervention drug administered at time of operation via femoral nerve block under ultrasound guidance</p> <p>2 study phases:</p> <p>Phase 1:</p> <p>Participants randomised 1:1:1:1 to receive a femoral nerve block with:</p> <ul style="list-style-type: none"> • Arm 1: placebo. Normal saline 20 mL <p>Intervention:</p> <ul style="list-style-type: none"> • Arm 2: liposomal bupivacaine 67 mg • Arm 3: liposomal bupivacaine 133 mg • Arm 4: liposomal bupivacaine 266 mg <p>Phase 2:</p> <p>Participants randomised 1:1 to receive a femoral nerve block with:</p> <ul style="list-style-type: none"> • Arm 1: placebo. Normal saline 20 mL <p>Intervention:</p> <ul style="list-style-type: none"> • Arm 2: liposomal bupivacaine optimum dose from Phase 1
Outcomes	<p>Primary outcomes:</p> <ul style="list-style-type: none"> • Cumulative pain score (AUC) 0 to 72 hours • Cumulative postsurgical opioid consumption • Time to first rescue opioid within 96 hours • Adverse events <p>Secondary outcomes:</p> <ul style="list-style-type: none"> • Pain score (NRS) with bowel movement 0 to 96 hours • Time to first bowel movement • Cumulative opioid consumption (mg) 0 to 72 and 96 hours • Time to first rescue opioid within 96 hours • Proportion of participants not requiring rescue opioids • Blinded care provider's satisfaction with analgesia within 96 hours • Quality of life (EuroQol EQ-5D) • Time to resumption of work or daily activities within day 30 • Readiness for discharge using the modified Postanesthesia Discharge Scoring System • Adverse events day 0 to day 30

NCT01683071 (Continued)

Notes	Clinical trials reference: NCT01683071 Sponsor: Pacira Pharmaceuticals Incorporated	
<i>Risk of bias</i>		
Bias	Authors’ judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Not reported
Allocation concealment (selection bias)	Unclear risk	Not reported
Blinding of participants and personnel (performance bias) All outcomes	Low risk	Femoral nerve block performed under ultrasound guidance
Blinding of outcome assessment (detection bias) All outcomes	Low risk	Double-blind study with the participant, investigator, and outcome assessor blind to treatment allocation
Incomplete outcome data (attrition bias) All outcomes	Unclear risk	No outcome data reported
Selective reporting (reporting bias)	Unclear risk	No outcome data reported
Other bias	Unclear risk	Unclear risk of bias - sample size not reported Unclear risk of bias - trial conducted by the manufacturer of liposomal bupivacaine. Adaptive design trial with conditional escalation/de-escalation of drug dose

NCT01802411

Methods	Phase III parallel arm blinded RCT in people undergoing posterolateral thoracotomy under intercostal nerve block Study recorded as completed but results not reported
Participants	People undergoing posterolateral thoracotomy (sample size not reported) Age \geq 18 years ASA 1 to 3 Location: 7 centres (USA) Dates: December 2012 to June 2013
Interventions	Single dose of control or intervention drug administered at time of operation via intercostal nerve block using standardised technique <ul style="list-style-type: none"> • Arm 1: placebo. Normal saline Intervention:

NCT01802411 (Continued)

	<ul style="list-style-type: none">● Arm 2: liposomal bupivacaine 266 mg	
Outcomes	Primary outcome: <ul style="list-style-type: none">● Cumulative pain score (AUC) at rest 0 to 72 hours Secondary outcomes: <ul style="list-style-type: none">● Cumulative postsurgical opioid consumption● Time to first opioid within 24 hours	
Notes	Clinical trials reference: NCT01802411 Sponsor: Pacira Pharmaceuticals Incorporated	
<i>Risk of bias</i>		
Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Not reported
Allocation concealment (selection bias)	Unclear risk	Not reported
Blinding of participants and personnel (performance bias) All outcomes	Low risk	Method of administration of trial/control drug was specified with 6.6 mL, of the total of 20 mL, administered at each of the 3 nerve segments
Blinding of outcome assessment (detection bias) All outcomes	Low risk	Double-blind study with the participant, investigator, and outcome assessor blind to treatment allocation
Incomplete outcome data (attrition bias) All outcomes	Unclear risk	No outcome data reported
Selective reporting (reporting bias)	Unclear risk	No outcome data reported
Other bias	Unclear risk	Unclear risk of bias - sample size not reported Unclear risk of bias - trial conducted by the manufacturer of liposomal bupivacaine

NCT01919190

Methods	<p>Phase III parallel arm blinded RCT in people undergoing laparoscopic lower abdominal surgery (hysterectomy, myomectomy, or colectomy) under TAP block</p> <p>Study recorded as terminated due to reasons unrelated to safety. Trial had reached milestone for prespecified interim analysis. No results reported</p>
---------	---

Participants	Participants undergoing elective laparoscopic lower abdominal surgery (sample size not reported) Age \geq 18 years ASA 1 to 3 Location: 10 centres (USA) Dates: August 2013 to December 2013
Interventions	Single dose of control or intervention drug administered at time of operation via bilateral TAP block using standardised technique <ul style="list-style-type: none"> • Arm 1: no TAP block Intervention: <ul style="list-style-type: none"> • Arm 2: liposomal bupivacaine 266 mg
Outcomes	Primary outcomes: <ul style="list-style-type: none"> • Total opioid consumption 0 to 96 hours • Overall benefit of analgesic score 0, 24, 48, 72, and 96 hours Secondary outcomes: <ul style="list-style-type: none"> • Extent and degree of anaesthetic blockade 0, 24, 48, 72, and 96 hours • Severity of postsurgical pain • Quality of recovery 15 • Frequency of participant calls postdischarge related to pain and unscheduled hospital/surgeon visits. Discharge to 96 hours
Notes	Clinical trials reference: NCT001919190 Sponsor: Pacira Pharmaceuticals Incorporated

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Not reported
Allocation concealment (selection bias)	Unclear risk	Not reported
Blinding of participants and personnel (performance bias) All outcomes	High risk	No placebo
Blinding of outcome assessment (detection bias) All outcomes	High risk	Participants not blinded
Incomplete outcome data (attrition bias) All outcomes	Unclear risk	Study terminated
Selective reporting (reporting bias)	Unclear risk	No outcome data reported

Other bias	Unclear risk	Unclear risk of bias - sample size not reported Unclear risk of bias - study sponsored by the manufacturer of liposomal bupivacaine
------------	--------------	--

Nicholson 2014

Methods	Phase III parallel arm blinded RCT in people undergoing inflatable penile prosthesis implantation under dorsal penile nerve block. 3 arms comparing: no nerve block (n = 44), ropivacaine hydrochloride (n = 47), and liposomal bupivacaine (n = 40)
Participants	People undergoing inflatable penile prosthesis implantation (n = 131) Location: 1 centre Dates: January 2013 to June 2013
Interventions	Single dose of control or intervention drug administered at time of operation as a dorsal penile nerve block Control <ul style="list-style-type: none"> • Arm 1: no nerve block (n = 44) • Arm 2: ropivacaine hydrochloride, dose not specified (n = 47) Intervention: <ul style="list-style-type: none"> • Arm 3: liposomal bupivacaine, dose not specified (n = 40)
Outcomes	Outcomes: <ul style="list-style-type: none"> • Pain scores (visual analogue scale) • Time to first rescue opioid within 96 hours • Daily supplemental analgesic medication requirement within 7 days postoperatively
Notes	Clinical trials reference: not identified

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Not reported
Allocation concealment (selection bias)	Unclear risk	Not reported
Blinding of participants and personnel (performance bias) All outcomes	Unclear risk	Not reported
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	Not reported

Nicholson 2014 (Continued)

Incomplete outcome data (attrition bias) All outcomes	Low risk	No withdrawals or loss to follow-up reported
Selective reporting (reporting bias)	Low risk	Reported all outcome measures recorded
Other bias	High risk	High risk of bias - sample size < 50 participants/arm

ASA: American Society of Anaesthesiologists Score;

AUC: area under curve;

n: number of participants;

NRS: numerical rating scale;

PACU: postanesthesia care unit;

RCT: randomised controlled trial;

TAP: transversus abdominis plane

.

Characteristics of excluded studies [ordered by study ID]

Study	Reason for exclusion
Boogaerts 1994	Non-randomised controlled trial. People administered liposomal bupivacaine postoperatively
Feierman 2014	Open-label sequential cohort study
Gasanova 2015	Randomised controlled trial comparing liposomal bupivacaine at the surgical site with bupivacaine hydrochloride TAP block. Participants not blinded
Hutchins 2015b	Retrospective cohort study
Ilfeld 2013	Review of clinical trials efficacy and pharmacokinetics
Ilfeld 2015	Review of clinical trials safety and adverse events
Jrebi 2014	Retrospective cohort study
Khalil 2015	Open-label sequential cohort study
Lagergren 2015	Retrospective case control series
Morales 2013	Open-label sequential cohort study
NCT00807209	Study terminated early (after 3 participants enrolled) due to administrative reasons. Study not blinded

(Continued)

NCT01801124	Open-label sequential cohort study
Oppenheimer 2016	Open-label sequential cohort study
Sternlicht 2014	Open-label sequential cohort study (NCT01582477)

TAP: transversus abdominis plane.

Characteristics of ongoing studies *[ordered by study ID]*

[NCT01826851](#)

Trial name or title	Parasternal Nerve Block in Cardiac Patients
Methods	Parallel arm randomised controlled trial
Participants	Participants undergoing median sternotomy for primary cardiopulmonary bypass grafting surgery
Interventions	Liposomal bupivacaine (parasternal nerve block) vs. placebo (parasternal nerve block)
Outcomes	Efficacy Time to extubation (hours) Intensive care unit length of stay (hours) Time to return of bowel function (days) Hospital length of stay (days)
Starting date	March 2013
Contact information	ClinicalTrials.gov/show/NCT01826851 Last accessed 24 March 2016
Notes	Currently recruiting

[NCT01977352](#)

Trial name or title	Efficacy of Interscalene Brachial Plexus Block with Liposomal Bupivacaine for Arthroscopic Shoulder Surgery
Methods	Parallel arm randomised controlled trial
Participants	Participants undergoing elective arthroscopic shoulder surgery
Interventions	Liposomal bupivacaine (interscalene nerve block) vs. bupivacaine hydrochloride (interscalene nerve block)

NCT01977352 (Continued)

Outcomes	Total opioid consumption 0 to 72 hours Quality of analgesia. NRS at 24, 48, and 72 hours and 1 week postoperatively Onset and duration of sensory block 0 to 72 hours Time to first pain medicine 0 to 72 hours Time to discharge home 0 to 72 hours Incidence of postoperative nausea and vomiting 0 to 72 hours
Starting date	January 2014
Contact information	ClinicalTrials.gov/show/NCT01977352 Last accessed 24 March 2016
Notes	Recruitment complete Sponsor contacted 28 January 2016 - results not available

NCT02058303

Trial name or title	Study of a Long Lasting Local Anesthetic for Hand, Wrist or Finger Surgery
Methods	Parallel arm randomised controlled trial
Participants	Participants undergoing hand, wrist, or finger surgery
Interventions	Liposomal bupivacaine (supraclavicular nerve block) vs. bupivacaine hydrochloride (supraclavicular nerve block)
Outcomes	Onset of sensorimotor block
Starting date	February 2014
Contact information	ClinicalTrials.gov/show/NCT02058303 Last accessed 24 March 2016
Notes	Currently recruiting

NCT02178553

Trial name or title	Study of Exparel versus Epidural for Pain Control after Thoracotomy
Methods	Parallel arm randomised controlled trial
Participants	Participants undergoing thoracotomy (lobectomy, segmentectomy, wedge resection, or pneumonectomy)
Interventions	Liposomal bupivacaine (intercostal nerve block) vs. epidural analgesia
Outcomes	Pain scores with cough within first 48 hours Pain scores and medication at 3-month follow-up

NCT02178553 (Continued)

Starting date	August 2014
Contact information	ClinicalTrials.gov/show/NCT02178553 Last accessed 24 March 2016
Notes	Currently recruiting

NCT02179892

Trial name or title	Comparison of Exparel to Bupivacaine with Dexamethasone in TAP Block
Methods	Parallel arm randomised controlled trial
Participants	Participants undergoing scheduled abdominal surgery
Interventions	Liposomal bupivacaine vs. bupivacaine hydrochloride
Outcomes	Total amount of opioid consumption at 72 hours after surgery VAS pain score at rest VAS pain score with movement Time of first opioid use after surgical procedure
Starting date	July 2014
Contact information	ClinicalTrials.gov/show/NCT02179892 Last accessed 24 March 2016
Notes	Currently recruiting

NCT02197273

Trial name or title	Liposomal Bupivacaine versus Standard Analgesia in TJA
Methods	Parallel arm randomised controlled trial
Participants	Participants undergoing TJA (hip, knee, shoulder)
Interventions	Liposomal bupivacaine vs. standard care (spinal anaesthetic plus joint infiltration, spinal anaesthetic plus adductor canal block plus joint infiltration, interscalene block plus joint infiltration with indwelling catheter)
Outcomes	Length of stay in hospital (days) Time to postoperative rescue opioids (minutes) Re-admission or emergency department visit due to pain control within 30 days
Starting date	July 2014

NCT02197273 (Continued)

Contact information	ClinicalTrials.gov/show/NCT02197273 Last accessed 24 March 2016
Notes	Currently recruiting

NCT02197988

Trial name or title	TAP versus Thoracic Epidural in Major Abdominal Resections
Methods	Parallel arm randomised controlled trial
Participants	Participants undergoing major abdominal resection (including: pancreaticoduodenectomies, distal pancreatectomies, bowel resection, liver resection, oesophagectomies, heated intraperitoneal chemotherapy, retroperitoneal excisions, and large genitourinary procedures)
Interventions	Liposomal bupivacaine (TAP block) vs. bupivacaine hydrochloride (thoracic epidural)
Outcomes	Hypotension Participant satisfaction relative to pain control and amount of additional narcotic usage
Starting date	July 2014
Contact information	ClinicalTrials.gov/show/NCT02197988 Last accessed 24 March 2016
Notes	Currently recruiting

NCT02274077

Trial name or title	Transverse Abdominal Plane Anesthesia for Abdominal Wall Reconstruction
Methods	Parallel arm randomised controlled trial
Participants	Participants undergoing open abdominal wall reconstruction
Interventions	Liposomal bupivacaine (TAP block) vs. placebo (TAP block)
Outcomes	Length of stay Postoperative nausea Postoperative emesis Postoperative return of bowel function Postoperative pain score Adjunct narcotic pain medication use
Starting date	January 2016

NCT02274077 (Continued)

Contact information	ClinicalTrials.gov/show/NCT02274077 Last accessed 24 March 2016
Notes	Yet to recruit

NCT02356198

Trial name or title	Exparel Transversus Abdominis Plane Block vs Intrathecal Analgesia in Colorectal Surgery
Methods	Parallel arm randomised controlled trial
Participants	Participants undergoing colorectal surgery
Interventions	Liposomal bupivacaine (TAP block) vs. intrathecal analgesia
Outcomes	Pain scores, length of stay
Starting date	March 2015
Contact information	ClinicalTrials.gov/show/NCT02356198 Last accessed 24 March 2016
Notes	Currently recruiting

NCT02519023

Trial name or title	TAP vs Surgical Infiltration of Local Anesthetic in Laparoscopic and Robotic Hysterectomy
Methods	Parallel arm randomised controlled trial
Participants	Participants undergoing laparoscopic and robotic hysterectomy
Interventions	Liposomal bupivacaine (TAP block) vs. bupivacaine hydrochloride (local infiltration)
Outcomes	Total opioid use for pain control Maximum and minimum pain scores as measured by pain NRS (0 to 10) Total opioid taken by participant as tabulated and converted to morphine equivalents Quality of Recovery 15 (QoR15) Score, Overall Benefit of Analgesia Score Incidences of nausea and vomiting Length of time in phase 1 and phase 2 of recovery Number of participants admitted postoperatively
Starting date	September 2015
Contact information	ClinicalTrials.gov/show/NCT02519023 Last accessed 24 March 2016

NCT02519023 (Continued)

Notes	Yet to recruit
-------	----------------

NCT02554357

Trial name or title	Quality of Analgesia after Interscalene Block after Arthroscopic Shoulder Surgery
Methods	Parallel arm randomised controlled trial
Participants	Participants undergoing arthroscopic shoulder surgery
Interventions	Liposomal bupivacaine (interscalene nerve block) vs. bupivacaine hydrochloride (interscalene nerve block)
Outcomes	Total opioid consumption for 72 hours postsurgery Onset of sensory block Duration of sensory block Onset of motor block Duration of motor block
Starting date	July 2015
Contact information	ClinicalTrials.gov/show/NCT02662036 Last accessed 24 March 2016
Notes	Currently recruiting

NCT02591407

Trial name or title	Trial Comparing Transversus Abdominis Plane Block versus Epidural Anesthesia for Pain Management in Colorectal Surgery
Methods	Parallel arm randomised controlled trial
Participants	Participants undergoing elective colorectal surgery
Interventions	Liposomal bupivacaine (TAP block) vs. epidural
Outcomes	Postoperative pain control day 1 using pain NRS Postoperative pain control day 2 using pain NRS Postoperative pain control day 3 using pain NRS Overall benefits of analgesia treatment postoperative day 1 Overall benefits of analgesia treatment postoperative day 2 Overall benefits of analgesia treatment postoperative day 3
Starting date	October 2015
Contact information	ClinicalTrials.gov/show/NCT02591407 Last accessed 24 March 2016

NCT02591407 (Continued)

Notes	Currently recruiting
-------	----------------------

NCT02607579

Trial name or title	Comparing Exparel & Ropivacaine for Pain Relief in Total Knee Arthroplasty
Methods	Parallel arm randomised controlled trial
Participants	Participants undergoing total knee arthroplasty
Interventions	Liposomal bupivacaine (adductor canal block) vs. ropivacaine hydrochloride (adductor canal block)
Outcomes	Pain relief Length of stay Postoperative range of motion Postoperative distance walked Quantity of narcotics required
Starting date	January 2015
Contact information	ClinicalTrials.gov/show/NCT02607579 Last accessed 24 March 2016
Notes	Currently recruiting

NCT02624856

Trial name or title	Liposomal Bupivacaine Versus Standard Bupivacaine Plus Dexamethasone in Quadriceps Sparing Femoral Nerve Block and Wound Infiltration for Total Knee Arthroplasty
Methods	Parallel arm randomised controlled trial
Participants	Participants undergoing total knee arthroplasty
Interventions	Liposomal bupivacaine (femoral nerve block plus local infiltration) vs. bupivacaine hydrochloride (femoral nerve block plus local infiltration)
Outcomes	Achievement of rehabilitative goals Mean postoperative pain score assessment (24, 48, and 72 hours postoperatively)
Starting date	November 2015
Contact information	ClinicalTrials.gov/show/NCT02624856 Last accessed 24 March 2016
Notes	Currently recruiting

NCT02652156

Trial name or title	TAP Block for Postoperative Pain Control
Methods	Parallel arm randomised controlled trial
Participants	Participants undergoing open abdominal surgery
Interventions	Liposomal bupivacaine (TAP block) vs. bupivacaine hydrochloride (TAP block) vs. ropivacaine hydrochloride (TAP block with continuous infiltration)
Outcomes	Total dosage of narcotic Postoperative vomiting (events) Participant-reported pain by VAS Number of days required for a participant to get out of bed Number of days required for a participant to walk unassisted
Starting date	November 2015
Contact information	ClinicalTrials.gov/show/NCT02652156 Last accessed 24 March 2016
Notes	Study ongoing

NCT02662036

Trial name or title	Analgesic Efficacy of Liposomal Bupivacaine vs. Bupivacaine HCl as a Tap Block after Abdominally Based Autologous Breast Reconstruction
Methods	Parallel arm randomised controlled trial
Participants	Participants undergoing abdominal-based autologous breast reconstruction (DIEP, MS-TRAM, or TRAM)
Interventions	Liposomal bupivacaine (TAP block) vs. bupivacaine hydrochloride (TAP block)
Outcomes	Total opioid use during hospital stay Total antiemetic use during the hospital stay Length of hospital stay Time until ambulation Time until urinary catheter removal Pain scores Participant satisfaction with recovery Cost when accounting for length of hospital stay and use of other analgesics
Starting date	February 2016
Contact information	ClinicalTrials.gov/show/NCT02662036 Last accessed 24 March 2016
Notes	Yet to recruit

DIEP: deep inferior epigastric perforators;
MS-TRAM: muscle-sparing transverse rectus abdominis myocutaneous;
NRS: numerical rating scale;
TAP: transversus abdominis plane;
TJA: total joint arthroplasty;
TRAM: transverse rectus abdominis myocutaneous;
VAS: visual analogue scale.

DATA AND ANALYSES

This review has no analyses.

APPENDICES

Appendix I. Search strategies

CENTRAL (*The Cochrane Library*)

- #1 (Liposom* near/5 bupivacaine) or (depo* near/5 bupivacaine):ti,ab,kw (Word variations have been searched)
- #2 exparel or SKY0402:ti,ab,kw (Word variations have been searched)
- #3 #1 or #2
- #4 MeSH descriptor: [Pain, Postoperative] this term only
- #5 ((postoperative near/4 pain*) or (post-operative near/4 pain*) or post-operative-pain* or (post* near/4 pain*) or (postoperative near/4 analgesi*) or (post-operative near/4 analgesi*) or ("post-operative analgesi*")):ti,ab,kw (Word variations have been searched)
- #6 ((post-surgical near/4 pain*) or ("post surgical" near/4 pain*) or (post-surgery near/4 pain*)):ti,ab,kw (Word variations have been searched)
- #7 ("pain-relief after surg*" or "pain following surg*" or "pain control after"):ti,ab,kw (Word variations have been searched)
- #8 ("post surg*" or post-surg*) and (pain* or discomfort):ti,ab,kw (Word variations have been searched)
- #9 ((pain* near/4 "after surg*") or (pain* near/4 "after operat*") or (pain* near/4 "follow* operat*") or (pain* near/4 "follow* surg*")):ti,ab,kw (Word variations have been searched)
- #10 ((analgesi* near/4 "after surg*") or (analgesi* near/4 "after operat*") or (analgesi* near/4 "follow* operat*") or (analgesi* near/4 "follow* surg*")):ti,ab,kw (Word variations have been searched)
- #11 #4 or #5 or #6 or #7 or #8 or #9 or #10
- #12 #3 and #11

MEDLINE (Ovid)

- 1. (Liposom* adj5 bupivacaine).mp. or (depo* adj5 bupivacaine).tw. [mp=title, abstract, original title, name of substance word, subject heading word, keyword heading word, protocol supplementary concept word, rare disease supplementary concept word, unique identifier]
- 2. exparel.mp. or SKY0402.tw. [mp=title, abstract, original title, name of substance word, subject heading word, keyword heading word, protocol supplementary concept word, rare disease supplementary concept word, unique identifier]
- 3. Pain, Postoperative/
- 4. ((postoperative adj4 pain*) or (post-operative adj4 pain*) or post-operative-pain* or (post* adj4 pain*) or (postoperative adj4 analgesi*) or (post-operative adj4 analgesi*) or "post-operative analgesi*").mp.
- 5. ((post-surgical adj4 pain*) or ("post surgical" adj4 pain*) or (post-surgery adj4 pain*)).mp.
- 6. ("pain-relief after surg*" or "pain following surg*" or "pain control after").mp.
- 7. (("post surg*" or post-surg*) and (pain* or discomfort)).mp.
- 8. ((pain* adj4 "after surg*") or (pain* adj4 "after operat*") or (pain* adj4 "follow* operat*") or (pain* adj4 "follow* surg*")).mp.
- 9. ((analgesi* adj4 "after surg*") or (analgesi* adj4 "after operat*") or (analgesi* adj4 "follow* operat*") or (analgesi* adj4 "follow* surg*")).mp.
- 10. or/3-9
- 11. randomized controlled trial.pt.
- 12. controlled clinical trial.pt.
- 13. randomized.ab.
- 14. placebo.ab.
- 15. drug therapy.fs.
- 16. randomly.ab.
- 17. trial.ab.
- 18. or/11-17

19. exp animals/ not humans.sh.

20. 18 not 19

21. 1 or 2

22. 10 and 20 and 21

EMBASE (Ovid)

1. (Liposom* adj5 bupivacaine).mp. or (depo* adj5 bupivacaine).tw. [mp=title, abstract, subject headings, heading word, drug trade name, original title, device manufacturer, drug manufacturer, device trade name, keyword]

2. exparel.mp. or SKY0402.tw. [mp=title, abstract, subject headings, heading word, drug trade name, original title, device manufacturer, drug manufacturer, device trade name, keyword]

3. Pain, Postoperative/

4. ((postoperative adj4 pain*) or (post-operative adj4 pain*) or post-operative-pain* or (post* adj4 pain*) or (postoperative adj4 analgesi*) or (post-operative adj4 analgesi*) or "post-operative analgesi*").mp.

5. ((post-surgical adj4 pain*) or ("post surgical" adj4 pain*) or (post-surgery adj4 pain*)).mp.

6. ("pain-relief after surg*" or "pain following surg*" or "pain control after").mp.

7. (("post surg*" or post-surg*) and (pain* or discomfort)).mp.

8. ((pain* adj4 "after surg*") or (pain* adj4 "after operat*") or (pain* adj4 "follow* operat*") or (pain* adj4 "follow* surg*")).mp.

9. ((analgesi* adj4 "after surg*") or (analgesi* adj4 "after operat*") or (analgesi* adj4 "follow* operat*") or (analgesi* adj4 "follow* surg*")).mp.

10. or/3-9

11. 1 or 2

12. 10 and 11

13. random\$.tw.

14. factorial\$.tw.

15. crossover\$.tw.

16. cross over\$.tw.

17. cross-over\$.tw.

18. placebo\$.tw.

19. (doubl\$ adj blind\$).tw.

20. (singl\$ adj blind\$).tw.

21. assign\$.tw.

22. allocat\$.tw.

23. volunteer\$.tw.

24. Crossover Procedure/

25. double-blind procedure.tw.

26. Randomized Controlled Trial/

27. Single Blind Procedure/

28. or/13-27

29. (animal/ or nonhuman/) not human/

30. 28 not 29

31. 12 and 30

ISI Web of Science

#16 #15 AND #11

#15 #14 OR #13 OR #12

#14 TOPIC: (((singl* OR doubl* OR trebl* OR tripl*) SAME (blind* OR mask*))))

#13 TOPIC: (((controlled clinical trial OR controlled trial OR clinical trial OR placebo)))

#12 TOPIC: (((randomised OR randomized OR randomly OR random order OR random sequence OR random allocation OR randomly allocated OR at random OR randomized controlled trial)))

#11 #10 AND #3

#10 #9 OR #8 OR #7 OR #6 OR #5 OR #4

#9 TOPIC: (((analgesi* near/4 "after surg*" or (analgesi* near/4 "after operat*") or (analgesi* near/4 "follow* operat*") or (analgesi* near/4 "follow* surg*")))

#8 TOPIC: (((pain* near/4 "after surg*" or (pain* near/4 "after operat*") or (pain* near/4 "follow* operat*") or (pain* near/4 "follow* surg*")))

#7 TOPIC: (((“post surg*” or post-surg*) and (pain* or discomfort)))
 #6 TOPIC: ((“pain-relief after surg*” or “pain following surg*” or “pain control after”))
 #5 TOPIC: (((post-surgical near/4 pain*) or (“post surgical” near/4 pain*) or (post-surgery near/4 pain*)))
 #4 TOPIC: (((postoperative near/4 pain*) or (post-operative near/4 pain*) or post-operative-pain* or (post* near/4 pain*) or (postop-
 erative near/4 analgesi*) or (post-operative near/4 analgesi*) or (“post-operative analgesi*”)))
 #3 #2 OR #1
 #2 TOPIC: (exparel or SKY0402)
 #1 TOPIC: ((Liposom* near/5 bupivacaine) or (depo* near/5 bupivacaine))

FEEDBACK

Feedback received, 12 September 2016

Summary

Name: Simon Dagenais

Email Address:

simon.dagenais@pacira.com

Affiliation: Pacira Pharmaceuticals, Inc.

Role: Senior director, health outcomes and value assessment

Comment: To whom it may concern:

I work in the health outcomes and value assessment group at Pacira Pharmaceuticals, Inc., the manufacturer of EXPAREL® (bupivacaine liposome injectable suspension), which is occasionally referred to as “liposomal bupivacaine” in the literature. I therefore read the review by Hamilton et al (“Liposomal bupivacaine peripheral nerve block for the management of postoperative pain”) with great interest (Hamilton, 2016). And while I agree with the authors that postoperative pain is a significant issue and that inadequate management is associated with a variety of important clinical and economic outcomes, I must question two aspects of their review.

First, it is unclear why a Cochrane review would be initiated to synthesize evidence pertaining to an unapproved use of a relatively new drug. EXPAREL (“liposomal bupivacaine”) was approved by the United States (US) Food and Drug Administration (FDA) in October 2011 for “single-dose infiltration into the surgical site to produce postsurgical analgesia” (Pacira Pharmaceuticals Inc., 2012). Since this indication precludes using EXPAREL for peripheral nerve block, it should come as no surprise that the review concluded “A lack of evidence has prevented an assessment of the efficacy of liposomal bupivacaine administered as a peripheral nerve block”. It’s somewhat unclear why the authors expected a different conclusion.

Second, although this review was focused on the use of EXPAREL for peripheral nerve block, it included two studies in which EXPAREL was administered into the transversus abdominis plane (TAP). Despite its name, a TAP “block” is not considered a peripheral nerve block because it targets a specific tissue plane (ie, TAP) rather than a specific peripheral nerve. The use of EXPAREL for TAP “block” is therefore consistent with its currently approved indication of infiltration into the surgical site, as described in a letter from the US FDA (Woodcock, 2015). The authors should reconsider the inclusion of these studies in their review pertaining to peripheral nerve block and perhaps include them in their review on the use of EXPAREL for local infiltration, which appears to be in development (Hamilton, 2014).

Respectfully,

Simon Dagenais, PhD, MSc

References

Hamilton TW, Athanassoglou V, Mellon S, Trivella M, Murray D, Pandit HG, et al. Liposomal bupivacaine infiltration at the surgical site for the management of postoperative pain. 2014.

Hamilton TW, Athanassoglou V, Trivella M, Strickland LH, Mellon S, Murray D, et al. Liposomal bupivacaine peripheral nerve block for the management of postoperative pain. *Cochrane Database Syst Rev*. 2016;8:CD011476.

Pacira Pharmaceuticals Inc. EXPAREL Prescribing Information (old). Pacira Pharmaceuticals Inc.; Parsippany, NJ; 2012.

Woodcock J. Pacira Pharmaceuticals, Inc. U.S. Food and Drug Administration; Rockville, MD; 2015.

Do you have any affiliation with or involvement in any organisation with a financial interest in the subject matter of your comment?

Full-time employee of Pacira Pharmaceuticals, Inc., the manufacturer of EXPAREL, which is referred to as “liposomal bupivacaine” in this review.

Reply

Dear Dr Dagenais,

Thank you for your interest in our review.

In our review we have acknowledged that liposomal bupivacaine is a recent addition to our armamentarium and as such further evidence as to its effectiveness is required, and that future studies may change our estimate of effect. We have performed the review as local anaesthetic peripheral nerve blocks using a range of drugs are common. As such, where evidence exists around the effectiveness of a drug we feel that it is important that this is reviewed. Whilst, as you state, EXPAREL (bupivacaine liposome injectable suspension) is currently not licenced for peripheral nerve block we think that the information presented in this review is relevant in cases where the drug is used outside of its current licenced indications, for example in clinical trials. Additionally, the information presented in this review will be relevant should EXPAREL be licenced for use in peripheral nerve blocks, in which case we would update the information presented.

Thank you for confirming that the use of EXPAREL for a TAP block is consistent with its currently approved indication as outlined in a letter from the US FDA (Woodcock, 14 December 2015). As a TAP block is a field block, administered proximal to the surgical site, providing blockade to the lower thoracic and upper lumbar spinal nerves, we decided to include it in the current review as it is administered proximal to the surgical site. We acknowledge that the effectiveness of liposomal bupivacaine TAP blocks and liposomal bupivacaine peripheral nerve blocks have the potential to be different and as such have considered the data separately. In future updates of this review we will continue to consider these two techniques separately and will explicitly state the current licencing status for each.

Yours sincerely,

Thomas Hamilton, Vassilis Athanassoglou & Hemant Pandit

Contributors

Feedback Editor Kate Seers, Managing Editor Anna Erskine, and Co-ordinating Editor Christopher Eccleston.

WHAT'S NEW

Last assessed as up-to-date: 15 January 2016.

Date	Event	Description
2 February 2017	Amended	Hamilton reference updated.

HISTORY

Protocol first published: Issue 1, 2015

Review first published: Issue 8, 2016

Date	Event	Description
3 October 2016	Feedback has been incorporated	See Feedback .

CONTRIBUTIONS OF AUTHORS

Thomas Hamilton lead this review and wrote the protocol and manuscript.

Vassilis Athanassoglou and Louise Strickland identified relevant studies, extracted data, and assessed studies for risk of bias.

Marialena Trivella wrote the statistical methods.

Joanne Abbott, Information Specialist, designed the search strategy with input from Thomas Hamilton.

The other review authors provided input throughout the development of the protocol and writing of this review.

DECLARATIONS OF INTEREST

TWH: none known; TWH is an orthopaedic registrar and manages patients with peri- and postoperative pain. TWH receives funding from the National Institute for Health Research (NIHR).

VA: none known; VA is a consultant anaesthetist and manages patients with peri and postoperative pain.

MT: none known.

LHS: none known; LHS is a nurse and surgical assistant and manages people with peri- and postoperative pain.

SM: none known.

DM is a consultant orthopaedic surgeon and manages patients with peri- and postoperative pain. DM receives funding from Zimmer Biomet (1998 to present) who manufacture orthopaedic implants, including knee replacements.

HGP is a consultant orthopaedic surgeon and manages patients with peri- and postoperative pain. HGP receives funding from Zimmer Biomet (2015 to present) who manufacture orthopaedic implants, including knee replacements.

SOURCES OF SUPPORT

Internal sources

- No sources of support supplied

External sources

- National Institute for Health Research (NIHR), UK.

TWH is supported by the NIHR Biomedical Research Centre, based at Oxford University Hospitals Foundation Trust, Oxford.

DIFFERENCES BETWEEN PROTOCOL AND REVIEW

We completed a GRADE assessment for all included studies, in line with current Cochrane guidance. This was not included in the protocol ([Hamilton 2015](#)).

INDEX TERMS

Medical Subject Headings (MeSH)

Anesthetics, Local [*administration & dosage]; Bupivacaine [*administration & dosage]; Liposomes; Nerve Block [*methods]; Pain Measurement; Pain, Postoperative [*therapy]; Peripheral Nervous System; Randomized Controlled Trials as Topic

MeSH check words

Humans