Cochrane Library

Cochrane Database of Systematic Reviews

Parenteral opioids for maternal pain management in labour (Review)

Smith LA, Burns E, Cuthbert A

Smith LA, Burns E, Cuthbert A.
Parenteral opioids for maternal pain management in labour.
Cochrane Database of Systematic Reviews 2018, Issue 6. Art. No.: CD007396.
DOI: 10.1002/14651858.CD007396.pub3.

www.cochranelibrary.com

WILEY

TABLE OF CONTENTS

[Intervention Review]

Parenteral opioids for maternal pain management in labour

Lesley A Smith[1], Ethel Burns[2], Anna Cuthbert[3]

[1]Department of Psychology, Social Work and Public Health, Oxford Brookes University, Oxford, UK. [2]Department of Psychology, Social Work and Public Health, Faculty of Health and Life Sciences, Oxford Brookes University, Oxford, UK. [3]Cochrane Pregnancy and Childbirth Group, Department of Women's and Children's Health, The University of Liverpool, Liverpool, UK

Contact address: Lesley A Smith, Department of Psychology, Social Work and Public Health, Oxford Brookes University, Jack Straws Lane, Marston, Oxford, OX3 0FL, UK. Lesley.Smith@hull.ac.uk.

Editorial group: Cochrane Pregnancy and Childbirth Group.
Publication status and date: New search for studies and content updated (no change to conclusions), published in Issue 6, 2018.

Citation: Smith LA, Burns E, Cuthbert A. Parenteral opioids for maternal pain management in labour. *Cochrane Database of Systematic Reviews* 2018, Issue 6. Art. No.: CD007396. DOI: 10.1002/14651858.CD007396.pub3.

ABSTRACT

Background

Parenteral opioids (intramuscular and intravenous drugs including patient-controlled analgesia) are used for pain relief in labour in many countries throughout the world. This review is an update of a review first published in 2010.

Objectives

To assess the effectiveness, safety and acceptability to women of different types, doses and modes of administration of parenteral opioid analgesia in labour. A second objective is to assess the effects of opioids in labour on the baby in terms of safety, condition at birth and early feeding.

Search methods

We searched Cochrane Pregnancy and Childbirth's Trials Register, ClinicalTrials.gov, the WHO International Clinical Trials Registry Platform (ICTRP) (11 May 2017) and reference lists of retrieved studies.

Selection criteria

We included randomised controlled trials examining the use of intramuscular or intravenous opioids (including patient-controlled analgesia) for women in labour. Cluster-randomised trials were also eligible for inclusion, although none were identified. We did not include quasi-randomised trials. We looked at studies comparing an opioid with another opioid, placebo, no treatment, other non-pharmacological interventions (transcutaneous electrical nerve stimulation (TENS)) or inhaled analgesia.

Data collection and analysis

Two review authors independently assessed trials for inclusion and risk of bias, extracted data and checked them for accuracy. We assessed the quality of each evidence synthesis using the GRADE approach.

Main results

We included 70 studies that compared an opioid with placebo or no treatment, another opioid administered intramuscularly or intravenously or compared with TENS applied to the back. Sixty-one studies involving more than 8000 women contributed data to the review and these studies reported on 34 different comparisons; for many comparisons and outcomes only one study contributed data. All of the studies were conducted in hospital settings, on healthy women with uncomplicated pregnancies at 37 to 42 weeks' gestation. We excluded studies focusing on women with pre-eclampsia or pre-existing conditions or with a compromised fetus. Overall,

the evidence was graded as low- or very low-quality regarding the analgesic effect of opioids and satisfaction with analgesia; evidence was downgraded because of study design limitations, and many of the studies were underpowered to detect differences between groups and so effect estimates were imprecise. Due to the large number of different comparisons, it was not possible to present GRADE findings for every comparison.

For the comparison of intramuscular pethidine (50 mg/100 mg) versus placebo, no clear differences were found in maternal satisfaction with analgesia measured during labour (number of women satisfied or very satisfied after 30 minutes: 50 women; 1 trial; risk ratio (RR) 7.00, 95% confidence interval (CI) 0.38 to 128.87, very low-quality evidence), or number of women requesting an epidural (50 women; 1 trial; RR 0.50, 95% CI 0.14 to 1.78; very low-quality evidence). Pain scores (reduction in visual analogue scale (VAS) score of at least 40 mm: 50 women; 1 trial; RR 25, 95% CI 1.56 to 400, low-quality evidence) and pain measured in labour (women reporting pain relief to be "good" or "fair" within one hour of administration: 116 women; 1 trial; RR 1.75, 95% CI 1.24 to 2.47, low-quality evidence) were both reduced in the pethidine group, and fewer women requested any additional analgesia (50 women; 1 trial; RR 0.71, 95% CI 0.54 to 0.94, low-quality evidence).

There was limited information on adverse effects and harm to women and babies. There were few results that clearly showed that one opioid was more effective than another. Overall, findings indicated that parenteral opioids provided some pain relief and moderate satisfaction with analgesia in labour. Opioid drugs were associated with maternal nausea, vomiting and drowsiness, although different opioid drugs were associated with different adverse effects. There was no clear evidence of adverse effects of opioids on the newborn. We did not have sufficient evidence to assess which opioid drug provided the best pain relief with the least adverse effects.

Authors' conclusions

Though most evidence is of low- or very-low quality, for healthy women with an uncomplicated pregnancy who are giving birth at 37 to 42 weeks, parenteral opioids appear to provide some relief from pain in labour but are associated with drowsiness, nausea, and vomiting in the woman. Effects on the newborn are unclear. Maternal satisfaction with opioid analgesia was largely unreported. The review needs to be examined alongside related Cochrane reviews. More research is needed to determine which analgesic intervention is most effective, and provides greatest satisfaction to women with acceptable adverse effects for mothers and their newborn.

PLAIN LANGUAGE SUMMARY

Intramuscular and intravenous opioid pain relieving drugs in labour

What is the issue?

We set out to determine the effectiveness, side effects and acceptability to women of different opioids (pain killers), the doses used and how they are given during labour. We were also concerned about the effects of the opioids on the baby in terms of its safety, alertness at birth and early feeding.

Uterine contractions cause pain during labour, particularly as they reach their peak. The pain lessens as the contraction goes and the uterus relaxes. As labour progresses the uterine contractions become stronger, more frequent and longer lasting; at the same time they become more painful. The strongest, most frequent, and most intense uterine contractions generally occur at the end of the first stage of labour as the cervix reaches full dilatation. The mother then has the urge to push or bear down, which assists the birth of the baby. The severity of the pain varies considerably from woman to woman, and is influenced by mental and emotional factors. For example, continuous support during labour can help women to cope with the pain and help with their overall satisfaction with the childbirth experience.

Why is this important?

In many maternity units, intramuscular injections of opioid drugs are widely used for pain relief in labour. Options for intravenous administrations, often controlled by the woman, may also be available. Injected opioids can make women drowsy and interfere with their ability to engage in decision making about their care. They may also experience nausea and vomiting. Opioids can increase variations in fetal heart rate during labour and depress breathing. A number of different opioid drugs are available. The increasing use of epidural analgesia in resource-rich countries means that opioids are now less likely to be the drugs of choice in these settings. Yet in many parts of the world and in midwifery-led settings epidural analgesia is not available, and injected opioids are still widely used. They are relatively inexpensive. It is not clear how effective these drugs are, which opioid is best, and how adverse effects (such as vomiting or sleepiness) or harm to women or their babies can be avoided. This review is an update of a review first published in 2010.

What evidence did we find?

We searched for trials on 11 May 2017. We included 70 studies though only 61 studies involving more than 8000 women contributed data to the review. All of the trials were conducted in hospital settings, on healthy women with uncomplicated pregnancies at 37 to 42 weeks' gestation. The trials compared an opioid (intramuscular or intravenous) with placebo (dummy treatment), no treatment, another opioid (or in three trials another medication or inhaled nitrous oxide) or transcutaneous electrical nerve stimulation (TENS) in 34 different comparisons. There were few opportunities to pool the findings, and for many outcomes only one trial contributed findings. The quality of the evidence was mainly assessed as low or very low for the outcomes of pain in labour and satisfaction with analgesia. Many of the studies included insufficient numbers of women to detect differences between groups.

What does this mean?

Overall, our findings indicate that opioids provided some pain relief during labour, although substantial proportions of women still reported moderate or severe pain. Opioid drugs were associated with nausea, vomiting and drowsiness, with different types of opioids causing different side effects. We did not have sufficient evidence to assess which opioid drug provided the best pain relief with the least adverse effects. Nor did we find clear evidence of adverse effects of opioids on the newborn. Maternal satisfaction with opioid analgesia appeared moderate although it was often unreported or reported in different ways. We did not have sufficient evidence to assess which opioid drugs women were most satisfied with.

In this review we did not examine the effectiveness and safety of intramuscular or intravenous opioids compared with other methods of pain relief in labour such as epidural analgesia. The review needs to be examined alongside related Cochrane reviews. As injected opioid drugs are so widely used it is important that more research is carried out so that women can make informed choices about pain relief.

SUMMARY OF FINDINGS FOR THE MAIN COMPARISON [Explanation]

IM pethidine compared to placebo for pain management for women in labour

Patient or population: women in labour
Setting: hospital settings in South Africa and Hong Kong
Intervention: IM pethidine 50 mg/100 mg
Comparison: placebo

Outcomes	Anticipated absolute effects* (95% CI)		Relative effect (95% CI)	№ of participants (studies)	Certainty of the evidence (GRADE)	Comments
	Risk with IM pethidine 50 mg/100 mg	Risk with placebo				
Maternal satisfaction with analgesia measured during labour (number of women satisfied or very satisfied after 30 minutes)	Study population		RR 7.00 (0.38 to 128.87)	50 (1 RCT)	⊕◯◯◯ VERY LOW [12]	
	0 per 1000 (0 to 0)	0 per 1000				
Maternal pain score or pain measured in labour (described as good or fair after 1 hour)	Study population		RR 1.75 (1.24 to 2.47)	116 (1 RCT)	⊕⊕◯◯ LOW [13]	
	724 per 1000 (513 to 1000)	414 per 1000				
Maternal pain score or pain measured in labour (reduction in VAS of at least 40 mm after 30 minutes)	Study population		RR 25.00 (1.56 to 400.54)	50 (1 RCT)	⊕⊕◯◯ LOW [14]	
	0 per 1000 (0 to 0)	0 per 1000				
Additional analgesia required (epidural, pethidine and Entonox)	Study population		RR 0.71 (0.54 to 0.94)	50 (1 RCT)	⊕⊕◯◯ LOW [13]	

	682 per 1000 (518 to 902)	960 per 1000			
Epidural	Study population		RR 0.50 (0.14 to 1.78)	50 (1 RCT)	⊕◯◯◯ VERY LOW [12]
	120 per 1000 (34 to 427)	240 per 1000			

SEE ADDITIONAL** Table 1**FOR FURTHER GRADE COMPARISONS

***The risk in the intervention group** (and its 95% confidence interval) is based on the assumed risk in the comparison group and the **relative effect** of the intervention (and its 95% CI).

CI: confidence interval; **RR:** risk ratio

GRADE Working Group grades of evidence
High certainty: we are very confident that the true effect lies close to that of the estimate of the effect
Moderate certainty: we are moderately confident in the effect estimate: The true effect is likely to be close to the estimate of the effect, but there is a possibility that it is substantially different
Low certainty: our confidence in the effect estimate is limited: The true effect may be substantially different from the estimate of the effect
Very low certainty: we have very little confidence in the effect estimate: The true effect is likely to be substantially different from the estimate of effect

[1] Risk of bias: serious (effect estimate from single study with design limitations)
[2] Imprecision: very serious (wide confidence interval crossing the line of no effect, few events, and small sample size)
[3] Imprecision: serious (small sample size)
[4] Imprecision: serious (small sample size and few events)

BACKGROUND

This review was last published in 2010 (Ullman 2010) as one of a series of Cochrane reviews examining pain management in labour. These reviews contributed to an overview of systematic reviews of pain management for women in labour (Jones 2012), and shared a generic protocol (Jones 2011). This current review is an update from the previous version (Ullman 2010).

Description of the condition

Pain during labour is a physiological phenomenon, being one of the few examples of pain which does not signal pathology or harm. This does not make the experience of pain any less, but it may alter the way pain is perceived, both by the labouring woman and those providing her care.

Pain during labour is intermittent; it accompanies uterine contractions, particularly as they reach their peak with the activation of oxytocin receptors around the cervix, and then diminishes as the contraction goes and the uterus relaxes (Eisenach 2010). Between contractions the uterus is at rest and there is usually no associated pain. As labour progresses the uterine contractions grow stronger, more frequent and longer lasting; at the same time they become more painful. Typically, the strongest, most frequent, and most intense uterine contractions occur at the end of the first stage of labour as the cervix reaches full dilatation. While the vast majority of women will describe at least some stages of labour as painful, the severity of reported pain varies considerably (Jones 2011a).

Pain relief in labour - physiology and pain perceptions

Labour pain as perceived by women is a unique, subjective and complex neuro-hormonal phenomenon, which involves the interaction of physiological and psychological factors (Genesi 1998a; Genesi 1998b; Trout 2004). Several factors have been shown to reduce pain experienced by women in labour. These include continuous support of a caregiver, attendance of a birth companion and a relaxed birth environment (Bohren 2017; Hodnett 2012; Sandall 2016). Additional key determinants that may influence the pain that a woman experiences are feeling in control, level of anxiety, her rapport with her caregivers and her birth companions, and the care setting where she gives birth (Anim-Somuah 2018; Klomp 2014; Lang 2006). Having more control fosters a woman's sense of self-belief and confidence in her capacity to labour and give birth, which also affects her pain perception (Cook 2012; Lowe 2002). The extent to which a woman can actively participate in negotiating the care she receives has also been linked to overall maternal satisfaction with the childbirth experience (Green 2003; Hodnett 2002). The degree to which a woman is satisfied with the birth experience is not, therefore, solely associated with the pain felt. From the clinical point of view, the management of pain during labour involves much more than simply the provision of a pharmacological intervention. It is important that decisions for coping with the pain of labour are based on informed choice (Green 2003; Hawkins 2003).

Practitioners' attitudes to maternal pain vary (Leap 2004). Characteristics such as philosophical perspective, length of time in practice, knowledge and experience, care setting, cultural differences, and beliefs may all influence the approach midwives will adopt when caring for women during labour; some adopt a rescue position to relieve the pain and recommend the use of analgesia, whilst others facilitate the woman to optimise coping mechanisms, using strategies involving breathing and/or relaxation techniques and positions that offer her more comfort (Aziato 2016; Lally 2014; Lamm 2007; Leap 2004; Williams 2013).

Women's attitudes towards, and preferences for, intrapartum pain relief vary widely. Whilst some women prefer to labour without the use of pharmacological analgesia, others opt, for example, to use epidural analgesia throughout labour. Good communication and sensitive support from caregivers improves a woman's experience of labour, and her overall satisfaction with care, regardless of her choice of pain relief or levels of reported pain (Hodnett 2002). It is important that decisions for coping with the pain of labour are based on informed choice (Green 2003; Hawkins 2003).

Description of the intervention

Pain relief in labour - the use of opioids

The use of pain-relieving drugs during labour is now standard care in many countries throughout the world (Bricker 2002; Tveit 2009; Wong 2009). The extent of usage of parenteral (intramuscular and intravenous drugs including patient-controlled analgesia) opioids during labour is unclear; however, most obstetric units in middle- and high-income countries offer intramuscular opioids, along with facilities for epidural analgesia. Opioids are relatively inexpensive, and use of the opioid drugs pethidine, meptazinol or diamorphine during labour is common midwifery and obstetric practice in some countries. In other parts of the world, parenteral opioids commonly used in labour include morphine, nalbuphine, fentanyl and remifentanil (Evron 2007). Worldwide, pethidine is the most commonly used opioid (Bricker 2002; Wong 2009). Other opioids include: meperidine, butorphanol, buprenorphine, pentazocine, tramadol, alfentanil and sufentanil. In the UK, a midwife can take responsibility for giving a woman an intramuscular injection of either pethidine or diamorphine, without a prescription from a medical practitioner, whether she is working in the hospital or community care setting (MHRA 2007).

In the UK, data from a random sample of 4571 women who gave birth over a two-week period during 2014 showed that 25% used pethidine or a similar opioid during labour (Redshaw 2015). This reflects a decreasing trend in parenteral opioid use from 33% of women in a similar survey in 2006 (Redshaw 2007). In contrast, reported epidural/regional analgesia use has remained con-

stant; 28% in 2006 (Redshaw 2007), and 29% in 2014 (Redshaw 2015). This latest survey indicates a higher proportion of nulliparous women using an opioid (with or without an epidural) compared with multiparous women (Redshaw 2015). Studies in New Zealand and the UK have revealed that more than 95% of hospitals surveyed routinely offered intramuscular pethidine (Lee 2004; Saravanakumar 2007). In the UK study, approximately half (49%) of the units surveyed offered patient-controlled intravenous opioid analgesia for use in labour (Saravanakumar 2007).

Some maternity practitioners have voiced concerns about the use of parenteral opioid analgesia during labour. These centre on doubt about analgesic effectiveness, and anxiety about the sedative effects on women and babies. Concerns relating to maternal outcomes include an impaired capacity to engage in decision making about care, nausea and/or vomiting, and the slowing down of gastric emptying, which increases the risk of inhalation of gastric contents should a general anaesthetic be required in an emergency situation. If a woman feels drowsy or sedated, she is less likely to mobilise and adopt an upright position, and as a result this may lengthen her labour, and make it more painful (Lawrence 2013). These concerns are particularly relevant to midwives who are caring for women in midwifery-led community settings where strategies such as mobilisation and water immersion are implemented to optimise labour progress.

Effects on the baby

Opioids readily cross the placenta by passive diffusion, and have been shown to compromise fetal well-being during labour (Reynolds 2002; Sosa 2006). Pethidine has been shown to significantly affect fetal heart rate variability, accelerations and decelerations during labour (Solt 2002). Changes in normal fetal heart indices have consequences for the woman. She will be required to have electronic fetal heart rate monitoring (EFM) if she is in hospital, and transfer to hospital if she is in a community setting. Results from observational studies have reported effects of opioids on the newborn that include inhibited sucking at the breast and decreased alertness, resulting in delayed effective breastfeeding (Brimdyr 2015; Fleet 2017; Jordan 2005; Lind 2014; Nissen 1995; Ransjo-Arvidson 2001; Righard 1990). There is clear evidence showing that early skin-to-skin contact and the successful onset of early breastfeeding have major benefits for mothers and their babies with far-reaching benefits into adulthood (Aghdas 2014; Carberry 2013; Moore 2016; Victora 2016; Widstrom 2011). It has been suggested that interventions which compromise this contact and early suckling can impact on neonatal mortality (Edmond 2006). It is estimated that it can take a newborn three to six days to eliminate pethidine, and its metabolite, norpethidine, from its system (Hogg 1977).

How the intervention might work

Opioid drugs are narcotic drugs that work by binding to opioid receptors in the brain and spinal cord, thereby inhibiting the transmission of pain signals. A range of opioids have been used to treat both acute and chronic pain, and they are often used to control cancer pain. Opioids have mainly been used to treat moderate and severe pain. Although opioids have been used to treat pain in labour for many years, there have been concerns about their use relating to their sedative effects, and questions have been raised about their effectiveness in labour and about their safety for women and babies (Lawrence 2013).

Why it is important to do this review

This review evaluates the effectiveness and safety of parenteral opioids for analgesia in labour. The use of intramuscular injections of opioid analgesia in labour became a traditional part of midwifery practice without evidence from randomised controlled trials demonstrating analgesic effectiveness, impact on labour outcomes or acceptability to women. It is thought that the perceived analgesic efficacy of parenteral opioids may be due, at least in part, to their sedative effects rather than a true reduction in maternal pain perception (NICE 2014; Wong 2009). There remains uncertainty amongst practitioners as to which opioid provides the most effective pain relief, and whether opioids used during labour are acceptable to women. The most effective and acceptable mode of administration also remains unknown. In addition, there are concerns about the potential adverse effects associated with the use of opioids in labour, particularly the effects on the newborn in relation to infant feeding.

At present, the choice of opioid for analgesia in labour depends on what is available in different hospitals. However, no matter what facilities and drugs are available, women often have no choice as to which drug is used, and healthcare professionals have little information to guide decision-making. Whilst there have been previous reviews on this topic (Bricker 2002; Elbourne 2006), this review provides an up-to-date summary of existing knowledge. We aim to provide best evidence to facilitate discussions between maternity practitioners and women to enable them to make informed decisions about their choice of analgesia during labour. This review is an update of a review first published in 2010 (Ullman 2010).

OBJECTIVES

To assess the effectiveness, safety and acceptability to women of different types, doses and modes of administration of parenteral opioid analgesia in labour. A second objective is to assess the effects of opioids in labour on the baby in terms of safety, condition at birth and early feeding.

METHODS

Criteria for considering studies for this review

Types of studies

Randomised controlled trials. Cluster-randomised trials were also eligible for inclusion, although none were identified. We did not include quasi-randomised or cross-over trials. Trials using a cross-over design are not suitable for interventions in labour. We included studies presented only in abstracts provided that there was enough information to allow us to assess eligibility and risk of bias; if there was insufficient information we attempted to contact study authors.

Types of participants

Women in labour. We excluded studies focusing specifically and exclusively on women in high-risk groups, or women in premature labour (before 37 weeks' gestation), but have included studies which include such women as part of a broader sample.

Types of interventions

Parenteral opioids (intramuscular and intravenous drugs, including patient-controlled analgesia).

Drugs for comparison include pethidine or meperidine, morphine, nalbuphine, butorphanol, diamorphine, buprenorphine, meptazinol, pentazocine, tramadol, alfentanil, sufentanil, remifentanil and fentanyl.

The following comparisons were eligible for the review.

1. An opioid versus placebo using the same route of administration.
2. An opioid versus another opioid using the same route of administration.
3. An opioid plus an add-on drug versus another opioid plus the same add-on drug using the same route of administration.
4. One opioid versus the same opioid but a different dose.

We planned to use trialists' definitions of higher and lower doses of the same drugs, as high and low doses are different for different opioids.

Where different doses of the same drug were compared with the same comparator (e.g. 40 mg pethidine versus placebo, and 80 mg pethidine versus placebo), we planned to use subgroup analyses to examine findings.

This previous version of this review was one in a series of Cochrane reviews examining pain management in labour. These reviews contributed to an overview of systematic reviews of interventions for pain management in labour (Jones 2012), and shared a generic protocol (Jones 2011). To avoid duplication, the different methods of pain management were listed in a specific order, from one to 15. Individual reviews focusing on particular interventions included comparisons with only the interventions above it on the list. The current list is as follows.

1. Placebo
2. No treatment
3. Hypnosis (Madden 2016)
4. Biofeedback (Barragán 2011)
5. Intracutaneous or subcutaneous sterile water injection (Derry 2012)
6. Immersion in water (Cluett 2009)
7. Aromatherapy (Smith 2011a)
8. Relaxation techniques (yoga, music, audio) (Smith 2018a)
9. Acupuncture or acupressure (Smith 2011b)
10. Massage, reflexology and other manual methods (Smith 2018b)
11. Transcutaneous electrical nerve stimulation (TENS) (Dowswell 2009)
12. Inhaled analgesia (Klomp 2012)
13. Opioids (this review)
14. Non-opioid drugs (Othman 2012)
15. Local anaesthetic nerve blocks (Novikova 2011)
16. Epidural (including combined spinal epidural) (Anim-Somuah 2018; Simmons 2012)

Accordingly, this review includes comparisons of an opioid with: 1. placebo/no treatment; 2. hypnosis; 3. biofeedback; 4. intracutaneous or subcutaneous sterile water injection; 5. immersion in water; 6. aromatherapy; 7. relaxation techniques (yoga, music, audio); 8. acupuncture or acupressure; 9. manual methods (massage, reflexology); 10. TENS; 11. inhaled analgesia; or 12. another opioid (as specified above).

Types of outcome measures

Primary outcomes

1. Maternal satisfaction with analgesia measured during labour
2. Maternal satisfaction with analgesia in labour measured during the postnatal period

Secondary outcomes

For women

1. Maternal pain score or pain measured in labour
2. Additional analgesia required
3. Epidural
4. Maternal sleepiness during labour
5. Nausea and vomiting in labour
6. Caesarean section
7. Assisted vaginal birth
8. Postpartum haemorrhage (as defined by the trial authors)
9. Breastfeeding at discharge

10. Breastfeeding in the postnatal period (four to six weeks)
11. Sense of control in labour (as defined by trialists)
12. Satisfaction with childbirth experience (as defined by trialists)
13. Effect (negative) on mother/baby interaction

For babies

1. Fetal heart rate changes in labour (persistent decelerations or tachycardia)
2. Naloxone administration
3. Neonatal resuscitation
4. Apgar score less than seven at one minute
5. Apgar score less than seven at five minutes
6. Apgar score less than seven at ten minutes
7. Admission to special care baby unit/neonatal intensive care unit (as defined by trialists)
8. Newborn neuro-behavioural scores
9. Neurodevelopment outcomes during infancy

Other

1. Cost (as defined by trialists)

Search methods for identification of studies

The following search methods section of this review is based on a standard template used by Cochrane Pregnancy and Childbirth.

Electronic searches

We searched Cochrane Pregnancy and Childbirth's Trials Register by contacting their Information Specialist (11 May 2017).
The Register is a database containing over 24,000 reports of controlled trials in the field of pregnancy and childbirth. For full search methods used to populate Pregnancy and Childbirth's Trials Register including the detailed search strategies for CENTRAL, MEDLINE, Embase and CINAHL; the list of handsearched journals and conference proceedings, and the list of journals reviewed via the current awareness service, please follow this link to the editorial information about the Cochrane Pregnancy and Childbirth in the Cochrane Library and select the '***Specialized Register***' section from the options on the left side of the screen.
Briefly, Cochrane Pregnancy and Childbirth's Trials Register is maintained by their Information Specialist and contains trials identified from:

1. monthly searches of the Cochrane Central Register of Controlled Trials (CENTRAL);
2. weekly searches of MEDLINE (Ovid);
3. weekly searches of Embase (Ovid);
4. monthly searches of CINAHL (EBSCO);
5. handsearches of 30 journals and the proceedings of major conferences;
6. weekly current awareness alerts for a further 44 journals plus monthly BioMed Central email alerts.

Search results are screened by two people and the full text of all relevant trial reports identified through the searching activities described above is reviewed. Based on the intervention described, each trial report is assigned a number that corresponds to a specific Pregnancy and Childbirth review topic (or topics), and is then added to the Register. The Information Specialist searches the Register for each review using this topic number rather than keywords. This results in a more specific search set that has been fully accounted for in the relevant review sections (Included studies; Excluded studies; Studies awaiting classification; Ongoing studies).
In addition, we searched ClinicalTrials.gov and the WHO International Clinical Trials Registry Platform (ICTRP) for unpublished, planned and ongoing trial reports using the methods detailed in Appendix 1 (searched 11 May 2017).

Searching other resources

We searched the reference lists of background review articles and the reference lists of papers retrieved by the search.
We did not apply any language or date restrictions.

Data collection and analysis

For methods used in the previous version of this review, *see* Ullman 2010.
For this update, the following methods were used for assessing the 70 reports that were identified as a result of the updated search.
The following methods section of this review is based on a standard template used by Cochrane Pregnancy and Childbirth.

Selection of studies

In this update two review authors (A Cuthbert (AC), Lesley Smith (LS) independently assessed for inclusion all the new reports identified as a result of the search strategy. We resolved any disagreement through discussion or, if required, we consulted a third author (E Burns).

Data extraction and management

For eligible studies, two same two review authors extracted the data using an agreed form. We resolved discrepancies through discussion or, if required, we consulted the third review author. Data were entered into Review Manager software (RevMan 2014) and checked for accuracy.
When information regarding any of the above was unclear, we contacted authors of the original reports to provide further details.

Assessment of risk of bias in included studies

Two review authors independently assessed risk of bias for each study using the criteria outlined in the *Cochrane Handbook for Systematic Reviews of Interventions* (Higgins 2011a). Any disagreement was resolved by discussion or by involving the third assessor.

(1) Random sequence generation (checking for possible selection bias)

We described the method used to generate the allocation sequence in sufficient detail to allow an assessment of whether it should produce comparable groups.

For each included study we assessed the method as being at:

- low risk of bias (any truly random process, e.g. random number table; computer random number generator);
- high risk of bias (any non-random process, e.g. odd or even date of birth; hospital or clinic record number);
- unclear risk of bias.

(2) Allocation concealment (checking for possible selection bias)

For each included study we described the method used to conceal allocation to interventions prior to assignment and assessed whether intervention allocation could have been foreseen in advance of, or during recruitment, or changed after assignment.

We assessed the methods as being at:

- low risk of bias (e.g. telephone or central randomisation; consecutively numbered sealed opaque envelopes);
- high risk of bias (open random allocation; unsealed or non-opaque envelopes, alternation; date of birth);
- unclear risk of bias.

(3.1) Blinding of participants and personnel (checking for possible performance bias)

For each included study we described the methods used, if any, to blind study participants and personnel from knowledge of which intervention a participant received. We considered that studies were at low risk of bias if they were blinded, or if we judged that the lack of blinding was unlikely to affect results. We assessed blinding separately for different outcomes or classes of outcomes.

We assessed the methods as being at:

- low, high or unclear risk of bias for participants;
- low, high or unclear risk of bias for personnel.

(3.2) Blinding of outcome assessment (checking for possible detection bias)

For each included study we described the methods used, if any, to blind outcome assessors from knowledge of which intervention a participant received. We assessed blinding separately for different outcomes or classes of outcomes.

We assessed methods used to blind outcome assessment as being at:

- low, high or unclear risk of bias.

(4) Incomplete outcome data (checking for possible attrition bias due to the amount, nature and handling of incomplete outcome data)

For each included study, and for each outcome or class of outcomes, we described the completeness of data including attrition and exclusions from the analysis. We stated whether attrition and exclusions were reported and the numbers included in the analysis at each stage (compared with the total randomised participants), reasons for attrition or exclusion where reported, and whether missing data were balanced across groups or were related to outcomes. Where sufficient information was reported, or could be supplied by the trial authors, we planned to re-include missing data in the analyses that we undertook.

We assessed methods as being at:

- low risk of bias (e.g. no missing outcome data; missing outcome data balanced across groups);
- high risk of bias (e.g. numbers or reasons for missing data imbalanced across groups; 'as treated' analysis done with substantial departure of intervention received from that assigned at randomisation);
- unclear risk of bias.

(5) Selective reporting (checking for reporting bias)

For each included study we described how we investigated the possibility of selective outcome reporting bias and what we found.

We assessed the methods as being at:

- low risk of bias (where it was clear that all of the study's prespecified outcomes and all expected outcomes of interest to the review have been reported);
- high risk of bias (where not all the study's prespecified outcomes were reported; one or more reported primary outcomes were not prespecified; outcomes of interest were reported incompletely and so could not be used; study failed to include results of a key outcome that would have been expected to have been reported);
- unclear risk of bias.

(6) Other bias (checking for bias due to problems not covered by (1) to (5) above)

For each included study we described any important concerns we had about other possible sources of bias.

(7) Overall risk of bias

We made explicit judgements about whether studies were at high risk of bias, according to the criteria given in the *Cochrane Handbook for Systematic Reviews of Interventions* (Higgins 2011a). With

reference to (1) to (6) above, we planned to assess the likely magnitude and direction of the bias and whether we considered it was likely to have an impact on the findings. In future updates, we will explore the impact of the level of bias through undertaking sensitivity analyses (Sensitivity analysis).

Measures of treatment effect

Dichotomous data

For dichotomous data, we presented results as summary risk ratio with 95% confidence intervals.

Continuous data

We used the mean difference if outcomes were measured in the same way between trials. In future updates as appropriate, we will use the standardised mean difference to combine trials that measure the same outcome, but use different methods.

Unit of analysis issues

Cluster-randomised trials

We intended to include cluster-randomised trials in the analyses along with individually-randomised trials, no cluster-randomised trials were identified for inclusion in this version of the review. If such trials are identified in future updates, we will adjust their sample sizes using the methods described in the *Handbook* using an estimate of the intracluster correlation co-efficient (ICC) derived from the trial (if possible), from a similar trial or from a study of a similar population. If we use ICCs from other sources, we will report this and conduct sensitivity analyses to investigate the effect of variation in the ICC. If we identify both cluster-randomised trials and individually-randomised trials, we plan to synthesise the relevant information. We will consider it reasonable to combine the results from both if there is little heterogeneity between the study designs and the interaction between the effect of intervention and the choice of randomisation unit is considered to be unlikely. We will also acknowledge heterogeneity in the randomisation unit and perform a sensitivity analysis to investigate the effects of the randomisation unit.

Cross-over trials

Trials using a cross-over design are not suitable for interventions in labour and were not included.

Other unit of analysis issues

In this update, trials with more than two treatment groups only contributed data into different comparisons and so unit of analysis error was not an issue. In future updates, where necessary, we will follow the methods as described in the *Cochrane Handbook for Systematic Reviews of Interventions* (Higgins 2011b, Section 16.5.4) in order to avoid unit of analysis errors (combine groups to create a single pair-wise comparison, divide the control group between intervention arms to avoid double-counting or select one pair of interventions and exclude others).

Dealing with missing data

For included studies, we noted levels of attrition. In future updates, if more eligible studies are included in any of the comparisons, we will explore the impact of including studies with high levels of missing data in the overall assessment of treatment effect by using sensitivity analysis.

For all outcomes, we carried out analyses, as far as possible, on an intention-to-treat basis, i.e. we attempted to include all participants randomised to each group in the analyses. The denominator for each outcome in each trial was the number randomised minus any participants whose outcomes were known to be missing.

Assessment of heterogeneity

We assessed statistical heterogeneity in each meta-analysis using the Tau^2, I^2 and Chi^2 statistics. We regarded heterogeneity as substantial if an I^2 was greater than 30% and either a Tau^2 was greater than zero, or there was a low P value (less than 0.10) in the Chi^2 test for heterogeneity. Had we identified substantial heterogeneity (above 30%), we planned to explore it by pre-specified subgroup analysis.

Assessment of reporting biases

In future updates, if there are 10 or more studies in the meta-analysis we will investigate reporting biases (such as publication bias) using funnel plots. We will assess funnel plot asymmetry visually. If asymmetry is suggested by a visual assessment, we will perform exploratory analyses to investigate it.

Data synthesis

We carried out statistical analysis using the Review Manager software (RevMan 2014). We used fixed-effect meta-analysis for combining data where it was reasonable to assume that studies were estimating the same underlying treatment effect: i.e. where trials were examining the same intervention, and the trials' populations and methods were judged sufficiently similar.

If there was clinical heterogeneity sufficient to expect that the underlying treatment effects differed between trials, or if substantial statistical heterogeneity was detected, we used random-effects

meta-analysis to produce an overall summary if an average treatment effect across trials was considered clinically meaningful. The random-effects summary was treated as the average range of possible treatment effects and we discussed the clinical implications of treatment effects differing between trials. If the average treatment effect was not clinically meaningful, we did not combine trials. Where we used random-effects analyses, we presented the results as the average treatment effect with 95% confidence intervals, and the estimates of Tau^2 and I^2.

Subgroup analysis and investigation of heterogeneity

We intended to conduct planned subgroup analysis using the methods described by Deeks 2001 and set out in the *Cochrane Handbook for Systematic Reviews* (Higgins 2011a).

We had planned to carry out the following subgroup analyses.

1. By parity (nulliparous versus multiparous women).
2. By spontaneous versus induced or augmented labour.
3. Term versus preterm birth.
4. Continuous support in labour versus no continuous support.

Where different doses of the same drug were examined (e.g. pethidine 40 mg or pethidine 80 mg versus a placebo), we separated analyses into subgroups to examine the impact of different doses. We planned to assess subgroup differences by interaction tests available within RevMan (RevMan 2014) reporting the results of subgroup analyses quoting the Chi^2 statistic and P value, and the interaction test I^2 value. In this version of the review there were too few studies contributing data to any particular comparison to make such additional analyses worthwhile. If more data become available in the future we will carry out planned subgroup analysis.

Sensitivity analysis

We planned to carry out sensitivity analyses to explore the effect of risk of bias for important outcomes in the review. Where there was risk of bias associated with a particular risk of bias domain (e.g. inadequate allocation concealment), we planned to explore this by temporarily excluding studies at high risk of bias to see if this had any impact on the results. In this version of the review we did not carry out this planned analysis due to too few studies contributing data.

Summary of findings tables

For this update we assessed the quality of the evidence using the GRADE approach as outlined in the GRADE handbook; we assessed the quality of the body of evidence relating to the following outcomes.

1. Maternal satisfaction with analgesia measured during labour
2. Maternal satisfaction with analgesia in labour measured during the postnatal period
3. Maternal pain score or pain measured in labour
4. Additional analgesia required

Selecting the most important comparisons for GRADE and the 'Summary of findings' tables was not simple, as different types and routes of opioid drugs are used in different parts of the world and in different settings. We therefore created a single table summarising findings for pain outcomes for all comparisons which involved an opioid versus placebo/no treatment, or where comparisons included pethidine as a control group. Whilst there are several other comparisons between different opioids in the review, most were reported in single studies which were of low quality.

We used the GRADEpro Guideline Development Tool to import data from Review Manager 5.3 (RevMan 2014) in order to create the 'Summary of findings' tables. We produced a summary of the intervention effect and a measure of quality for each of the above outcomes using the GRADE approach. 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 evidence can be downgraded from 'high quality' by one level for serious (or by two levels for very serious) limitations, depending on assessments for risk of bias, indirectness of evidence, serious inconsistency, imprecision of effect estimates or potential publication bias.

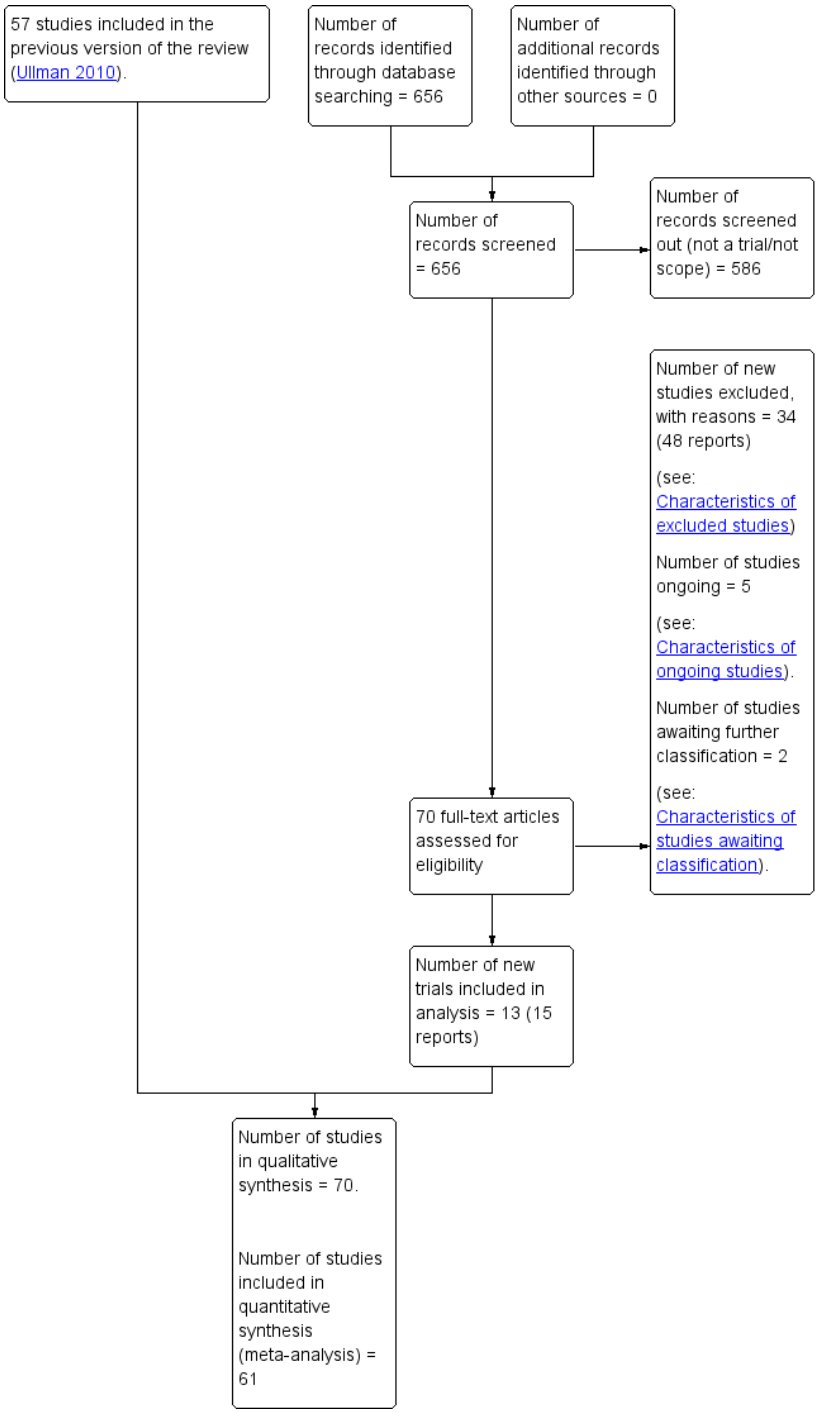
RESULTS

Description of studies

Results of the search

See: Figure 1.

Figure 1. Study flow diagram.



We retrieved 656 citations from the updated search in May 2017. We screened out 586 (not scope or not a trial), and assessed 70 trial reports which related to 54 new trials. We included 13 new trials and excluded 34 trials. Two trials are awaiting classification (Mohan 2015; Sereshti 2013), and five are ongoing (Kokki 2015; Raheja 2016; Reyes 2013; Sahin 2012; Shen 2008).

Included studies

Altogther in this update we have included 70 studies, 61 of which contributed data. The studies that contributed data involved more than 8000 women (*see* Characteristics of included studies).
Trials with more than two arms may be included in more than one comparison. Nine studies did not contribute any data to this review: Fieni 2000; Kamyabi 2003; Kermani 2015; Lalooha 2017; Lisboa 1997; Tharamas 1999; Wahab 1988; Wali 2012; Zhu 2013.

Design

All included studies were randomised controlled trials although the randomisation method was not always well described. All studies involved two trial arms except for Douma 2010, Kainz 1992, and Nelson 2005, which had three trial arms, and Liu 2015, which had four although only three were relevant to this review.
All women were randomised in labour. Though most studies do not report specifically when randomisation took place, 26 studies reported that women were randomised when they requested pain relief (Atkinson 1994; Campbell 1961; Frank 1987; Kainz 1992; Khooshideh 2009; Lardizabal 1999; Li 1988; Mitterschiffthaler 1991; Morley-Forster 2000; Morrison 1987; Mowat 1970; Nel 1981; Nelson 2005; Nicholas 1982; O'Dwyer 1971; Osler 1987; Prasertsawat 1986; Rayburn 1989a; Refstad 1980; Sekhavat 2009; Sheikh 1986; Sliom 1970; Tsui 2004; Viegas 1993; Volikas 2001; Wilson 1986).

Participants

All studies included healthy pregnant women in either induced or spontaneous early labour. All women were classed as having a 'low-risk' pregnancy. Most studies included both nulliparous and multiparous women, or did not specify parity. Thirteen studies included nulliparous women only (Direkvand-Moghadam 2014; El-Refaie 2012; Hamann 1972; Kamyabi 2003; Keskin 2003; Lalooha 2017; Levy 1971; Li 1988; Olofsson 1996; Tawfik 1982; Tharamas 1999; Viegas 1993; Zhu 2013), and two included multiparous women only (Jahani 2013; Wahab 1988).

Interventions and comparisons

Most of the studies included in the review examined an opioid drug administered intramuscularly (IM) and compared with either a placebo, no treatment, or with another opioid. A smaller number of studies examined opioid drugs administered intravenously (IV), sometimes with a degree of patient control over the amount of drug infused (patient-controlled anaesthesia; PCA). None of the included studies examined subcutaneous administration of opioids. Some of the studies compared opioids with other non-pharmacological interventions such as transcutaneous electrical nerve stimulation (TENS) (four studies).

IM comparisons

1. IM pethidine versus IM placebo (all studies used saline as placebo) (four studies) (Direkvand-Moghadam 2014; Sekhavat 2009; Sliom 1970; Tsui 2004).
2. IM pentazocine versus placebo (saline placebo) (one study) (Zafar 2016).
3. IM tramadol versus no treatment (one study) (Li 1994).
4. IM meptazinol versus IM pethidine (eight studies) (De Boer 1987; Jackson 1983; Morrison 1987; Nel 1981; Nicholas 1982; Osler 1987; Sheikh 1986; Wheble 1988) (in the studies by De Boer 1987 and Jackson 1983, women in both study groups also received add-on drugs).
5. IM diamorphine + prochlorperazine versus IM pethidine + prochlorperazine (one study) (Fairlie 1999).
6. IM tramadol versus IM pethidine (six studies) (Bitsch 1980; Husslein 1987; Keskin 2003; Khooshideh 2009; Prasertsawat 1986; Viegas 1993). Fieni 2000 did not contribute any data.
7. IM tramadol + triflupromazine versus pethidine + triflupromazine (one study) (Kainz 1992).
8. IM dihydrocodeine versus IM pethidine (one study) (Sliom 1970).
9. IM pentazocine versus IM pethidine (six studies) (Borglin 1971; Duncan 1969; Levy 1971; Moore 1970; Mowat 1970; Refstad 1980). Refstad 1980 gave both group promazine - subtotals only reported.
10. IM nalbuphine versus IM pethidine (three studies) (Lardizabal 1999; Mitterschiffthaler 1991; Wilson 1986).
11. IM phenazocine versus IM pethidine (one study) (Grant 1970).
12. IM morphine or diamorphine versus pethidine (two studies) (Prasertsawat 1986; Wee 2014).
13. IM butorphanol versus IM pethidine (one study) (Maduska 1978).
14. IM pentazocine versus a spasmolytic drug (Avacan ®) (one study) (Hamann 1972).
15. IM pentazocine versus IM Pethilorphan® (one study) (O'Dwyer 1971).

16. IM pentazocine versus complementary and alternative medicine (one study) (Zafar 2016).
17. IM pentazocine versus IM tramadol (one study) (Kuti 2008).
18. IM pethidine versus inhaled nitrous oxide (one study) (Mobaraki 2016).

IV comparisons

1. IV pethidine versus placebo (one study) (El-Refaie 2012).
2. IV fentanyl versus no treatment (one study) (Jahani 2013).
3. IV fentanyl versus IV pethidine (one study) (Rayburn 1989).
4. IV nalbuphine versus IV pethidine (one study) (Giannina 1995).
5. IV phenazocine versus IV pethidine (one study) (Olson 1964).
6. IV butorphanol versus IV pethidine (three studies) (Hodgkinson 1979; Nelson 2005; Quilligan 1980).
7. IV morphine versus IV pethidine (two studies) (Campbell 1961; Olofsson 1996).
8. IV alphaprodine (Nisentil) versus IV pethidine (one study) (Gillam 1958).
9. IV fentanyl versus butorphanol (one study) (Atkinson 1994).

IV/PCA comparisons

1. PCA pentazocine versus PCA pethidine (one study) (Erskine 1985).
2. PCA remifentanil versus PCA pethidine (three studies) (Blair 2005; Douma 2010; Volikas 2001).
3. PCA nalbuphine versus PCA pethidine (one study) (Frank 1987).
4. PCA fentanyl versus PCA alfentanil (one study) (Morley-Forster 2000).
5. PCA fentanyl versus PCA pethidine (one study) (Douma 2010).

IM/PCA comparisons

1. IM meptazinol PCA versus IM pethidine PCA administration (one study) (Li 1988).

Opioids versus TENs

1. IV pethidine (50 mg) versus TENS to lower back (Neumark 1978), IM pethidine (50 mg) versus TENS to back (Tawfik 1982), IM tramadol (100 mg) versus TENS to back (Thakur 2004), PCA ondansetron and tramadol versus Han's acupoint nerve stimulator (Liu 2015).

Outcomes

There are pain outcomes reported under most comparisons including maternal satisfaction with analgesia, pain severity, or additional analgesia required. The way that pain outcomes were reported in studies were not consistent. Adverse effects, neonatal outcomes, and costs were not reported in all the studies.

Setting

All studies took place in hospital settings. Most studies were conducted in the USA (Atkinson 1994; Campbell 1961; Giannina 1995; Gillam 1958; Hodgkinson 1979; Levy 1971; Maduska 1978; Nelson 2005; Olson 1964; Quilligan 1980; Rayburn 1989a), or the UK (Blair 2005; De Boer 1987; Duncan 1969; Fairlie 1999; Frank 1987; Grant 1970; Jackson 1983; Moore 1970; Morrison 1987; Mowat 1970; Nicholas 1982; O'Dwyer 1971; Sheikh 1986; Volikas 2001; Wee 2014; Wheble 1988; Wilson 1986). Eight were conducted in Iran (Direkvand-Moghadam 2014; Jahani 2013; Kamyabi 2003; Kermani 2015; Khooshideh 2009; Lalooha 2017; Mobaraki 2016; Sekhavat 2009), three each in Germany (Bitsch 1980; Kainz 1992; Mitterschiffthaler 1991), Egypt (El-Refaie 2012; Tawfik 1982; Wahab 1988), South Africa (Erskine 1985; Nel 1981; Sliom 1970), and China (Li 1988; Li 1994; Liu 2015), and one in each of the Netherlands (Douma 2010), Italy (Fieni 2000), Austria (Husslein 1987), Turkey (Keskin 2003), Nigeria (Kuti 2008), Argentina (Lardizabal 1999), Brazil (Lisboa 1997), Canada (Morley-Forster 2000), Sweden (Olofsson 1996), Denmark (Osler 1987), Thailand (Prasertsawat 1986), Norway (Refstad 1980), India (Thakur 2004), Hong Kong (Tsui 2004), Singapore (Viegas 1993), and Pakistan (Zafar 2016).
Six studies did not explicitly state where they were conducted (Borglin 1971; Hamann 1972; Neumark 1978; Tharamas 1999; Wali 2012; Zhu 2013).

Dates of study

Hamann 1972 took place between 1969 and 1971; Bitsch 1980 in the 1970s; Prasertsawat 1986, Rayburn 1989a, and Wahab 1988 in the 1980s; Atkinson 1994, Fairlie 1999, Giannina 1995, Lardizabal 1999, Li 1994, and Tharamas 1999 in the 1990s; El-Refaie 2012, Khooshideh 2009, Kuti 2008, Sekhavat 2009, Tsui 2004, and Zafar 2016 in the 2000s; and Direkvand-Moghadam 2014, Liu 2015, and Mobaraki 2016 in the 2010s.
All other studies did not report study dates.

Funding

Smith and Nephew (Pharmaceutics) Ltd provided the marked drug ampoules in Grant 1970; Bronovo Research Fund funded Douma 2010; pentazocine was supplied by Bayer products in Duncan 1969; Dupont (UK) Ltd funded Frank 1987; The Scientific Achievement and Appropriate Technology Extension Project

of Beijing Municipal Commission of Health and Family Planning (TG-2014-12) funded Liu 2015; Bristol laboratories, Syracuse, New York funded Maduska 1978; Ardabil Medical Sciences University funded Mobaraki 2016; Sterling Winthrop Research Division supplied the drugs in Mowat 1970; National Institutes of Health, Bethesda, Maryland (grant No. NS41386) funded Nelson 2005; Karolinska Institute foundations and the Swedish Medical Research Council funded Olofsson 1996; Sterling-Winthrop company supplied trial drugs in Refstad 1980; Sekhavat 2009 reported to not be funded be any pharmaceutical company; Wyeth laboratories supplied the coded ampoules of the trial drugs in Sheikh 1986; BDH (South Africa) Pty Ltd supplied dihydrocodeine bitartrate in Sliom 1970; Wee 2014 was independent research funded by the National Institute for Health Research (NIHR) under its Research for Patient Benefit (RfPB) Programme (Grant Reference Number PB-PG-0407-13170) with additional support costs funded by the Western Comprehensive Local Research Network; Medical Research Council and Wyeth Research (UK) funded Wheble 1988; and the Higher Education Commission (Pakistan) funded Zafar 2016.

All other studies did not report funding sources.

Conflicts of interest

Two studies declared to have no conflicts of interest (Direkvand-Moghadam 2014; Wee 2014).

All other studies did not report whether or not there were conflicts of interest.

Excluded studies

We have excluded 121 studies (*see* Characteristics of excluded studies).

Reasons for exclusions (some of the studies were excluded for more than one reason).

1. In 26 studies, the focus was on epidural analgesia (Camann 1992; El-Kerdawy 2010; Evron 2007; Evron 2008; Freeman 2012; Gambling 1998; Ginosar 2003; Grandjean 1979; John 2013; Karadjova 2016; Logtenberg 2017; Marshalov 2012; McGrath 1992; Morris 1994; Nafisi 2006; Polley 2000; Rabie 2006; Sabry 2011; Samanta 2013; Solek-Pastuszka 2009; Stocki 2014; Stourac 2014; Volmanen 2008; Weissman 2006; Wiener 1979; Wong 2005). The use of epidural analgesia for pain management in labour is covered in related Cochrane reviews (Anim-Somuah 2018; Simmons 2012).
2. In 13 studies, women in both groups received the same opioid and the focus of studies was on add-on drugs; so, for example, both groups received pethidine with one group, in addition, receiving a sedative. The focus of these trials was on the effects of the add-on drug (Aiken 1971; Ballas 1976; De Lamerens 1964; Hodgkinson 1978; Malkasian 1967; McQuitty 1967; Posner 1960; Powe 1962; Ron 1984; Roberts 1960; Spellacy 1966; Wan 1965; Williams 1962).
3. Nineteen studies were not randomised trials, or it was not clear that there was any random allocation to groups (Balcioglu 2007; Bredow 1992; Brelje 1966; Callaghan 1966; Chandnani 2013; Cincadze 1978; Cullhed 1961; Eliot 1975; MacVicar 1960; Moore 1974; Pandole 2003; Rowley 1963; Savage 1955; Singh 2001; Soontrapa 2002; Suvonnakote 1986; Tripti 2006; Vavrinkova 2005; Volmanen 2005).
4. In three studies, it was not clear that participants were in labour (Chang 1976; Krins 1969; Tomlin 1965).
5. In three studies, the intervention was not an opioid (Abd-El-Maeboud 2014; Bare 1962; Elhalwagy 2017).
6. In the study by Kaltreider 1967, the focus was on a high-risk group (women in preterm labour) and post-randomisation exclusions meant that results were difficult to interpret.
7. We excluded two studies as levels of attrition meant that results were at high risk of bias. There were serious methodological problems in the study by Robinson 1980 and complete data were available for only approximately one-third of those randomised. In the study by De Kornfeld 1964, data on pain outcomes were available for less than half the sample at one hour; results from this study were therefore very difficult to interpret.
8. Five trials were reported in trial registers or in brief abstracts and we were unable to assess risk of bias or extract results. We attempted to contact authors for more information without success (Goodlin 1988; Kalaskar 2007; Morgan 2004; Overton 1992; Taskin 1993).
9. The focus of four studies was not on pain relief, so women may have received an opioid with the purpose of promoting progress in labour (Sosa 2004; Tournaire 1980; Treisser 1981; Von Vorherr 1963). In one of these studies, women were specifically excluded if they complained of pain (Sosa 2004), and in another, women in the two groups also received oxytocin with each study group receiving a different dose (Von Vorherr 1963). A further two studies did not focus on pain relief but rather on newborn serum bilirubin (McDonald 1964) or platelet function (Greer 1988).
10. Seven studies focused on drugs no longer in use, or drugs not used nowadays for obstetric analgesia (Cahal 1960; Cavanagh 1966; Eames 1964; Ransom 1966; Roberts 1957; Sentnor 1966; Walker 1992).
11. In eight studies, the same opioid was given to women in both arms of trials and the difference between groups was mode of administration; (different modes of administration of parenteral opioids will be considered in a separate Cochrane review) (Balki 2007; Balki 2012; Isenor 1993; Khooshideh 2015; McInnes 2004; Rayburn 1989; Rayburn 1991; Volmanen 2009).
12. In four studies, women in one arm of the trial, as well as receiving an opioid, were also given another add-on drug that the comparison group did not receive. In these studies results are difficult to interpret, as any differences between groups may be due to the add-on drug rather than the opioid (Busacca 1982;

Calderon 2006; Dan 1991; Fernandez 2015).

13. In the studies by Brookes 2013, Calderon 2006, Evron 2005, Fleet 2015, Li 1995, Ng 2011, Nikkola 2000; Shahriari 2007, Thurlow 2002, and Wilson 2016, different drugs were administered using different methods, and so it is difficult to interpret results as any differences between groups may be due to drug, method or both together.

14. In one study, the effect of the opioid analgesia was not assessed during childbirth, but for second trimester labour following termination of pregnancy (Castro 2004).

15. Opioid was compared with a non-opioid drug: IV paracetamol (Abdollahi 2014; Alhashemi 2011; Ankumah 2016; Bhatia 2013; Dahiya 2015; Elbohoty 2012; Gupta 2016; Hashemiyan 2014; Kaur 2015; Lallar 2015), NSAIDs (El Kinawy 2015b).

16. Four trials were cross-over trials (Easton 2016; Jost 2015; Rahimi 2012; Volmanen 2005).

Risk of bias in included studies

See Figure 2; Figure 3. We have only described the 61 studies below that contributed data to the review; Fieni 2000; Kamyabi 2003; Kermani 2015; Lalooha 2017; Lisboa 1997; Tharamas 1999; Wahab 1988; Wali 2012; Zhu 2013 are therefore not included in the descriptions below.

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

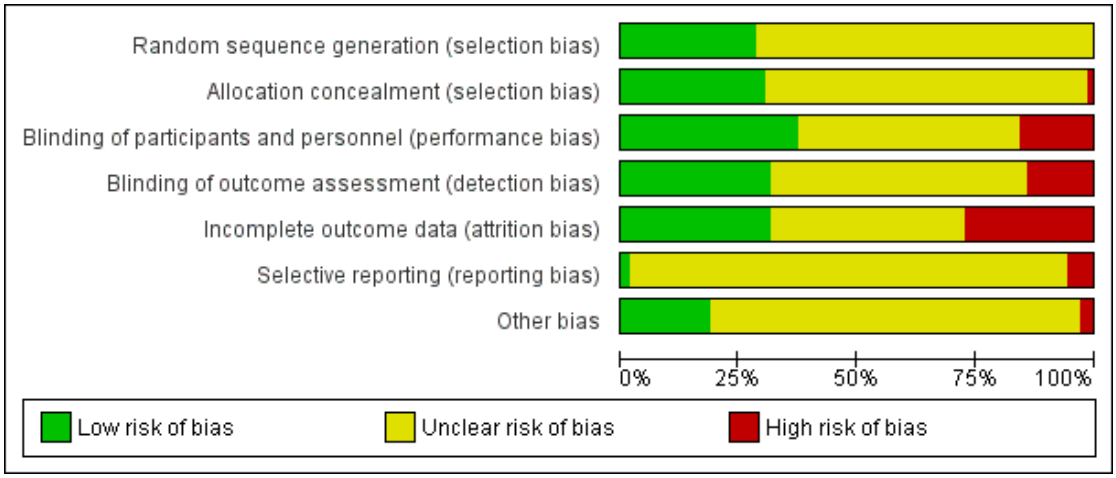
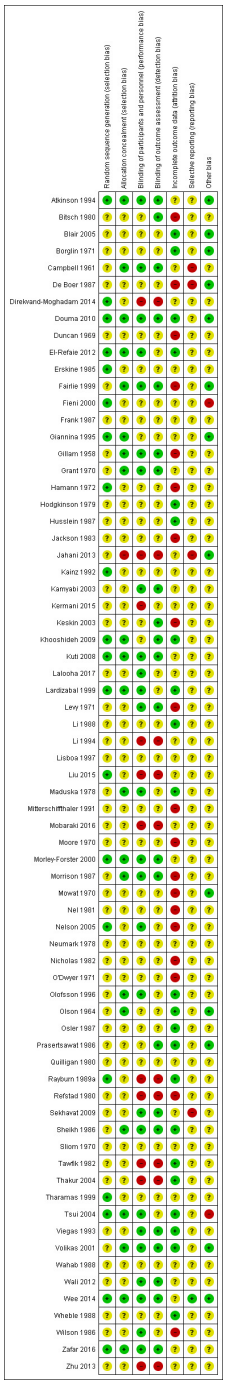


Figure 3. 'Risk of bias' summary: review authors' judgements about each risk of bias item for each included study.



Allocation

Sequence generation

Eighteen studies were assessed as having adequate random sequence generation: in 11 studies a computer-generated random sequence was used (Atkinson 1994; Douma 2010; El-Refaie 2012; Giannina 1995; Khooshideh 2009; Kuti 2008; Lardizabal 1999; Nelson 2005; Tsui 2004; Wee 2014; Zafar 2016); two used an external randomisation service (Morley-Forster 2000; Rayburn 1989a); and five studies used random number tables (Direkvand-Moghadam 2014; Erskine 1985; Hamann 1972; Kainz 1992; Liu 2015). The remaining 43 included studies were unclear about how the randomisation sequence was generated.

Allocation concealment

Allocation concealment was not generally described in sufficient detail to allow assessment of risk of bias; it was not always clear at what stage randomisation took place, and whether or not the person carrying out randomisation was aware of group allocation. Seven studies described using numbered opaque sealed envelopes to conceal allocation (El-Refaie 2012; Giannina 1995; Khooshideh 2009; Kuti 2008; Tsui 2004; Volikas 2001; Zafar 2016). Thirteen studies described using identical coded drug boxes (although it may not have been clear who had access to the code or when the code was broken) (Atkinson 1994; Campbell 1961; Douma 2010; Fairlie 1999; Gillam 1958; Grant 1970; Lardizabal 1999; Maduska 1978; Morley-Forster 2000; Morrison 1987; Olofsson 1996; Olson 1964; Sheikh 1986). One trial used two identical syringes labelled only with the trial number to conceal group allocation and to ensure that if two doses were given, the same opioid was given both times, which were prepared by trial centre pharmacies (Wee 2014). One study appeared to randomise at the time of a coin toss and did not attempt allocation concealment (Jahani 2013), so was assessed to be at high risk of selection bias. In the remaining studies it was not clear what steps were taken to conceal allocation at the point of randomisation.

Blinding

Many of the studies were described as double-blind; in the majority of these trials women in the control arms were given preparations of similar appearance to those given to women in the experimental arms (either a placebo or an indistinguishable comparison drug). It was not always clear that blinding was effective; for example, some IM drugs may appear similar, but different consistencies may be apparent to experienced staff. It was also not generally clear at what point blinding ended, and whether outcome assessors were blind to group allocation.

Performance bias (participants and personnel)

In 25 studies it appears that adequate blinding of women and caregivers was achieved with identical administration of placebo or comparison drugs. Nine studies were at high risk of performance bias: four administered study drugs of interventions via different routes (Direkvand-Moghadam 2014; Mobaraki 2016; Tawfik 1982; Thakur 2004); three compared the study drug with no analgesia (Jahani 2013; Li 1994; Liu 2015); two did not blind staff to the intervention (Rayburn 1989a; Refstad 1980). Blinding of women and caregivers was unclear in 28 studies (Bitsch 1980; Blair 2005; Borglin 1971; De Boer 1987; Duncan 1969; Erskine 1985; Frank 1987; Giannina 1995; Hamann 1972; Hodgkinson 1979; Husslein 1987; Jackson 1983; Kainz 1992; Keskin 2003; Khooshideh 2009; Li 1988; Moore 1970; Mowat 1970; Nel 1981; Neumark 1978; Nicholas 1982; O'Dwyer 1971; Olson 1964; Osler 1987; Prasertsawat 1986; Quilligan 1980; Sliom 1970; Wheble 1988). Some studies reported to be double-blind but did not give details of blinding. The remaining studies blinded the women and caregivers by using identical volumes and syringes.

Detection bias (outcome assessor)

Twenty studies reported blinding of outcome assessor (Atkinson 1994; Bitsch 1980; Campbell 1961; Douma 2010; Fairlie 1999; Gillam 1958; Grant 1970; Keskin 2003; Khooshideh 2009; Kuti 2008; Levy 1971; Morley-Forster 2000; Morrison 1987; Prasertsawat 1986; Sekhavat 2009; Sheikh 1986; Viegas 1993; Volikas 2001; Wee 2014; Zafar 2016). Nine studies did not blind outcome assessors or likely used caregivers to record labour outcomes (Direkvand-Moghadam 2014; Jahani 2013; Li 1994; Liu 2015; Mobaraki 2016; Rayburn 1989a; Refstad 1980; Tawfik 1982; Thakur 2004). In the remaining studies, it was unclear if outcome assessors were blinded or not.

Incomplete outcome data

Assessing levels of attrition was very difficult in these studies, as denominators were frequently absent from results tables. In addition, even where all women appeared to be accounted for at follow-up, there were frequently missing data for specific outcomes. Nineteen studies were assessed to be at high risk of bias. In 14 studies loss to follow-up or missing data were greater than 10% (Bitsch 1980; Fairlie 1999; Hamann 1972; Levy 1971; Moore 1970; Mowat 1970; Wilson 1986), or greater than 20% (De Boer 1987; Frank 1987; Giannina 1995; Gillam 1958; Nicholas 1982; O'Dwyer 1971; Refstad 1980). Jackson 1983 excluded on the grounds of fetal distress and heart defects post randomisation. Four studies (Duncan 1969; Keskin 2003; Mowat 1970; Nel 1981) reported unexplained loss to follow-up. Sixty-five women were

excluded due to clerical errors or administration of wrong drug in Morrison 1987.

In several studies there were missing data on pain outcomes. This may have occurred because drugs were given at a late stage in labour, so that women had already given birth before the first scheduled pain assessment. For example, in Fairlie 1999 17%, and in O'Dwyer 1971 and Refstad 1980 more than one-third of women had given birth within an hour of drug administration. These three studies were rated as high risk of bias.

In some studies women were explicitly excluded from the analysis because of factors that may have related to study medication; in Hamann 1972, 13% of women were excluded after randomisation because they had a long labour or a caesarean section, and in Moore 1970, women were excluded because they received additional pain relief. Wilson 1986 excluded 10% of the sample because women reported that they received inadequate pain relief. Mitterschiffthaler 1991 excluded women who reported insufficient pain relief. In the study by Nelson 2005, any woman undergoing artificial rupture of membranes, commencing oxytocin or requesting epidural was excluded after randomisation and were replaced. Further, any women who reached 10 cm cervical dilation within one hour of drug administration were also excluded from the analysis; it was not clear how many women were lost and replaced for these reasons.

Twenty-two studies reported little explained, or no loss to follow-up. The remaining studies were assessed to be at unclear risk of attrition bias (Atkinson 1994; Campbell 1961; Direkvand-Moghadam 2014; Erskine 1985; Frank 1987; Giannina 1995; Grant 1970; Jahani 2013; Kainz 1992; Kuti 2008; Li 1994; Liu 2015; Mobaraki 2016; Morley-Forster 2000; Neumark 1978; Quilligan 1980; Sekhavat 2009; Sliom 1970; Wee 2014; Zafar 2016).

Selective reporting

Most of the studies were assessed to have unclear risk of reporting bias as we had access only to study reports and without study protocols for most studies, it is difficult to assess whether all outcomes have been accounted for. One study reported all outcomes pre-specified in their protocol (Wee 2014). Four studies (Campbell 1961; De Boer 1987; Jahani 2013; Sekhavat 2009) did report all the outcomes pre-specified in their methods and were at high risk of reporting bias (see Characteristics of included studies).

We were not able to explore possible publication bias by using funnel plots as too few studies were included in different comparisons.

Other potential sources of bias

Most of the studies reported that there was no apparent baseline imbalance between groups although this was not always explicit, and where tables describing characteristics of the two groups were provided, they frequently included only a small number of obstetric or demographic variables. In the study by Tsui 2004, there was imbalance between groups in terms of the numbers of women undergoing induction of labour in the two groups (20/25 in the pethidine group and 12/25 in the placebo group), and this may have had an impact on outcomes so this study was assessed to be at high risk of other bias. In the study by Rayburn 1989a, women were only recruited to the study at very limited times (weekdays 8am to 3pm), and while this may not put findings at high risk of bias, it may mean that those recruited were not representative of the population served by the study hospital. Most studies were assessed to be at unclear risk of other bias due to lack of information to adequately assess, or poor reporting. Thirteen studies had no other apparent risk of bias and were assessed to be at low risk (Atkinson 1994; Blair 2005; Borglin 1971; De Boer 1987; Douma 2010; Fairlie 1999; Giannina 1995; Jahani 2013; Mowat 1970; Olson 1964; Prasertsawat 1986; Volikas 2001; Wee 2014). In the Characteristics of included studies and 'Risk of bias' tables, we have set out more information which will assist in the interpretation of results.

Effects of interventions

See: **Summary of findings for the main comparison** IM pethidine compared to placebo for pain management in labour; **Summary of findings 2** Placebo and pethidine comparisons for pain management in labour

In this section where several studies have contributed data to a comparison, we have reported primary and secondary outcomes separately. For some comparisons single studies provided data on a very limited number of outcomes; for these comparisons we have reported outcomes under one heading. We had planned subgroup analysis by parity, by whether or not the labour was induced or augmented, by gestational age (preterm versus term birth), and by whether or not women had continuous support during labour. In this version of the review we were unable to carry out this analysis, as data were not provided by subgroups. In addition, we did not carry out planned sensitivity analysis by risk of bias domains because for most outcomes only one or two studies contributed data.

Intramuscular opioids for pain relief in labour

1. IM pethidine 50 mg/100 mg versus placebo

Four studies with 486 women contributed data to this comparison (Direkvand-Moghadam 2014; Sekhavat 2009; Sliom 1970; Tsui 2004), although for most outcomes only a single study contributed data. Kamyabi 2003 did not contribute any data.

Primary outcomes

Maternal satisfaction with analgesia measured during labour

One study involving 50 women (Tsui 2004) showed no clear difference in maternal satisfaction 30 minutes after administration of study drug (risk ratio (RR) 7.00, 95% confidence interval (CI) 0.38 to 128.87, very low-quality evidence); only three of 25 women receiving pethidine and none of the women receiving placebo reported to be 'satisfied' or 'very satisfied' with analgesia (Analysis 1.1).

Maternal satisfaction with analgesia in labour measured during the postnatal period

No study reported this outcome.

Secondary outcomes

Maternal

Maternal pain score or pain measured in labour

One study involving 116 women (Sliom 1970), reported more women in the pethidine group with "fair" or "good" pain relief within an hour of receiving the drug (RR 1.75, 95% CI 1.24 to 2.47, low-quality evidence; Analysis 1.2).

Maternal pain relief 30 minutes after study drug administration, defined as a reduction in visual analogue scale (VAS) score of at least 40 mm, was measured in one study with 50 women (Tsui 2004), and was greater for pethidine 100 mg compared with placebo (RR 25.00, 95% CI 1.56 to 400.54, low-quality evidence) though the CI for this estimate is very wide (Analysis 1.3).

Additional analgesia required

In one study (Tsui 2004), the majority of women in both groups required additional analgesia (epidural, pethidine, and Entonox); this applied to fewer women with pethidine 100 mg compared with placebo (RR 0.71, 95% CI 0.54 to 0.94, low-quality evidence; Analysis 1.4). However, 12/25 women in the placebo group had pethidine at 30 minutes as rescue analgesia confounding interpretation of reported outcomes after 30 minutes.

Epidural

There was no evidence of clear differences between groups the number of women requiring an epidural (RR 0.50, 95% CI 0.14 to 1.78; 1 study, 50 women; very low-quality evidence; Analysis 1.5).

Maternal sleepiness during labour

More women reported sleepiness with pethidine 100 mg, with half of those receiving pethidine feeling sedated compared with 11% of controls (RR 4.67, 95% CI 2.43 to 8.95; 2 studies, 166 women; Analysis 1.7).

There was no evidence of clear differences between groups in:

1. nausea and vomiting (RR 1.47, 95% CI 0.65 to 3.31; 2 studies, 166 women; Analysis 1.6);
2. caesarean sections (RR 0.71, 95% CI 0.36 to 1.37; 2 studies, 140 women; Analysis 1.9);
3. assisted vaginal births (RR 0.86, 95% CI 0.34 to 2.19; 1 study, 50 women; Analysis 1.8).

Postpartum haemorrhage (as defined by the trial authors), breastfeeding at discharge, breastfeeding in the postnatal period (four to six weeks), sense of control in labour (as defined by trialists), satisfaction with childbirth experience (as defined by trialists), effect (negative) on mother/baby interaction, and cost (as defined by trialists) were not reported for this comparison.

Neonatal

Neonatal resuscitation

The incidence of newborn resuscitation was low; no clear differences between groups was detected (RR 1.67, 95% CI 0.45 to 6.24; 1 study; 50 infants; Analysis 1.10).

Apgar score less than seven at one minute and Apgar score less than seven at five minutes

The number of babies with Apgar scores of seven or less at one minute did not differ between the placebo and pethidine groups; for this outcome we used a random-effects model because of high heterogeneity (average RR 1.64, 95% CI 0.52 to 5.18); 2 studies, 166 infants; (heterogeneity: I^2 = 61%, Tau^2 = 0.46, Chi^2 test for heterogeneity P = 0.11) (Analysis 1.11). No babies had Apgar scores less than or equal to seven at five minutes in two studies that reported this outcome (200 infants; Analysis 1.11).

Admission to special care baby unit/neonatal intensive care unit (as defined by trialists)

Admission to neonatal intensive care unit (NICU) was low; no clear differences between groups was detected (RR 1.00, 95% CI 0.07 to 15.12; 1 study; 50 infants; Analysis 1.12).

One study reported the incidence of fetal respiratory depression, but the study drugs were given late in labour to assess maximum fetal effect. Participants were not included in the analysis if birth was less than 30 minutes or more than four hours after administration of study drugs (Sliom 1970).

We were unable to include any results from one study that met the inclusion criteria, as it was unclear when outcomes were measured how they were defined and how many participants were included in the analysis (Kamyabi 2003). In this study, mean Apgar scores at one minute were reported to be higher (P = 0.008) in the pethidine 75 mg group compared with placebo group (data not shown).

No other neonatal outcomes were reported.

2. IM pentazocine versus placebo

IM pentazocine versus placebo was reported by one three-armed study involving 150 women (Zafar 2016). One hundred women contributed to the data for this comparison.

Primary outcomes

No outcomes regarding maternal satisfaction were reported.

Secondary outcomes

Maternal

This small study reported no clear differences between groups for:

1. maternal pain scores measured during labour (measured on a VAS) (mean difference (MD) -3.60, 95% CI -9.91 to 2.71; 1 study, 89 women; low-quality evidence;Analysis 2.1)
2. nausea and vomiting (no events reported in either group; 1 study, 89 women; Analysis 2.2);
3. caesarean section (RR 0.89, 95% CI 0.24 to 3.35; 1 study, 89 women; Analysis 2.3);
4. assisted vaginal births (RR 0.60, 95% CI 0.10 to 3.39; 1 study, 89 women; Analysis 2.4).

No other maternal or neonatal outcomes were reported.

3. IM tramadol versus no treatment

IM tramadol versus no treatment was reported by one small study involving 60 women (Li 1994). This study reported one outcome relevant to this review. Maternal satisfaction with analgesia was reported as "analgesic effect" and was described as "satisfactory" by 5/30 women in the tramadol group, and 0/30 in the no treatment group (RR 11.00, 95% CI 0.64 to 190.53; very low-quality evidence; Analysis 3.1). It is not clear from the trial report when this outcome was measured.

4. IM meptazinol versus IM pethidine

IM meptazinol versus IM pethidine was evaluated in six studies with 1898 women (Morrison 1987; Nel 1981; Nicholas 1982; Osler 1987; Sheikh 1986; Wheble 1988), and in two additional studies where women in both study groups also received add-on drugs (De Boer 1987; Jackson 1983). These two studies are reported at the end of this comparison.

Primary outcomes

Maternal satisfaction with analgesia measured during labour and Maternal satisfaction with analgesia in labour measured during the postnatal period

One study (Morrison 1987), involving 801 women showed no evidence of a difference between meptazinol 100 mg to 150 mg compared with pethidine 100 mg to 150 mg for assessment of analgesic effect measured at three to five days postpartum (RR 1.01, 95% CI 0.91 to 1.12; low-quality evidence; Analysis 4.1). In this study, more than half of the women receiving either of these opioids reported that they received no or poor relief despite the fact that women in both groups could also receive an additional dose of study drug, epidural or nitrous oxide as required.

Secondary outcomes

Maternal

Maternal pain score or pain measured in labour

In two studies (Nel 1981; Sheikh 1986), involving 239 women, there was no evidence of a difference between groups in pain intensity one hour after administration of meptazinol 100 mg or pethidine 100 mg; more than two-thirds of women in both groups were rating their pain as severe (four or five on a five-point scale) at one hour (average RR 1.11, 95% CI 0.69 to 1.80 (random-effects; heterogeneity: I^2 = 43%, Tau^2 = 0.08, Chi^2 test for heterogeneity P = 0.18, very low-quality evidence; Analysis 4.2)).

Additional analgesia required

Two studies (Osler 1987; Wheble 1988), involving 233 women found no evidence of a difference in requirement for additional analgesia between those who received meptazinol compared with pethidine (RR 1.03, 95% CI 0.88 to 1.20, very low-quality evidence; Analysis 4.3). This outcome is difficult to interpret as women in the study by Osler 1987 were allowed up to three doses of study drug (meptazinol 100 mg or pethidine 75 mg). Overall, 56 women required a second dose and 15 a third dose, but

the number per group was not reported. Whereas in the study by Wheble 1988, women were allowed a second dose of study drug (meptazinol 100 mg or 150 mg or pethidine 100 mg or 150 mg) or epidural or nitrous oxide at the discretion of the caregiver. Additional analgesia relates to a pudendal block in the one study (Osler 1987), and a second dose of study drug in the other (Wheble 1988).

Epidural

The use of epidural analgesia was similar between meptazinol and pethidine (RR 0.96, 95% CI 0.71 to 1.29, very low-quality evidence) in four studies (Nicholas 1982; Osler 1987; Sheikh 1986; Wheble 1988) involving 788 women (Analysis 4.4).

Maternal sleepiness during labour

Fewer women in the meptazinol group reported sleepiness (average RR 0.55, 95% CI 0.28 to 1.07; 3 studies, 1590 women), although there was moderate heterogeneity for this outcome (heterogeneity: I^2 = 44%, Tau^2 = 0.18, Chi^2 test for heterogeneity P = 0.17) and the CIs crossed the line of no effect (Analysis 4.5).

Nausea and vomiting in labour

Three studies each reported nausea and vomiting (Morrison 1987; Nicholas 1982; Sheikh 1986). There was no evidence for a difference in nausea (RR 1.11, 95% CI 0.95 to 1.28; 3 studies, 1590 women; Analysis 4.6); however, more women reported vomiting (RR 1.25, 95% CI 1.06 to 1.47; 3 studies, 1589 women; Analysis 4.6) with meptazinol compared with pethidine.

Caesarean section

There was no evidence of a difference in rates of caesarean section between meptazinol and placebo. However, substantial heterogeneity was detected; therefore, we used a random-effects model (average RR 0.56, 95% CI 0.16 to 2.00) (heterogeneity: I^2 = 75%, Tau^2 = 0.84, Chi^2 test for heterogeneity P = 0.02; Analysis 4.7).

Assisted vaginal birth

Instrumental birth was reported in three studies (Morrison 1987; Osler 1987; Wheble 1988) involving 1266 women, and rates were similar between groups (RR 1.00, 95% CI 0.81 to 1.22; Analysis 4.8).

No other maternal outcomes were reported.

Neonatal

Fetal heart rate changes in labour (persistent decelerations or tachycardia)

One study (34 women) (De Boer 1987) reported decelerations during labour but found no clear difference between the meptazinol or pethidine groups (RR 1.23, 95% CI 0.92 to 1.64; Analysis 4.10). One study compared IM meptazinol 1.8 mg/kg with IM pethidine 1.8 mg/kg; all women also received promazine 25 mg IM (Jackson 1983). A second study compared IM meptazinol 1.5 mg/kg with IM pethidine 1.5 mg/kg; all women also received metoclopramide 10 mg IM (De Boer 1987). Women could receive a second dose of study drug after three hours in both studies. Both studies were conducted to assess effects of the study drugs on the newborn only. There was no evidence of difference in the number of babies with fetal heart rate changes (decelerations).

Naloxone administration

We found no evidence of a difference between meptazinol compared with pethidine for naloxone administration (RR 0.89, 95% CI 0.77 to 1.02; 1 study, 998 infants; Analysis 4.11). In one study (Morrison 1987), 40% of the babies were given naloxone, reflecting local practice at the time rather than low Apgar scores; with 41% of the babies having Apgar scores greater than or equal to eight at the time of administration.

Neonatal resuscitation

We found no evidence of a difference between meptazinol compared with pethidine for newborn resuscitation before and after 36 weeks' gestation (RR 1.00, 95% CI 0.95 to 1.05; 2 studies, 1356 infants; Analysis 4.12). In one study (Jackson 1983), three babies in the meptazinol group and two in the pethidine group required resuscitation (RR 1.50, 95% CI 0.26 to 8.60; 100 infants; Analysis 4.13).

Apgar score less than seven at one minute and Apgar score less than seven at five minutes and Apgar score less than seven at 10 minutes

Six studies involving 791 women reported number of babies with Apgar scores less than or equal to seven at one minute (De Boer 1987; Jackson 1983; Nel 1981; Nicholas 1982; Osler 1987; Wheble 1988), and three studies reported this outcome at five minutes (Nel 1981; Nicholas 1982; Osler 1987). There was no evidence of a difference between groups at one minute (RR 0.79, 95% CI 0.56 to 1.11; 6 studies; 791 infants; Analysis 4.14) or five minutes (RR 0.49, 95% CI 0.05 to 5.37; 3 studies, 616 infants; Analysis 4.15) with three babies with low scores at five minutes reported in one study (Osler 1987), and none in the other two (Nel 1981; Nicholas 1982).

In the study by De Boer 1987, Apgar at five and 10 minutes were reported as 'similar' in both groups. No babies in either group had Apgar scores less than or equal to seven at 10 minutes.

5. IM diamorphine + prochlorperazine versus IM pethidine + prochlorperazine

One study involving 133 women compared IM diamorphine 5 mg with 7.5 mg versus IM pethidine 100 mg to 150 mg. All women also received IM prochlorperazine 12.5 mg at the same time as the study drug (Fairlie 1999).

Primary outcomes

Maternal satisfaction with analgesia in labour measured during the postnatal period

Global assessment of pain relief was evaluated at 24 hours; there was no evidence of a difference between groups in the number of women reporting 'fair' or 'poor' as opposed to 'good' pain relief, with more than half of the women in both groups having inadequate relief (RR 0.88, 95% CI 0.67 to 1.16; very low-quality evidence; Analysis 5.1). Maternal satisfaction was not measured in labour.

Secondary outcomes

Maternal

Maternal pain score or pain measured in labour

More women reported pain intensity as moderate or severe one hour post administration of study drug with pethidine compared with diamorphine, though there was no evidence of a clear difference between groups, with the majority of women in both groups reporting moderate or severe pain (RR 0.85, 95% CI 0.72 to 1.01; very low-quality evidence; Analysis 5.2).

Additional analgesia required

There was no evidence for a difference between groups in the number of women requiring additional analgesia (second dose of study drug) (RR 1.35, 95% CI 0.53 to 3.40; very low-quality evidence; Analysis 5.3).

Epidural

There was no evidence for a difference between groups in the number of women requiring an epidural (RR 1.22, 95% CI 0.72 to 2.07; very low-quality evidence; Analysis 5.4).

Maternal sleepiness during labour

The number of women moderately drowsy or asleep one hour after study drug administration was similar between groups (RR 0.93, 95% CI 0.52 to 1.66; Analysis 5.5). The attending midwife measured sedation on a four-point scale where: 0 = alert; 1 = mildly drowsy; 2 = moderately drowsy; 3 = asleep.

Nausea and vomiting in labour

The number of women vomiting was lower with diamorphine compared with pethidine (RR 0.39, 95% CI 0.17 to 0.86; Analysis 5.6).

Caesarean section

There was no evidence for a difference between groups in the number of women who had a caesarean section (RR 0.52, 95% CI 0.10 to 2.76; Analysis 5.7).

Assisted vaginal birth

There was no evidence for a difference between groups in the number of women who had an assisted vaginal birth (RR 0.96, 95% CI 0.46 to 2.02; Analysis 5.8).

No other maternal outcomes were reported.

Neonatal

Neonatal resuscitation

There were no clear differences between groups for the number of babies needing resuscitation (RR 1.21, 95% CI 0.73 to 2.02; 133 infants; Analysis 5.9).

Apgar score less than seven at one minute and Apgar score less than seven at five minutes

Fewer babies had Apgar scores less than seven at one minute with diamorphine compared with pethidine (RR 0.41, 95% CI 0.18 to 0.91; 133 infants; Analysis 5.10). However, there was no evidence of a clear difference between groups at five minutes, with few babies with an Apgar score less than seven in either group (RR 0.35, 95% CI 0.04 to 3.27; 133 infants; Analysis 5.11).

Admission to special care baby unit/neonatal intensive care unit (as defined by trialists)

There were no clear differences between groups for the number of babies needing admission to NICU (RR 0.58, 95% CI 0.21 to 1.64; 133 infants; Analysis 5.12).

No other neonatal outcomes were reported.

6. IM tramadol versus IM pethidine

Seven studies involving 569 women compared IM tramadol versus IM pethidine (Bitsch 1980; Fieni 2000; Husslein 1987; Keskin 2003; Khooshideh 2009; Prasertsawat 1986; Viegas 1993). Tramadol and pethidine doses varied between studies and were 50 mg, 75 mg or 100 mg.

Primary and secondary outcomes

Maternal

Women's satisfaction with analgesia was not measured in any of the studies.

Maternal pain score or pain measured in labour

Pain intensity was defined in disparate ways in the studies; however, more women had poor pain relief with tramadol compared with pethidine (RR 1.56, 95% CI 1.10 to 2.21; 4 studies, 243 women; low-quality evidence; Analysis 6.1).

Additional analgesia required

In three studies which reported requirement for additional analgesia, no evidence of a difference was detected (average RR 1.07, 95% CI 0.60 to 1.91; 3 studies, 295 women; very low-quality evidence; Analysis 6.2). Bitsch 1980 administered second and third doses of the study drug, Khooshideh 2009 offered a second dose, and Prasertsawat 1986 gave a second dose but half the amount.

Maternal sleepiness during labour

More women in the pethidine group reported sleepiness although heterogeneity was high and we used a random-effects model (average RR 0.57, 95% CI 0.33 to 0.97; 5 studies, 409 women) (heterogeneity I^2 = 72%, Tau^2 = 0.24, Chi^2 test for heterogeneity P = 0.007; Analysis 6.3).

Nausea and vomiting in labour

There was no evidence for a clear difference in incidence of nausea and/or vomiting with tramadol compared with placebo (average RR 0.97, 95% CI 0.34 to 2.76; 6 studies, 454 women; Analysis 6.4). There was a substantial level of heterogeneity detected for this outcome (I^2 = 72%, Tau^2 = 1.09, Chi^2 test for heterogeneity P = 0.003) therefore we used a random-effects model for the analysis.

Caesarean section and assisted vaginal birth

There was no clear difference between the tramadol and pethidine groups for incidence of caesarean section (RR 0.71, 95% CI 0.23 to 2.18; 3 studies, 260 women; Analysis 6.5) or assisted vaginal birth (RR 0.56, 95% CI 0.12 to 2.56; 3 studies, 260 women; Analysis 6.6).

Neonatal

Only two studies reported Apgar scores (Khooshideh 2009; Prasertsawat 1986), and reported no babies in either group with Apgar scores less than or equal to seven at one or five minutes, and no babies requiring resuscitation (Analysis 6.8; Analysis 6.7).

One study (Keskin 2003), reported the incidence of respiratory distress and admission to NICU which occurred more frequently with tramadol 100 mg compared with pethidine 100 mg, though CIs crossed the line of no effect for both outcomes (RR 2.26, 95% CI 0.64 to 7.89; 1 study; 59 infants; Analysis 6.9 and RR 2.26, 95% CI 0.64 to 7.89; 1 study; 59 infants; Analysis 6.10).

No other maternal or neonatal outcomes were reported.

7. IM tramadol + triflupromazine versus IM pethidine + triflupromazine

One study involving 66 women compared tramadol 500 mg with pethidine 50 mg, and both groups also received triflupromazine 10 mg (Kainz 1992). A third study arm received tramadol 100 mg.

Primary and secondary outcomes

Maternal satisfaction with analgesia measured during labour or maternal satisfaction with analgesia in labour measured during the postnatal period was not reported.

Data for effects on pain were not reported (P values for the change within groups were reported; not the between group differences; data not shown).

Sleepiness was more frequently reported by women who received tramadol, though CIs crossed the line of no effect (RR 2.86, 95% CI 0.68 to 12.12; 1 study, 40 women; Analysis 7.1). The incidence of nausea or vomiting was reported and was infrequent, with no evidence of differences between groups (RR 0.82, 95% CI 0.13 to 5.25 and RR 0.40, 95% CI 0.02 to 9.35, respectively; 1 study, 40 women; Analysis 7.2).

The authors report that there were no negative effects on the newborn; though no data were presented.

8. IM dihydrocodeine versus IM pethidine

One study involving 196 women compared a single dose of IM dihydrocodeine 50 mg with IM pethidine 100 mg (Sliom 1970). An additional study arm received placebo.

Primary and secondary outcomes

Maternal pain score or pain measured in labour

There was no evidence of a clear difference in pain relief between groups with a substantial proportion of women in each group reporting poor pain relief one hour after administration of study drug (RR 1.09, 95% CI 0.64 to 1.86; 1 study, 138 women; very low-quality evidence; Analysis 8.1).

Maternal sleepiness and nausea and vomiting in labour

There was no evidence of a difference between dihydrocodeine and pethidine for nausea and vomiting (RR 0.87, 95% CI 0.40 to 1.88; 1 study, 138 women; Analysis 8.3), or sleepiness (RR 0.67, 95% CI 0.43 to 1.04; 1 study, 138 women; Analysis 8.2).

Apgar score less than seven at one minute

Fewer babies had Apgar scores less than or equal to seven at one minute with dihydrocodeine compared with pethidine (RR 0.57, 95% CI 0.39 to 0.84; 138 infants; Analysis 8.4). Apgar score at five minutes was reported as mean scores rather than number of babies in each group: there was no clear difference between groups reported (data not shown).

9. IM pentazocine versus pethidine

Five studies with 792 women compared IM pentazocine versus pethidine (Borglin 1971; Duncan 1969; Levy 1971; Moore 1970; Mowat 1970). One study with 85 women also compared IM pentazocine versus pethidine but all women received promazine 25 mg IM before first injection (Refstad 1980).

Primary outcomes

Maternal satisfaction with analgesia measured during labour

Two studies reported on the numbers of women rating pain relief as good or very good at birth (Borglin 1971; Mowat 1970), and there was no clear difference between IM pentazocine or IM pethidine without add-on drugs in either study, or when results were pooled (RR 1.08, 95% CI 0.92 to 1.27; 253 women; very low-quality evidence; Analysis 9.1).

Secondary outcomes

Maternal

Maternal pain score or pain measured in labour

Four studies reported poor pain relief (Duncan 1969; Levy 1971; Moore 1970; Refstad 1980). More than half of the women in both groups had only partial or poor relief and there was no clear difference between groups for women who received promazine (RR 1.53, 95% CI 0.66 to 3.58; 1 study, 85 women, very low-quality evidence) or those who did not (average RR 1.23, 95% CI 0.74 to 2.05; 3 studies, 365 women; very low-quality evidence; Analysis 9.2). There was a substantial level of heterogeneity detected for this outcome (I^2 = 83%, Tau^2 = 0.16, Chi^2 test for heterogeneity P = 0.003), therefore we used a random-effects model for the analysis.

Additional analgesia required

The use of additional analgesic drugs (second dose of study drug) was reported by two studies (Mowat 1970; Refstad 1980). There was no clear difference between groups in either study (Analysis 9.3): pentazocine and pethidine alone (RR 0.91, 95% CI 0.50 to 1.65; 94 women, very low-quality evidence); and with promazine (RR 1.67, 95% CI 0.73 to 3.84; 85 women, very low-quality evidence).

There was no clear evidence of a difference between groups for:

1. maternal sleepiness in labour (Analysis 9.4)
    i) pentazocine versus pethidine alone (RR 1.00, 95% CI 0.89 to 1.12; 3 studies, 391 women);
2. nausea in labour (Analysis 9.5)
    i) pentazocine versus pethidine alone (RR 0.46, 95% CI 0.24 to 0.90; 3 studies, 391 women);
3. vomiting in labour (Analysis 9.5)
    i) pentazocine versus pethidine alone (RR 0.92, 95% CI 0.27 to 3.14; 1 study, 73 women);
4. assisted vaginal birth (Analysis 9.6)
    i) pentazocine versus pethidine alone (RR 5.22, 95% CI 0.63 to 42.97; 1 study, 94 women);
    ii) pentazocine versus pethidine with promazine (RR 0.78, 95% CI 0.23 to 2.71; 1 study, 85 women).

No other maternal outcomes were reported.

Neonatal

There was no clear evidence of a difference between groups for:

1. naloxone administration (Analysis 9.7)
    i) pentazocine versus pethidine with promazine (RR 0.49, 95% CI 0.09 to 2.53; 1 study, 85 infants);

2. low Apgar score (less than seven) at one minute (Analysis 9.8)

i) pentazocine versus pethidine alone (average RR 1.39, 95% CI 0.06 to 32.97; 2 studies, 242 infants, I^2 = 67%, Tau^2 = 3.56; Chi^2 test for heterogeneity P = 0.08);

ii) pentazocine versus pethidine with promazine (RR 1.13, 95% CI 0.07 to 17.30; 1 study, 66 infants);

3. low Apgar score (less than seven) at five minutes (Analysis 9.9)

i) pentazocine versus pethidine alone (RR 0.23, 95% CI 0.01 to 4.54; 1 study, 62 infants);

ii) pentazocine versus pethidine with promazine (RR 0.38, 95% CI 0.02 to 8.88; 1 study, 66 infants).

No other neonatal outcomes were reported.

10. IM nalbuphine versus pethidine

Four studies with 486 women are included in this comparison (Lardizabal 1999; Lisboa 1997; Mitterschiffthaler 1991; Wilson 1986).

Primary outcomes

Maternal satisfaction with analgesia measured during labour and during the postnatal period

One study reported maternal satisfaction with analgesia at 24 hours (Wilson 1986). The majority of women receiving both nalbuphine and pethidine thought that analgesia had been "minimally effective" (63% and 85% respectively), although fewer women who received nalbuphine reported to be dissatisfied with their analgesia (RR 0.73, 95% CI 0.55 to 0.96; 72 women, 1 study; low-quality evidence; Analysis 10.1). One study reported the number of women that were free of pain (Mitterschiffthaler 1991); there was no clear difference between groups, with few women in either group having no pain (RR 6.00, 95% CI 0.79 to 45.42; 1 study, 40 women; very low-quality evidence; Analysis 10.2).

Secondary outcomes

Maternal

Maternal pain score or pain measured in labour

Two studies reported pain intensity: one reported severe pain at 30 minutes (Lardizabal 1999), and the other VAS at 60 minutes (Wilson 1986). There were no clear differences between groups in either analysis (RR 0.86, 95% CI 0.59 to 1.26; 1 study, 295 women; very low-quality evidence; Analysis 10.3; and (MD -8.00, 95% CI -18.55 to 2.55; 1 study, 72 women; very low-quality evidence; Analysis 10.4).

Additional analgesia required

One study reported the use of additional analgesia (second dose of study drug) but found no difference between the groups (RR 1.26, 95% CI 0.49 to 3.27; 1 study, 72 women; very low-quality evidence; Analysis 10.5).

Epidural

One study reported the use of epidural (Lardizabal 1999); there was no clear difference between groups (RR 1.65, 95% CI 0.55 to 4.94; 307 women; low-quality evidence; Analysis 10.6).

Nausea and vomiting in labour

One study reported nausea and vomiting as separate outcomes (Lardizabal 1999), and another reported nausea and vomiting as a single outcome (Wilson 1986). Fewer women who received nalbuphine reported nausea alone (RR 0.62, 95% CI 0.42 to 0.91, 301 women), or vomiting (RR 0.41, 95% CI 0.22 to 0.76; 301 women) compared with women who received pethidine. Likewise, fewer women who received nalbuphine reported nausea and vomiting combined (RR 0.41, 95% CI 0.18 to 0.94; 72 women; Analysis 10.8).

There was no evidence of clear differences between groups for:

1. maternal sleepiness (RR 3.78, 95% CI 0.86 to 16.60; 1 study, 72 women; Analysis 10.7);
2. caesarean section (RR 0.45, 95% CI 0.12 to 1.69; 1 study, 310 women; Analysis 10.9);
3. assisted vaginal births (average RR 0.98, 95% CI 0.25 to 3.85; 2 studies, 382 women; I^2 = 41%; Tau^2 = 0.50; Chi^2 test for heterogeneity P = 0.19; Analysis 10.10).

No other maternal outcomes were reported.

Neonatal

Two studies reported neonatal outcomes (Lardizabal 1999; Wilson 1986).

There was no clear difference between groups for:

1. naloxone administration (RR 6.63, 95% CI 0.35 to 123.93; 1 study, 72 infants; Analysis 10.11);
2. Apgar score less than seven at one (average RR 1.18, 95% CI 0.72 to 1.95; 2 studies, 382 infants; I^2 = 44%; Tau^2 = 0.07; Chi^2 test for heterogeneity P = 0.18), and Apgar score less than seven at five minutes (RR 0.47, 95% CI 0.04 to 4.99; 1 study, 72 infants; Analysis 10.12);
3. admission to NICU (RR 1.07, 95% CI 0.61 to 1.89; 1 study, 299 infants; Analysis 10.13).

Newborn neuro-behavioural scores

One study reported a neonatal neuro-behavioural score two to four hours following birth (Wilson 1986); babies of women who received nalbuphine had lower scores than babies born to women in the control group (MD -3.70, 95% CI -6.14 to -1.26; 72 infants; Analysis 10.14).

No other neonatal outcomes were reported.

11. IM phenazocine versus pethidine

One study with 212 women (Grant 1970) compared IM phenazocine versus IM pethidine.

Primary and secondary outcomes

This study reported only two outcomes: epidural and nausea and vomiting in labour. There was no clear difference between groups for epidural (RR 1.31, 95% CI 0.58 to 2.97; very low-quality evidence; Analysis 11.1), but fewer women who received phenazocine reported nausea and vomiting in labour (RR 0.39, 95% CI 0.20 to 0.78; Analysis 11.2) compared with those who received pethidine.

12. IM diamorphine/morphine versus pethidine

We included two studies with 619 women in this comparison (Prasertsawat 1986; Wee 2014).

Primary outcomes

Maternal satisfaction with analgesia measured during labour or during the postnatal period

One study (Wee 2014), found that more women in the diamorphine group reported to be 'satisfied' or 'very satisfied' with the analgesia compared with the pethidine group (RR 1.13, 95% CI 1.02 to 1.26; 484 women; high-quality evidence Analysis 12.1). However, the smaller study reported no clear difference between groups in the number of women describing their pain relief as poor (RR 1.22, 95% CI 0.56 to 2.66; 1 study, 90 women; very low-quality evidence; Analysis 12.2).

Secondary outcomes

Maternal

Maternal pain score or pain measured in labour

Women in the diamorphine group reported less pain than the pethidine group at 30 minutes (MD -0.80, 95% CI -1.24 to -0.36; 1 study, 484 women; high-quality evidence; Analysis 12.3), and at 60 minutes (MD -0.80, 95% CI -1.26 to -0.34; 1 study, 484 women; high-quality evidence; Analysis 12.4) after receiving analgesia.

There was no clear difference between groups for:

1. additional analgesia required (RR 1.00, 95% CI 0.92 to 1.10; 2 studies, 574 women; moderate-quality evidence; Analysis 12.5);
2. maternal sleepiness during labour (RR 0.60, 95% CI 0.29 to 1.23; 1 study, 90 women; Analysis 12.6);
3. nausea and vomiting in labour (RR 1.00, 95% CI 0.21 to 4.69; 1 study, 90 women; Analysis 12.7);
4. caesarean section (RR 0.94, 95% CI 0.66 to 1.35; 1 study, 484 women; Analysis 12.8);
5. assisted vaginal birth (RR 1.28, 95% CI 0.91 to 1.80; 1 study, 484 women; Analysis 12.9).

Neonatal

There was no clear difference between morphine and pethidine for:

- naloxone administration (RR 0.98, 95% CI 0.20 to 4.83; 1 study, 484 infants; Analysis 12.10);
- neonatal resuscitation (RR 0.96, 95% CI 0.66 to 1.41; 2 studies, 574 infants; Analysis 12.11). No babies received resuscitation in Prasertsawat 1986;
- Apgar score less than seven at one minute (RR 1.15, 95% CI 0.76 to 1.73; 2 studies, 574 infants; Analysis 12.12);
- admission to special care baby unit/neonatal intensive care unit (RR 0.87, 95% CI 0.34 to 2.23; 1 study, 484 infants; Analysis 12.13).

No other neonatal outcomes were reported.

13. IM butorphanol versus pethidine

One study with 80 women compared IM butorphanol with IM pethidine (Maduska 1978).

Primary and secondary outcomes

This study did not report on the review's primary outcomes. There was no evidence of clear differences between groups for additional analgesia required (second dose of study drug) (RR 0.89, 95% CI 0.55 to 1.45; very low-quality evidence; Analysis 13.1), nausea (RR 0.20, 95% CI 0.01 to 4.04; Analysis 13.2), or vomiting (RR 0.50, 95% CI 0.05 to 5.30; Analysis 13.3). Likewise, there was no clear difference between groups for neonatal resuscitation (RR 0.33, 95% CI 0.01 to 7.95; Analysis 13.4) or naloxone administration (RR 0.33, 95% CI 0.01 to 7.95; Analysis 13.5).

14. IM Avacan® versus IM pentazocine

We included one study with 185 women in this comparison (Hamann 1972).

Primary and secondary outcomes

This study did not report on either of our primary outcomes.
There were no clear differences between groups for additional analgesia required (Entonox) (RR 0.92, 95% CI 0.53 to 1.63; 1 study, 160 women; Analysis 14.1). More women in the Avacan® group received a pudendal-paracervical block (RR 2.02, 95% CI 1.16 to 3.53; 160 women; Analysis 14.2). There was no evidence of a clear difference between groups for the number of women having a caesarean section (RR 0.62, 95% CI 0.21 to 1.84; 184 women; Analysis 14.3), or babies born with an Apgar score less than or equal to seven at birth ((RR 0.59, 95% CI 0.27 to 1.26; 160 women; Analysis 14.4). This study did not report on any other maternal or neonatal outcomes.

15. IM pentazocine versus IM Pethilorfan®

One trial involving 98 women compared pentazocine with Pethilorfan® (O'Dwyer 1971).

Primary and secondary outcomes

This trial reported maternal satisfaction with analgesia in labour in the form of the number of women saying that they did not obtain any relief from medication at one hour. There were no clear differences between groups for this outcome (RR 1.22, 95% CI 0.77 to 1.95; 69 women; Analysis 15.1).
No clear differences were reported for any of the secondary outcomes recorded: additional analgesia required (second dose of study drug) (RR 0.52, 95% CI 0.10 to 2.71; 98 women; Analysis 15.2), assisted vaginal birth (RR 1.04, 95% CI 0.07 to 16.19; 98 women; Analysis 15.3). Apgars scores less than seven were not reported, however, Apgar scores less than eight were reported at one minute (RR 5.71, 95% CI 0.72 to 45.39; 82 infants; Analysis 15.4), and at five minutes (no events in either group, 82 infants; Analysis 15.5) finding no clear differences across groups.

16. IM pentazocine versus complementary and alternative medicine (CAM)

One study (Zafar 2016) involving 150 women contributed to this outcome, one control arm of 50 women were not included in this comparison. The homeopathy group received 1 mL of saline injection and oral homeopathic medicine prescribed by a qualified homeopath.

Primary and secondary outcomes

No primary outcomes were reported.
There were no clear differences between the groups for: maternal pain score during labour (MD -0.40, 95% CI -7.61 to 6.81; 89 women; Analysis 16.1), nausea and vomiting (RR 0.30, 95% CI 0.01 to 7.14; 89 women; Analysis 16.2), caesarean section (RR 0.89, 95% CI 0.24 to 3.35; 89 women; Analysis 16.3), and assisted vaginal birth (RR 0.89, 95% CI 0.13 to 6.07; 89 women; Analysis 16.4).

17. IM pentazocine versus IM tramadol

One study (Kuti 2008) involving 100 women reported this comparison.

Primary outcomes

Maternal satisfaction with analgesia measured during labour or during the postnatal period

More women in the pentazocine group than the tramadol group reported to be satisfied with their analgesia 30 minutes after receiving the injection (RR 2.40, 95% CI 1.28 to 4.48; 100 women; Analysis 17.1), however this difference was no longer clear after 60 minutes had passed (RR 1.62, 95% CI 0.91 to 2.86; 100 women; Analysis 17.2).

Secondary outcomes

Maternal

Maternal pain score or pain measured in labour

It appears that fewer women in the pentazocine group reported moderate or severe pain 30 minutes following administration of the drug however CIs cross the line of no effect so this result is not certain (RR 0.75, 95% CI 0.55 to 1.02; 100 women; Analysis 17.3). At 60 minutes following administration there is not a clear difference between the groups (RR 0.81, 95% CI 0.60 to 1.08; 100 women; Analysis 17.4) though results still appear to favour pentazocine.
There were no clear differences between the groups for:

1. maternal sleepiness during labour (RR 1.67, 95% CI 0.66 to 4.24; Analysis 17.5);
2. nausea and vomiting during labour (RR 1.00, 95% CI 0.06 to 15.55; Analysis 17.6);
3. caesarean section (RR 1.50, 95% CI 0.45 to 4.99; Analysis 17.7);
4. assisted vaginal birth (RR 2.00, 95% CI 0.19 to 21.36; Analysis 17.8).

No other maternal outcomes were reported.

Neonatal

There were no clear differences between the groups for:

1. Apgar score less than seven at one minute (RR 1.67, 95% CI 0.42 to 6.60; 100 infants; Analysis 17.9);

2. Apgar score less than seven at five minutes (RR 3.00, 95% CI 0.13 to 71.92; 100 infants; Analysis 17.10);
3. admission to neonatal intensive care unit (RR 2.87, 95% CI 0.12 to 68.47; 86 infants; Analysis 17.11).

No other neonatal outcomes were reported in this study.

18. IM pethidine versus inhaled nitrous oxide (Entonox)

One study (Mobaraki 2016) with 100 women reported this comparison.

Primary and secondary outcomes

Maternal pain score or pain measured during labour

This study only reported pain relief following analgesia using a pain score; at 30 minutes women who received pethidine reported better pain relief than those with inhaled nitrous oxide (MD 1.66, 95% CI 1.17 to 2.15; very low-quality evidence; Analysis 18.1). After 60 minutes, there was not a clear difference in pain relief reported by the groups (MD -0.36, 95% CI -0.85 to 0.13; very low-quality evidence; Analysis 18.2), although interestingly, pain relief reported in the pethidine group had dropped compared to 30 minute readings, whilst the pain relief in the nitrous oxide group had risen.

Intravenous opioids for pain relief in labour

19. IV pethidine versus placebo

One study (El-Refaie 2012) with 240 women contributed data to this comparison.

Primary and secondary outcomes

Maternal

This study did not report the primary outcomes.

Maternal pain score or pain measured in labour

Women who received IV pethidine reported lower pain scores than those who received a placebo (MD -4.10, 95% CI -4.56 to -3.64; moderate-quality evidence; Analysis 19.1).

Nausea and vomiting

Fewer women in the placebo group experienced nausea and vomiting in labour (RR 2.43, 95% CI 1.05 to 5.64; Analysis 19.2).

Caesarean section; assisted vaginal birth

There was no clear difference between the groups in number of women who had a caesarean section (RR 0.88, 95% CI 0.46 to 1.68; Analysis 19.3) or assisted vaginal birth (RR 0.75, 95% CI 0.33 to 1.71; Analysis 19.4).

No other maternal outcomes reported.

Neonatal

There was no clear difference between the groups in number of babies admitted to neonatal intensive care (RR 0.67, 95% CI 0.11 to 3.92; 240 infants; Analysis 19.5).

No other neonatal outcomes were reported.

20. IV fentanyl versus no treatment

One study (Jahani 2013) involving 70 women reported this comparison. It was not made clear in this study whether or not the women in the control group were able to request pain relief. The pain scores were noticeably worse in the control group with 31/35 women reporting severe pain, and 0/35 reporting this in the fentanyl group.

Primary and secondary outcomes

This study did not report the primary outcomes, many maternal, or any neonatal outcomes.

Maternal pain score or pain measured in labour

IV fentanyl resulted in lower pain scores (MD -5.00, 95% CI -5.47 to -4.53; very low-quality evidence; Analysis 20.1), and no women reporting "severe pain" after 60 minutes (RR 0.02, 95% CI 0.00 to 0.25; very low-quality evidence; Analysis 20.2). There was no clear difference between groups for the number of women who had caesarean sections (RR 1.50, 95% CI 0.27 to 8.43; Analysis 20.3).

21. IV fentanyl versus IV pethidine

We included one study with 105 women in this comparison (Rayburn 1989a). The study recruited women only during a limited time period Monday to Friday and allocation was not blinded due to the different half-lives of the treatment options.

Primary and secondary outcomes

The primary outcomes were not reported in this study.

Maternal

Maternal pain score or pain measured in labour

The mean maternal pain scores for women allocated to the IV fentanyl compared with those in the IV pethidine group were similar; women in both groups reported mean pain scores of approximately six on a 10 mm scale (MD -0.20, 95% CI -1.18 to 0.78; low-quality evidence; Analysis 21.1). It is not clear from the trial report whether 0 or 10 equalled less pain. It is reported that both treatments "took the edge off" the contraction pain (Rayburn 1989a).

Additional analgesia required

Women in the pethidine group required fewer doses than those in the fentanyl group (MD 0.40, 95% CI 0.14 to 0.66; low-quality evidence; Analysis 21.2).

Maternal sleepiness in labour

Maternal sedation was lower in women allocated to the IV fentanyl group compared with those in the IV pethidine group (RR 0.05, 95% CI 0.00 to 0.82; Analysis 21.3).

There were no clear differences for all other reported outcomes including nausea and vomiting (RR 0.51, 95% CI 0.17 to 1.55; Analysis 21.4), anti-emetic required (RR 0.09, 95% CI 0.01 to 1.52; Analysis 21.5), and caesarean section (RR 1.14, 95% CI 0.24 to 5.40; Analysis 21.6).

No further maternal outcomes were reported.

Neonatal

There were no clear differences for all neonatal outcomes reported:

1. naloxone required (RR 0.16, 95% CI 0.02 to 1.28; Analysis 21.7);
2. neonatal resuscitation/ventilatory support (RR 1.03, 95% CI 0.46 to 2.32; Analysis 21.8);
3. Apgar score less than seven at one minute (RR 0.63, 95% CI 0.23 to 1.77; Analysis 21.9);
4. Apgar score less than seven at five minutes (RR 0.38, 95% CI 0.02 to 9.12; Analysis 21.10);
5. newborn neuro-behavioural score (one to two hours after delivery) (MD 1.30, 95% CI 0.15 to 2.45; Analysis 21.11);
6. newborn neuro-behavioural score (two hours to 24 hours) (MD 0.90, 95% CI -0.42 to 2.22; Analysis 21.12).

No other neonatal outcomes were reported.

22. IV nalbuphine versus IV pethidine

We included one study involving 28 women compared IV nalbuphine with IV pethidine (Giannina 1995).

Primary and secondary outcomes

No outcomes relating to maternal pain during labour were reported.

This study reported estimable data for only two relevant secondary outcomes (caesarean section and Apgar score less than seven at one and five minutes), neither of which showed any clear difference between the two groups: caesarean section (RR 5.00, 95% CI 0.26 to 95.61; Analysis 22.1), Apgar scores less than seven at one minute (RR 3.00, 95% CI 0.13 to 67.91; Analysis 22.2; no babies had Apgar less than seven at five minutes; Analysis 22.3).

23. IV phenazocine versus IV pethidine

We included one study including 194 women compared IV phenazocine with IV pethidine (Olson 1964).

Primary and secondary outcomes

Maternal

There was no clear difference between groups for maternal satisfaction with analgesia measured during labour (comparing the number of women with "fair" or "poor" pain relief one hour after administration) (RR 0.72, 95% CI 0.48 to 1.10; very low-quality evidence; Analysis 23.1). No other primary outcomes were reported.

Only one identified secondary outcome reported estimable data: nausea with vomiting. There was no clear difference between the two groups for this outcome (RR 0.40, 95% CI 0.08 to 2.01; Analysis 23.2).

Neonatal

There were no babies that had an Apgar score less than seven at one minute (Analysis 23.3; Analysis 23.4).

24. IV butorphanol versus IV pethidine

Three studies involving a total of 330 women compared IV butorphanol with IV pethidine (Hodgkinson 1979; Nelson 2005; Quilligan 1980), though most outcomes only include data from single studies.

Primary outcomes

No outcomes relating to maternal satisfaction with analgesia were reported.

Secondary outcomes

Maternal

Maternal pain score or pain measured in labour

One study (Quilligan 1980), involving 100 women (findings for these primary outcomes reported for 80 women) included two measures of women's pain during labour; women's reported pain relief and pain score. Women's mean pain relief score was higher

for those in the group receiving butorphanol (MD 0.67, 95% CI 0.25 to 1.09; low-quality evidence; Analysis 24.1). This finding was supported by data regarding reported pain scores one hour after drug administration, which were lower for women in the butorphanol group (MD -0.60, 95% CI -1.02 to -0.18; low-quality evidence; Analysis 24.2). The clinical significance of a difference of this magnitude (i.e. 0.6 on a 10-point scale) is more difficult to determine.

Additional analgesia required

There was no clear difference between the groups for numbers of women requesting second doses of analgesia (RR 0.96, 95% CI 0.63 to 1.45; very low-quality evidence; Analysis 24.3). The other two studies comparing IV butorphanol with IV pethidine did not report any outcomes relating to women's pain during labour.

Epidural

Other secondary outcomes were reported by Hodgkinson 1979: no clear differences between groups were shown (RR 1.00, 95% CI 0.30 to 3.35; 200 women; very low-quality evidence; Analysis 24.4),

Nausea and vomiting

One study (Hodgkinson 1979) involving 200 women reported a lower incidence of nausea and vomiting associated with butorphanol compared with pethidine (0/100 in the butorphanol group versus 12/100 in the pethidine group; RR 0.04, 95% CI 0.00 to 0.67; Analysis 24.5).

Other secondary outcomes were reported by Hodgkinson 1979: no clear differences between groups were shown for caesarean section (RR 0.80, 95% CI 0.22 to 2.89; 200 women; Analysis 24.6), and assisted vaginal birth (RR 1.30, 95% CI 0.60 to 2.83; 200 women; Analysis 24.7).

No other maternal outcomes were reported.

Neonatal

There was no clear difference between groups for the only neonatal outcome reported: Apgar score less than seven at one (RR 0.50, 95% CI 0.15 to 1.61; 2 studies, 230 infants; Analysis 24.8) and five minutes (RR 1.00, 95% CI 0.06 to 15.77; 2 studies, 230 infants; Analysis 24.9).

25. IV morphine versus IV pethidine

Two trials involving a total of 163 women compared IV morphine with IV pethidine (Campbell 1961; Olofsson 1996).

Primary and secondary outcomes

One study involving 143 women reported maternal satisfaction with pain relief assessed three days postpartum (Campbell 1961). Fewer women allocated to receive IV morphine during labour were satisfied with pain relief than those allocated to receive pethidine (RR 0.87, 95% CI 0.78 to 0.98; low-quality evidence; 141 women; Analysis 25.1), although the proportion of women who reported that they were satisfied was high in both groups (60/72 and 66/69).

Campbell 1961 also reported that women allocated to receive IV morphine were more likely to request additional analgesia compared with women allocated to receive IV pethidine (RR 3.41, 95% CI 1.90 to 6.12; 143 women; low-quality evidence; Analysis 25.2). This difference may simply reflect a lack of equivalence in the study doses of analgesia given (pethidine initial dose = 100 mg; morphine initial dose = 8 mg) rather than true differences between analgesic effects.

A second study which investigated this comparison (Olofsson 1996) included only 10 women in each trial arm. No clear differences were found for each of the three secondary outcomes reported: nausea (RR 0.17, 95% CI 0.02 to 1.14), vomiting (RR 0.25, 95% CI 0.03 to 1.86; Analysis 25.3), and caesarean section (no events in either group; Analysis 25.4), although the incidence of nausea was lower in the morphine group (6/10 pethidine versus 1/10 morphine).

26. IV Nisentil versus IV pethidine

One study including 395 women compared IV Nisentil with IV pethidine (Gillam 1958).

Primary and secondary outcomes

The study did not report any outcomes relating to women's pain relief.

Women allocated to the Nisentil group were less likely to suffer vomiting than those receiving pethidine (RR 0.38, 95% CI 0.22 to 0.66). There was also less risk of nausea in the Nisentil group, although this difference was not clear (RR 0.71, 95% CI 0.33 to 1.52; Analysis 26.1).

The incidence of babies requiring resuscitation and/or ventilatory support was higher in babies born to women in the Nisentil group (14/185) compared to those in the pethidine group (8/210) (RR 1.99, 95% CI 0.85 to 4.63; Analysis 26.2). Although this difference is not clear due to wide CIs crossing the line of no effect, and this finding may have occurred by chance, if this is a true reflection of differences between groups then this degree of harmful effect on newborn babies is not clinically acceptable.

27. IV fentanyl versus IV butorphanol

One trial involving 100 women compared IV fentanyl with IV butorphanol (Atkinson 1994).

Primary and secondary outcomes

The study did not report any outcomes relating to maternal satisfaction with analgesia measured during labour or maternal satisfaction with analgesia in labour measured during the postnatal period.

Additional analgesia required

Women allocated to receive IV fentanyl were more likely to request additional doses (two or more) of the study analgesia compared with women allocated to receive IV butorphanol (RR 1.39, 95% CI 1.05 to 1.85; Analysis 27.1). The study author claims the study doses of drug were equivalent (IV fentanyl 50 µg to 100 µg every one to two hours; IV butorphanol 1 mg to 2 mg every one to two hours).

Epidural

Additionally, women in the fentanyl group were twice as likely as those in the butorphanol group to go on to request an epidural (RR 2.00, 95% CI 1.00 to 4.02; Analysis 27.2).

Other maternal outcomes reported (maternal sleepiness during labour and caesarean section) showed no clear difference between study groups (RR 3.00, 95% CI 0.64 to 14.16; Analysis 27.3, and RR 0.80, 95% CI 0.23 to 2.81; Analysis 27.4, respectively).

There were no clear differences observed between groups for any of the neonatal outcomes reported:

1. naloxone administration (RR 1.75, 95% CI 0.81 to 3.80; Analysis 27.5);
2. neonatal resuscitation (RR 11.00, 95% CI 0.62 to 193.80; Analysis 27.6);
3. Apgar score less than seven at five minutes (RR 1.20, 95% CI 0.39 to 3.68; Analysis 27.7);
4. newborn neuro-behavioural score at two to four hours (MD 0.00, 95% CI -1.61 to 1.61; Analysis 27.8);
5. newborn neuro-behavioural score at 24 to 36 hours (MD -0.50, 95% CI -1.62 to 0.62; Analysis 27.9).

No other outcomes were reported.

Intravenous patient-controlled opioids for pain relief in labour

28. PCA pentazocine versus PCA pethidine

One trial involving 29 women compared PCA pentazocine with PCA pethidine (Erskine 1985).

Primary and secondary outcomes

Maternal pan score or pain measured in labour

Women's self-reported pain score during labour was found to be lower for those allocated to the pentazocine group compared with women in the pethidine group, although this difference was not clear between the groups (SMD -0.76, 95% CI -1.62 to 0.09; 23 women; very low-quality evidence; Analysis 28.1), a difference of 1.6 cm on a 10 cm pain scale might be considered clinically important. Similar numbers of women in the two treatment groups rated their pain relief as good one day after the birth (RR 0.82, 95% CI 0.51 to 1.32; 28 women; very low-quality evidence; Analysis 28.2).

None of the maternal and neonatal secondary outcomes studied showed a clear difference between the two study groups with low numbers of events recorded for a number of these outcomes:

1. epidural (RR 1.50, 95% CI 0.29 to 7.65; 28 women; very low-quality evidence; Analysis 28.3);
2. maternal sleepiness during labour (not clear how this was measured) (RR 0.21, 95% CI 0.01 to 4.09; 29 women; Analysis 28.5);
3. nausea and vomiting in labour (RR 0.10, 95% CI 0.01 to 1.61; 29 women; Analysis 28.4);
4. caesarean section (RR 0.36, 95% CI 0.02 to 8.07; 29 women; Analysis 28.6);
5. breastfeeding at discharge (RR 1.00, 95% CI 0.85 to 1.17; 23 women; Analysis 28.7);
6. Apgar score less than seven at five minutes (no events in either group; Analysis 28.8).

29. PCA remifentanil versus PCA pethidine

Three trials involving a total of 161 women compared PCA remifentanil with PCA pethidine (Blair 2005; Douma 2010; Volikas 2001).

Primary

No primary outcomes were reported upon in these studies.

Secondary outcomes

Maternal

Maternal pain score or pain measured in labour

Two studies (Volikas 2001; Douma 2010), involving 122 women reported women's pain score during labour. In both studies pain was assessed using a VAS ranging from 0 ("no pain") to 10 cm ("worst imaginable pain"). In both studies women were asked to

mark the level of pain experienced every hour, starting before analgesia was administered. Results for the Volikas 2001 study were recorded in a graph and so values have been estimated from the graph. There was no evidence of a clear difference in mean pain scores at one hour between the remifentanil and pethidine groups (average MD -8.59, 95% CI -27.61 to 10.44; 122 women; low-quality evidence; Analysis 29.1). There was substantial heterogeneity for this outcome and so a random-effects model has been used (heterogeneity I^2 = 62%, Tau^2 = 136.73, Chi^2 test for heterogeneity P = 0.10).

Additional analgesia required

Two included studies (Blair 2005; Volikas 2001) reported number of women requiring additional analgesia (Entonox®) as an outcome, with most women in both study groups requiring additional analgesia (22/29 versus 24/27; RR 0.86, 95% CI 0.69 to 1.08; 56 women; very low-quality evidence; Analysis 29.2).

Epidural

Two studies reported number of women crossing over to epidural as an outcome (Douma 2010; Volikas 2001), with fewer women in the remifentanil group requiring an epidural (RR 0.42, 95% CI 0.20 to 0.89; 122 women; moderate-quality evidence; Analysis 29.3).

Maternal sleepiness during labour

Maternal sleepiness was reported in one study (Douma 2010). This outcome was assessed using an observer sedation score recorded hourly (1, awake; 2, sleepy; 3 eyes closed, but rousable by vocal stimuli; 4, eyes closed, but rousable by physical stimulus; and 5, un-rousable). Mean hourly scores at inclusion and then at one, two and three hours after analgesia were reported. There was no evidence of a clear difference in mean sedation scores at one hour between the remifentanil and pethidine groups (MD 0.40, 95% CI 0.14 to 0.66; 105 women; Analysis 29.4).

There was no clear difference found between groups for any of the other secondary outcomes reported:

1. nausea and vomiting (RR 0.95, 95% CI 0.61 to 1.49; 2 studies, 119 women; Analysis 29.5);
2. caesarean section (RR 1.81, 95% CI 0.60 to 5.46; 2 studies, 97 participants; Analysis 29.6);
3. assisted vaginal birth (RR 0.96, 95% CI 0.46 to 2.00; 2 studies, 97 participants; Analysis 29.7).

Satisfaction with childbirth experience

Satisfaction with childbirth experience was reported in one study (Douma 2010). Two hours after delivery women were asked to score their overall satisfaction on a 10-point scale (tool not specified). Women in the remifentanil groups had slightly higher mean satisfaction scores (MD 1.10, 95% CI 0.46 to 1.74; 68 women; Analysis 29.8).

Neonatal

There was no clear difference found between groups for any of the neonatal outcomes reported:

1. naloxone administration (RR 0.30, 95% CI 0.01 to 6.47; 2 studies, 56 infants; Analysis 29.9);
2. Apgar score less than seven at five minutes (RR 0.13, 95% CI 0.01 to 2.16; 1 study, 17 infants; Analysis 29.10); Douma 2010 provided mean and standard deviation (SD) values for Apgar scores at five minutes and so these data could not be included in an analysis;
3. admission to NICU (RR 0.30, 95% CI 0.01 to 6.47; 1 study, 17 infants; Analysis 29.11);
4. newborn neuro-behavioural scores - The Neurologic and Adaptive Capacity Score (NACS) was recorded at 15 minutes and two hours after delivery (MD 0.20, 95% CI -0.93 to 1.33; 1 study, 56 infants; Analysis 29.12; and MD 0.60, 95% CI -0.66 to 1.86; 1 study, 56 infants; Analysis 29.13; respectively). A maximum score of 40 indicates the neonate scored "normal" scores in all neuro-behavioural areas.

No other neonatal outcomes were reported under this comparison.

30. PCA nalbuphine versus PCA pethidine

One trial involving 60 women compared PCA nalbuphine with PCA pethidine (Frank 1987).

Primary outcomes

Maternal satisfaction with analgesia measured during labour

The included study did not report this outcome.

Maternal satisfaction with analgesia in labour measured during the postnatal period

There was no clear difference between the groups for this outcome (RR 1.29, 95% CI 0.88 to 1.89; very low-quality evidence; Analysis 30.1). Similarly, there was no clear difference between the groups in the frequency of women who reported that they would use the same pain relief in future (RR 1.06, 95% CI 0.79 to 1.43; 59 women; very low-quality evidence; Analysis 30.2).

Secondary outcomes

Maternal

Maternal pain score or pain measured in labour

Women who received PCA nalbuphine reported lower pain scores, measured on a five-point scale, than those who received PCA pethidine (MD -0.40, 95% CI -0.79 to -0.01; 60 women; low-quality evidence; Analysis 30.3).

Additional analgesia required

There was no clear difference between the groups for women required Entonox (RR 0.83, 95% CI 0.46, 1.48; 59 women; very low-quality evidence; Analysis 30.4).

Nausea and vomiting in labour

There was no clear difference between the groups for this outcome (RR 0.68, 95% CI 0.30 to 1.54; 59 women; Analysis 30.5).
The included study did not report any other maternal outcomes.
Neonatal

Apgar score less than seven at five minutes

There was no clear difference between the groups for this outcome (RR 0.42, 95% CI 0.02 to 9.76; 41 infants; Analysis 30.6).
The included study did not report any other neonatal outcomes.

31. PCA fentanyl versus PCA alfentanil

One study involving 23 women compared PCA fentanyl with PCA alfentanil (Morley-Forster 2000).

Primary outcomes

Maternal satisfaction with analgesia measured during labour

This outcome was not reported in the included study.

Maternal satisfaction with analgesia in labour measured during the postnatal period

There was no clear difference between the groups for this outcome, although women allocated to receive fentanyl were slightly less likely to describe their satisfaction with their pain relief as "adequate" or "good" within six hours of giving birth compared with women allocated to receive alfentanil (10/11 versus 7/12; RR 1.56, 95% CI 0.93 to 2.60; Analysis 31.1).

Secondary outcomes

Maternal

Maternal pain score or pain measured in labour

There was no clear difference between the groups in pain score measured in labour (MD -12.80, 95% CI -32.12 to 6.52; 21 women; Analysis 31.2).
No clear differences were found for any of the other secondary outcomes reported: nausea (RR 2.73, 95% CI 0.66 to 11.30; 23 women; Analysis 31.3), caesarean section (RR 1.64, 95% CI 0.33 to 8.03; 23 women; Analysis 31.4), naloxone administration (RR 2.36, 95% CI 0.53 to 10.55; 24 women; Analysis 31.5).
The included study did not report any other maternal outcome.
Neonatal
The included study did not report any of the neonatal outcome.

32. PCA fentanyl versus PCA pethidine

One trial involving 107 women compared PCA fentanyl with PCA pethidine (Douma 2010).

Primary outcomes

No primary outcomes were reported in this study (Douma 2010).

Secondary outcomes

Maternal

Maternal pain score or pain measured in labour

Pain scores were assessed using a VAS ranging from 0 ("no pain") to 10 cm ("worst imaginable pain"). Mean pain scores were presented at baseline and at one, two and three hours after analgesia. There was no clear difference in mean pain scores at one hour between the fentanyl and pethidine groups (MD -0.65, 95% CI -1.56 to 0.26; 107 women; low-quality evidence; Analysis 32.1).

Epidural

There was moderate-quality evidence to suggest that fewer women in the fentanyl group required epidural compared to pethidine group (RR 0.44, 95% CI 0.21 to 0.92; Analysis 32.2).

There was no clear difference found between groups for any of the other secondary outcomes reported:

1. maternal sleepiness during labour (MD -0.06, 95% CI -0.25 to 0.13; 107 women; Analysis 32.3); this outcome was assessed using an observer sedation score (1 = awake to 5 = unrousable) recorded hourly;
2. nausea and vomiting (RR 0.87, 95% CI 0.55 to 1.37; 102 women; Analysis 32.4);
3. caesarean section (RR 0.25, 95% CI 0.03 to 2.34; 81 women; Analysis 32.5);
4. assisted vaginal birth (RR 0.57, 95% CI 0.22 to 1.49; 81 women; Analysis 32.6).

Neonatal

Douma 2010 only provided mean and SD values for Apgar scores at five minutes and so these data could not be included in an analysis.

There was no clear difference found between groups for any of the other neonatal outcomes reported:

1. neurobehavioural score (NACS 15 minutes post delivery) (MD -0.90, 95% CI -2.31 to 0.51; 63 infants; Analysis 32.7);
2. neurobehavioural score (NACS two hours post delivery) (MD -0.50, 95% CI -1.95 to 0.95; 64 infants; Analysis 32.8).

33. PCA (IM) meptazinol versus PCA (IM) pethidine

One study involving 10 women examined the feasibility of IM meptazinol versus IM pethidine with PCA administration (Li 1988).

Primary outcomes

The included study did not report any of the primary outcomes.

Secondary outcomes

Maternal

Maternal pain score or pain measured in labour

Pain scores measured one day postpartum were lower with meptazinol compared with pethidine; however, there was no evidence of a clear difference (MD -17.60, 95% CI -49.93 to 14.73; 10 women; very low-quality evidence; Analysis 33.1). All women in both groups were satisfied with the mode of administration (very low-quality evidence; Analysis 33.2).

There were no clear differences found between groups for any of the other secondary outcomes reported: additional analgesia required: epidural (RR 3.00, 95% CI 0.15 to 59.89; very low-quality evidence; Analysis 33.3), maternal sleepiness during labour as measured by drowsiness scores one day postpartum (MD 5.60, 95% CI -28.19 to 39.39; Analysis 33.4), nausea measured one day postpartum (MD -8.00, 95% CI -48.70 to 32.70; Analysis 33.5).

Neonatal

There was no clear difference between groups for naloxone administration (RR 1.00, 95% CI 0.08 to 11.93; 10 infants; Analysis 33.6).

Opioids versus TENS for pain relief in labour

34. Opioids versus TENS

Four trials involving 365 women are included in this comparison. One trial compared IV pethidine (50 mg) versus TENS to the lower back (Neumark 1978), another IM pethidine (50 mg) versus TENS to the back (Tawfik 1982), another IM tramadol (100 mg) versus TENS to the back (Thakur 2004), and the fourth compared PCA IV ondansetron and tramadol versus HANS (Han's acupoint nerve stimulator) (Liu 2015).

Primary outcomes

Maternal satisfaction with analgesia measured during labour or during the postnatal period

Two studies (Neumark 1978; Tawfik 1982) involving 105 women reported on maternal satisfaction with analgesia measured post delivery. In the study by Neumark 1978 women were asked to rate their satisfaction with analgesia the day after the birth as having "good", "inadequate" or "no" analgesic effect. In the study by Tawfik 1982 women were asked about the degree of relief they had obtained during the whole period of delivery. This was scored as being "excellent", "good" or "satisfactory". We found no evidence of a clear difference in maternal satisfaction with analgesia rated as "good/excellent" between the TENS and opioid groups (RR 1.23, 95% CI 0.79 to 1.92, 2 studies; 104 women; very low-quality evidence; Analysis 34.1).

Secondary outcomes

Maternal

Maternal pain score measured in labour

Four studies (Liu 2015, Neumark 1978; Tawfik 1982; Thakur 2004) reported on maternal pain measured in labour. In the study by Neumark 1978, pain was assessed on a six-point pain scale for a 70-minute period (from 1, "no pain" through 6, "unbearable pain"). However, data were reported in graphical form which we were not able to include in the analysis. Tawfik 1982 assessed pain relief 30 minutes after analgesia as being complete, excellent or good versus slight relief, while Thakur 2004, assessed pain on a

verbal response scale during labour as complete or moderate relief; versus mild or no relief (the time of measurement was not stated). There was no evidence of a clear difference in maternal pain scores between the opioid and TENS groups (average RR 1.15, 95% CI 0.81 to 1.61, 2 studies; 290 women; very low-quality evidence; Analysis 34.2). There was substantial heterogeneity for this outcome and so a random-effects model has been used (heterogeneity I^2 = 64%, Tau^2 = 0.04, Chi^2 test for heterogeneity P = 0.10).
Liu 2015 reported pain scores 30, and 60 minutes following analgesia. Pain scores were lower in the opioids group compared with the TENS group at 30 minutes (MD -20.00, 95% CI -26.09 to -13.91; 60 women), and 60 minutes (MD -20.00, 95% CI -25.16 to -14.84; 60 women, low-quality evidence; Analysis 34.3).

Maternal sleepiness during labour

Two studies (Tawfik 1982; Thakur 2004), reported drowsiness in labour. Women in the opioid group were more likely to report drowsiness (RR 8.96, 95% CI 1.13 to 71.07; 290 women; Analysis 34.4) compared with those in the TENS group, although the 95% CIs were very wide for this outcome.

Nausea and vomiting

Three studies (Liu 2015; Tawfik 1982; Thakur 2004) reported nausea and vomiting in labour. Women in the opioid group were more likely to report nausea and vomiting compared to the TENS group (RR 13.73, 95% CI 2.72 to 69.24; 350 women; Analysis 34.5).

Caesarean section; assisted vaginal birth

Two studies reported on caesarean section and assisted vaginal birth rates (Liu 2015; Thakur 2004). There were no caesarean sections reported in either the opioid or TENS groups in Thakur 2004. There was no evidence of a clear difference in the number of caesarean sections (RR 2.00, 95% CI 0.19 to 20.90; 260 women; Analysis 34.6), or assisted vaginal births between groups (RR 1.80, 95% CI 0.40 to 8.18; 260 women; Analysis 34.7).
No other maternal outcomes were reported.

Neonatal

Fetal heart rate changes in labour (persistent decelerations or tachycardia)

One study reported on "fetal distress" (Thakur 2004) and found no evidence of a clear difference between groups (RR 5.00, 95% CI 0.24 to 102.85; 200 women; Analysis 34.8).
Two studies reported on Apgar scores (Tawfik 1982; Thakur 2004). However, both studies reported mean scores and these data are very difficult to interpret. None of the studies reported information on the number of babies with Apgar scores less than seven at five minutes (prespecified outcome).
No other neonatal outcomes were reported.

Subgroup analysis

We did not carry out planned subgroup analysis because most meta-analyses included data from only one or two studies and separate breakdown on subgroup categories were rarely provided. We therefore did not think that examining outcomes for subgroups would affect the conclusions of the review or offer any other helpful insights.

ADDITIONAL SUMMARY OF FINDINGS *[Explanation]*

OUTCOME	N STUDIES (n women)	EFFECT		CERTAINTY OF EVIDENCE
		Relative (95% CI)	Absolute (95% CI)	
IM pethidine 50 mg/100 mg versus placebo				
Maternal satisfaction with analgesia measured during labour (number of women satisfied or very satisfied after 30 minutes)	1 (50)	**RR 7.00** (0.38 to 128.87)	**0 fewer per 1000** (from 0 fewer to 0 fewer)	⊕◯◯◯ VERY LOW [a,b]
Maternal pain score or pain measured in labour (described as good or fair after 1 hour)	1 (118)	**RR 1.75** (1.24 to 2.47)	**310 more per 1000** (from 99 more to 608 more)	⊕⊕◯◯ LOW [a,c]
Maternal pain score or pain measured in labour (reduction in VAS of at least 40 mm after 30 minutes)	1 (50)	**RR 25.00** (1.56 to 400.54)	**0 fewer per 1000** (from 0 fewer to 0 fewer)	⊕⊕◯◯ LOW [a,d]
Additional analgesia required	1 (50)	**RR 0.71** (0.54 to 0.94)	**278 fewer per 1000** (from 58 fewer to 442 fewer)	⊕⊕◯◯ LOW [a,c]
Epidural	1 (50)	**RR 0.50** (0.14 to 1.78)	**120 fewer per 1000** (from 187 more to 206 fewer)	⊕◯◯◯ VERY LOW [a,b]
IM pentazocine versus placebo				
Maternal pain score measured during labour	1 (89)	-	MD **3.60 lower** (9.91 lower to 2.71 higher)	⊕⊕◯◯ LOW [e]
IM tramadol versus no treatment				

Maternal satisfaction with analgesia (Analgesic effect described as satisfactory (not clear when measured))	1 (60)	**RR 11.00** (0.64 to 190.53)	**0 fewer per 1000** (from 0 fewer to 0 fewer)	⊕◯◯◯ VERY LOW [b,f]
IM meptazinol versus pethidine				
Maternal pain score or pain measured in labour (Maternal pain relief poor or none (3-5 PN))	1 (801)	**RR 1.01** (0.91 to 1.12)	**6 more per 1000** (from 57 fewer to 77 more)	⊕⊕◯◯ LOW [a,g]
Maternal pain score or pain measured in labour (Pain intensity 4 or 5 on 5-point scale (1 hour))	2 (239)	**RR 1.11** (0.69 to 1.80)	**79 more per 1000** (from 223 fewer to 576 more)	⊕◯◯◯ VERY LOW [e,h]
Additional analgesia required	2 (233)	**RR 1.03** (0.88 to 1.20)	**20 more per 1000** (from 81 fewer to 134 more)	⊕◯◯◯ VERY LOW [e,h]
Epidural	4 (788)	**RR 0.96** (0.71 to 1.29)	**7 fewer per 1000** (from 52 fewer to 52 more)	⊕◯◯◯ VERY LOW [g,i]
IM diamorphine + prochlorperazine versus pethidine + prochlorperazine				
Maternal satisfaction with analgesia in labour measured during the postnatal period (Global assessment of pain relief at 24 hours)	1 (133)	**RR 0.88** (0.67 to 1.16)	**78 fewer per 1000** (from 104 more to 214 fewer)	⊕◯◯◯ VERY LOW [a,e]
Maternal pain score or pain measured in labour (Pain intensity at 1 hour (moderate or severe))	1 (133)	**RR 0.85** (0.72 to 1.01)	**130 fewer per 1000** (from 9 more to 243 fewer)	⊕◯◯◯ VERY LOW [a,e]
Additional analgesia required	1 (133)	**RR 1.35** (0.53 to 3.40)	**36 more per 1000** (from 48 fewer to 247 more)	⊕◯◯◯ VERY LOW [a,b]

Epidural	1 (133)	**RR 1.22** (0.72 to 2.07)	**58 more per 1000** (from 74 fewer to 283 more)	⊕◯◯◯ VERY LOW [a,b]
IM tramadol versus pethidine				
Maternal pain score or pain measured in labour (Pain intensity: women with poor pain relief)	4 (243)	**RR 1.56** (1.10 to 2.21)	**142 more per 1000** (from 25 more to 307 more)	⊕⊕◯◯ LOW [c,j]
Additional analgesia required	3 (295)	**RR 1.07** (0.60 to 1.91)	**11 more per 1000** (from 65 fewer to 149 more)	⊕◯◯◯ VERY LOW [e,j]
IM dihydrocodeine 50 mg versus pethidine 100 mg				
Maternal pain score or pain measured in labour (Maternal pain relief poor at 1 hour)	1 (138)	**RR 1.09** (0.64 to 1.86)	**25 more per 1000** (from 99 fewer to 237 more)	⊕◯◯◯ VERY LOW [a,e]
IM pentazocine versus pethidine				
Maternal satisfaction with analgesia measured during labour (Pain relief (good or very good) at delivery)	2 (253)	**RR 1.08** (0.92 to 1.27)	**51 more per 1000** (from 51 fewer to 171 more)	⊕◯◯◯ VERY LOW [e,h]
Maternal pain score or pain measured in labour (Pain relief poor (partial, none or worse)) - No add-on drugs	3 (365)	**Average RR 1.23** (0.74 to 2.05)	**135 more per 1000** (from 153 fewer to 616 more)	⊕◯◯◯ VERY LOW [g,i,k]
Maternal pain score or pain measured in labour (Pain relief poor (partial, none or worse)) - With promazine	1 (85)	**RR 1.53** (0.66 to 3.58)	**88 more per 1000** (from 57 fewer to 430 more)	⊕◯◯◯ VERY LOW [b,f]

Additional analgesia required - pentazocine	1 (94)	**RR 0.91** (0.50 to 1.65)	**30 fewer per 1000** (from 167 fewer to 217 more)	⊕◯◯◯ VERY LOW [b,f]
Additional analgesia required - pentazocine + promazine	1 (85)	**RR 1.67** (0.73 to 3.84)	**112 more per 1000** (from 45 fewer to 473 more)	⊕◯◯◯ VERY LOW [b,f]
IM nalbuphine versus pethidine				
Maternal satisfaction with analgesia measured during the postnatal period (numbers dissatisfied)	1 (72)	**RR 0.73** (0.55 to 0.96)	**231 fewer per 1000** (from 34 fewer to 386 fewer)	⊕⊕◯◯ LOW [a,c]
Maternal satisfaction with analgesia measured during labour (Pain free)	1 (40)	**RR 6.00** (0.79 to 45.42)	**250 more per 1000** (from 10 fewer to **1000** more)	⊕◯◯◯ VERY LOW [b,f]
Maternal pain score or pain measured in labour (Pain intensity at 30 minutes: women with severe pain)	1 (295)	**RR 0.86** (0.59 to 1.26)	**40 fewer per 1000** (from 75 more to 118 fewer)	⊕◯◯◯ VERY LOW [a,e]
Maternal pain score or pain measured in labour (VAS at 60 minutes (at peak of contraction))	1 (72)	-	MD **8.00 lower** (18.55 lower to 2.55 higher)	⊕◯◯◯ VERY LOW [a,e]
Additional analgesia required	1 (72)	**RR 1.26** (0.49 to 3.27)	**45 more per 1000** (from 87 fewer to 389 more)	⊕◯◯◯ VERY LOW [a,b]
Epidural	1 (307)	**RR 1.65** (0.55 to 4.94)	**21 more per 1000** (from 14 fewer to 126 more)	⊕⊕◯◯ LOW [l]
IM phenazocine versus pethidine				
Epidural	1 (212)	**RR 1.31** (0.58 to 2.97)	**27 more per 1000** (from 36 fewer to 169 more)	⊕◯◯◯ VERY LOW [a,b]

IM diamorphine/morphine versus pethidine				
Maternal satisfaction with analgesia (number of women satisfied or very satisfied)	1 (484)	**RR 1.13** (1.02 to 1.26)	**92 more per 1000** (from 14 more to 184 more)	⊕⊕⊕⊕ HIGH
Maternal satisfaction with analgesia measured during labour or during the postnatal period (Pain relief described as poor)	1 (90)	**RR 1.22** (0.56 to 2.66)	**44 more per 1000** (from 88 fewer to 332 more)	⊕◯◯◯ VERY LOW [a,b]
Additional analgesia required	2 (574)	**RR 1.00** (0.92 to 1.10)	**0 fewer per 1000** (from 57 fewer to 71 more)	⊕⊕⊕◯ MODERATE [g]
Maternal pain relief at 30 mins	1 (484)	-	MD **0.80 lower** (1.24 lower to 0.36 lower)	⊕⊕⊕⊕ HIGH
Maternal pain relief at 60 mins	1 (484)	-	MD **0.80 lower** (1.26 lower to 0.34 lower)	⊕⊕⊕⊕ HIGH
IM butorphanol versus pethidine				
Additional analgesia required	1 (80)	**RR 0.89** (0.55 to 1.45)	**52 fewer per 1000** (from 214 fewer to 214 more)	⊕◯◯◯ VERY LOW [a,b]
IM pethidine versus Entonox				
Maternal pain score or pain measured in labour (after 30 mins)	1 (100)	-	MD **1.66 higher** (1.17 higher to 2.15 higher)	⊕◯◯◯ VERY LOW [c,f]
Maternal pain score or pain measured in labour (after 60 mins)	1 (100)	-	MD **0.36 lower** (0.85 lower to 0.13 higher)	⊕◯◯◯ VERY LOW [e,f]
IV pethidine versus placebo				

Maternal pain score or pain measured in labour (Pain score 30 mins post analgesia)	1 (240)	-	MD **4.10 lower** (4.56 lower to 3.64 lower)	⊕⊕⊕◯ MODERATE [c]
IV fentanyl versus no treatment				
Maternal pain score or pain measured in labour (Pain score 1 hour post-analgesia)	1 (70)	-	MD **5.00 lower** (5.47 lower to 4.53 lower)	⊕◯◯◯ VERY LOW [d,f]
Maternal pain score or pain measured in labour (Pain intensity (Severe) after 1 hour)	1 (70)	**RR 0.02** (0.00 to 0.25)	**868 fewer per 1000** (from 664 fewer to 886 fewer)	⊕◯◯◯ VERY LOW [d,f]
IV fentanyl versus IV pethidine				
Maternal pain score or pain measured in labour (Pain score 1 hour after drug administration)	1 (105)	-	MD **0.20 lower** (1.18 lower to 0.78 higher)	⊕⊕◯◯ LOW [a,c]
Mean doses of analgesia (non pre-specified)	1 (105)	-	MD **0.40 higher** (0.14 higher to 0.66 higher)	⊕⊕◯◯ LOW [a,c]
IV phenazocine versus IV pethidine				
Maternal satisfaction with analgesia measured during labour (women with fair or poor relief)	1 (194)	**RR 0.72** (0.48 to 1.10)	**104 fewer per 1000** (from 37 more to 193 fewer)	⊕◯◯◯ VERY LOW [a,b]
IV butorphanol versus IV pethidine				
Maternal pain score or pain measured in labour (Pain relief score)	1 (80)	-	MD **0.67 higher** (0.25 higher to 1.09 higher)	⊕⊕◯◯ LOW [a,c]

Maternal pain score or pain measured in labour (Pain score (1 hour after drug administration))	1 (80)	-	MD **0.60 lower** (1.02 lower to 0.18 lower)	⊕⊕◯◯ LOW [a,c]
Additional analgesia required	1 (100)	**RR 0.96** (0.63 to 1.45)	**19 fewer per 1000** (from 178 fewer to 216 more)	⊕◯◯◯ VERY LOW [a,e]
Epidural	1 (200)	**RR 1.00** (0.30 to 3.35)	**0 fewer per 1000** (from 35 fewer to 118 more)	⊕◯◯◯ VERY LOW [a,b]
IV morphine versus pethidine				
Maternal satisfaction with analgesia (assessed 3 days postpartum)	1 (141)	**RR 0.87** (0.78 to 0.98)	**124 fewer per 1000** (from 19 fewer to 210 fewer)	⊕⊕◯◯ LOW [a,c]
Additional analgesia required	1 (143)	**RR 3.41** (1.90 to 6.12)	**373 more per 1000** (from 139 more to 793 more)	⊕⊕◯◯ LOW [a,d]
IV Nisentil versus IV pethidine				
Maternal satisfaction with analgesia, maternal pain score or pain measured in labour, additional analgesia, epidural	1 (395)	-	-	No trial reported these outcomes.
PCA pentazocine versus PCA pethidine				
Maternal pan score or pain measured in labour	1 (23)	-	SMD **0.76 lower** (1.62 lower to 0.09 higher)	⊕◯◯◯ VERY LOW [a,e]
Maternal pan score or pain measured in labour (rated as good one day after birth)	1 (28)	**RR 0.82** (0.51 to 1.32)	**141 fewer per 1000** (from 251 more to 385 fewer)	⊕◯◯◯ VERY LOW [a,e]

Epidural	1 (28)	**RR 1.50** (0.29 to 7.65)	**71 more per 1000** (from 101 fewer to 950 more)	⊕○○○ VERY LOW [a,e]
PCA remifentanil versus PCA pethidine				
Maternal pain score in labour	2 (122)	-	MD **8.59 lower** (27.61 lower to 10.44 higher)	⊕⊕○○ LOW [e]
Additional analgesia required	2 (56)	**RR 0.86** (0.69 to 1.08)	**124 fewer per 1000** (from 71 more to 276 fewer)	⊕○○○ VERY LOW [e,h]
Epidural	2 (122)	**RR 0.42** (0.20 to 0.89)	**181 fewer per 1000** (from 34 fewer to 249 fewer)	⊕⊕⊕○ MODERATE [d]
PCA nalbuphine versus PCA pethidine				
Maternal satisfaction with analgesia in labour measured during the postnatal period (rated good or excellent)	1 (60)	**RR 1.29** (0.88 to 1.89)	**164 more per 1000** (from 68 fewer to 504 more)	⊕○○○ VERY LOW [a,e]
Maternal satisfaction with analgesia in labour measured during the postnatal period (Would use the same pain relief again)	1 (59)	**RR 1.06** (0.79 to 1.43)	**43 more per 1000** (from 152 fewer to 311 more)	⊕○○○ VERY LOW [a,e]
Maternal pain score or pain measured in labour	1 (60)	-	MD **0.40 lower** (0.79 lower to 0.01 lower)	⊕⊕○○ LOW [a,c]
Additional analgesia required	1 (59)	**RR 0.83** (0.46 to 1.48)	**82 fewer per 1000** (from 232 more to 261 fewer)	⊕○○○ VERY LOW [a,b]
PCA fentanyl versus PCA pethidine				
Maternla pain score measured in labour	1 (107)	-	MD **0.65 lower** (1.56 lower to 0.26 higher)	⊕⊕○○ LOW [e]

Epidural	1 (107)	**RR 0.44** (0.21 to 0.92)	**190 fewer per 1000** (from 27 fewer to 268 fewer)	⊕⊕⊕◯ MODERATE [d]
PCA (IM) meptazinol versus PCA (IM) pethidine				
Maternal pain score or pain measured in labour (measured 1 day after delivery)	1 (10)	-	MD **17.60 lower** (49.93 lower to 14.73 higher)	⊕◯◯◯ VERY LOW [a,b]
Satisfied with mode of administration (PCA IM)	1 (10)	**RR 1.00** (0.71 to 1.41)	**0 fewer per 1000** (from 290 fewer to 410 more)	⊕◯◯◯ VERY LOW [a,b]
Epidural	1 (10)	**RR 3.00** (0.15 to 59.89)	**0 fewer per 1000** (from 0 fewer to 0 fewer)	⊕◯◯◯ VERY LOW [a,b]
Opioids versus TENS				
Maternal satisfaction with analgesia measured post delivery (rated as good)	2 (104)	**RR 1.23** (0.79 to 1.92)	**89 more per 1000** (from 81 fewer to 355 more)	⊕◯◯◯ VERY LOW [b,h]
Maternal pain score measured during labour	2 (290)	**Average RR 1.15** (0.81 to 1.61)	**97 more per 1000** (from 122 fewer to 393 more)	⊕◯◯◯ VERY LOW [a,e,k]
Maternal pain score measured during labour (after 30 minutes)	1 (60)	-	MD **20 lower** (26.09 lower to 13.91 lower)	⊕⊕◯◯ LOW [a,c]
Maternal pain score measured during labour (after 60 minutes)	1 (60)	-	MD **20.00 lower** (25.16 lower to 14.84 lower)	⊕⊕◯◯ LOW [a,c]

CI: confidence interval; **RR:** risk ratio; **MD:** mean difference

[a] **Risk of bias**: serious (Effect estimate from single study with design limitations)

[b] **Imprecision**: very serious (Wide confidence interval crossing the line of no effect, few events, and small sample size)

[c] **Imprecision:** serious (Small sample size)

[d] **Imprecision**: serious (Small sample size and few events)

[e] **Imprecision**: very serious (Wide confidence interval crossing the line of no effect, and small sample size)

[f] **Risk of bias**: very serious (Effect estimate from single study with serious design limitations)

[g] **Imprecision:** serious (Wide confidence interval crossing the line of no effect)
[h] **Risk of bias**: serious (Pooled effect provided by studies with design limitations)
[i] **Risk of bias**: very serious (Pooled effect provided by studies with serious design limitations)
[j] **Risk of bias**: serious (Pooled effect estimate mainly from studies with design limitations)
[k] **Inconsistency:** serious (unexplained substantial heterogeneity)
[l] **Imprecision**: very serious (Wide confidence interval crossing the line of no effect, and few events)

DISCUSSION

Summary of main results

We set out to answer the question of the effectiveness of parenteral opioids and their adverse effects for women and babies. We included a total of 70 studies, with 61 studies involving more than 8000 women contributing data. This updated review includes 34 different comparisons, where an opioid was compared with placebo, no treatment, with another opioid, or with transcutaneous electrical nerve stimulation (TENS). For many comparisons there was a lack of consistency in what outcomes were measured, how they were measured, and when they were recorded. For most comparisons, and many outcomes, only one or two studies contributed data, and there were few opportunities to pool data in meta-analysis. For many comparisons, data were not reported for many of our prespecified outcomes. The quality of the evidence was mainly assessed as low or very low for pain outcomes. Evidence was downgraded for study design limitations (most of the studies were not blinded), many of the studies had relatively small sample sizes and were underpowered to detect differences between groups and so results were downgraded for imprecision of effect estimates.

All of the studies were conducted in hospital settings, on healthy women with uncomplicated pregnancies at 37 to 42 weeks' gestation. We excluded studies focusing on women with pre-eclampsia or pre-existing conditions or with a compromised fetus.

Summary of results

1. Parenteral opioids provided some pain relief during labour as indicated in eight out of the 24 comparisons that reported maternal pain scores or pain measured in labour. The remainder did not report clear differences between the groups.

2. Satisfaction with analgesia was not reported under most comparisons, and was variable where reported.

3. Opioid drugs were associated with nausea, vomiting and drowsiness, although different types of opioids were associated with different adverse effects.

4. For most outcomes there was no good quality evidence of differences between treatment groups.

5. There was insufficient evidence to assess the safety of opioids in labour.

6. The quality of the evidence for pain and pain relief outcomes was predominantly poor or very poor.

Intramuscular (IM) administration

1. For pethidine versus placebo, there was better pain relief with pethidine measured by women describing pain relief as good or fair after one hour, or a reduction in visual analogue scale (VAS) of at least 40 mm after 30 minutes, with maternal sleepiness in labour as the main adverse effect. There was no evidence of clear differences in other adverse effects on the woman or on the neonate.

2. For pentazocine versus placebo, there was no clear evidence of differences between groups for any of the outcomes reported.

3. For tramadol versus no treatment, there was no clear difference in maternal satisfaction with analgesia. No other outcomes were reported.

4. For meptazinol versus pethidine, there was no clear evidence of a difference in maternal satisfaction with analgesia or pain measured in labour whether assessed either early or late during labour, although more women had vomiting with meptazinol. There was no clear evidence of a difference in outcomes for the neonate.

5. For diamorphine versus pethidine, when an antiemetic was given as co-therapy to both groups, there was no clear evidence of difference in maternal satisfaction, pain scores in labour, or maternal sleepiness in labour. Vomiting occurred more frequently in women given pethidine. Whilst more babies had an Apgar score less than seven at one minute with pethidine, by five minutes there was no difference between groups, and no clear evidence of differences in other neonatal outcomes.

6. For diamorphine versus pethidine, without an antiemetic, more women in the diamorphine group reported to be satisfied or very satisfied with their analgesia compared with the pethidine group. There was no clear difference between groups for number of women requesting additional analgesia, but women reported less pain at 30 and 60 minutes following administration of diamorphine compared with pethidine. This was high-quality evidence. No clear differences were seen between groups for adverse effects or neonatal outcomes.

7. For tramadol versus pethidine, maternal pain scores in labour were better with pethidine than tramadol, and there was no evidence of a difference in adverse effects on mother or baby.

8. For dihydrocodeine versus pethidine, only one study contributed data and there was no evidence of a clear difference in maternal pain scores in labour or adverse effects. More babies had Apgar scores less than seven at one minute with pethidine compared with dihydrocodeine, but the difference was not apparent by five minutes, and there was no evidence of other differences in neonatal adverse effects.

9. Other IM comparisons, most of which were tested in only one study, provided few clear differences in their findings. For pentazocine versus pethidine (six studies, one with antiemetic addition to opioid), phenazocine versus pethidine, morphine versus pethidine, butorphanol versus pethidine, and tramadol versus no treatment, there was no evidence of a clear difference in maternal or neonatal outcomes between groups.

10. For nalbuphine versus pentazocine, one study found a clear difference in maternal satisfaction with analgesia, in favour of nalbuphine. Fewer women who received nalbuphine experienced nausea or vomiting.

Intravenous (IV) administration including patient-controlled anaesthesia (PCA)

1. For most comparisons very few studies contributed data, and for most outcomes there was no clear evidence of differences between groups. Several IV opioids (including fentanyl, butorphanol and morphine) appeared to perform better than pethidine in terms of analgesic effect (either satisfaction with analgesia or pain scores). Pethidine was associated with worse side effects. Compared with pethidine, maternal sleepiness in labour was lower with fentanyl (one study), and nausea was less with butorphanol and morphine (one study for each comparison). When fentanyl and butorphanol were compared, butorphanol was associated with fewer requests for additional analgesia, a reduced need for neonatal resuscitation, and fewer babies required naloxone (one study).

Opioids versus transcutaneous electrical nerve stimulation (TENS)

1. For most outcomes there was no evidence of clear differences between groups (maternal satisfaction with analgesia; maternal pain scores; caesarean section; assisted vaginal birth; fetal distress). The only clear finding was that women in the opioid group were more likely to experience drowsiness and nausea and vomiting than women in the TENS group.

Overall completeness and applicability of evidence

This review is one of a series of Cochrane reviews examining pain management in labour; other reviews have examined pharmacological and non-pharmacological methods of pain management in labour including biofeedback (Barragán 2011), aromatherapy (Smith 2011a), relaxation techniques (Smith 2018a), acupuncture (Smith 2011b), manual methods (Smith 2018b), TENS (Dowswell 2009), epidural analgesia (Anim-Somuah 2018), and a range of other methods of pain management. Smith 2011b is currently being updated. No studies were identified that compared an opioid with hypnosis, biofeedback, intracutaneous or subcutaneous sterile water injection, immersion in water, aromatherapy, relaxation techniques (yoga, music, audio), acupuncture or acupressure, or manual methods (massage, reflexology).

Studies included in the review were carried out over a long time period (1958 to 2017), during which time there have been major changes in women's and clinicians' expectations and views of childbirth and analgesia during labour. Some drugs commonly used in the 1950s and 1960s may no longer be available in some countries. The increasing use of epidural analgesia in resource-rich countries means that opioids are now less likely to be the drugs of choice in these settings. However, in many parts of the world epidural analgesia is not available to all women, and parenteral opioids are still widely used. It is important for all women to make an informed choice about pain relief options available to them; however, providing clear information on the effectiveness and safety of parenteral opioids is a challenge in the light of the findings from this review.

With so many different comparisons and outcomes, we are not able to provide clear information on the acceptability, effectiveness and adverse outcomes associated with different opioids. In this review, we have not compared the effectiveness of parenteral opioids as a co-therapy although in many of the studies we looked at, women were in fact able to have other analgesia, and this may or may not have been reported. The use of other analgesia and co-interventions may have differed by randomisation group, and may have had an independent or synergistic effect on outcomes for women and babies which we were not able to detect. For example, women's use of nitrous oxide was not consistently reported; the fact that it was not mentioned in a study does not necessarily mean that it was not used by the women involved. It was also difficult to determine equivalence in terms of dosages of different trial drugs used, their duration of effect and speed of metabolism. Studies also varied in terms of number of doses available to women, and the stage of labour at which further doses were not allowed in order to avoid detrimental effects on the baby.

There was considerable heterogeneity between studies in the outcomes measured and how they were reported. In some of the older studies (pre-1970), maternal sedation may have been regarded as a desired effect of opioid drugs, and pain relief was sometimes reported by carers rather than by women themselves. There were varied definitions of similar outcomes such as nausea, vomiting (or both), sleepiness, drowsiness, etc. and even greater variation in the way pain and pain relief were measured, and the time points at which measurements were made.

Despite including 70 studies and including data from 61, there were relatively few clear results. Many of the studies had small samples and most did not have the statistical power (singly or pooled) to detect differences between groups for intended or unintended effects that occur infrequently or rarely. In view of the large number of comparisons and outcomes, it is likely that some of the findings where we have reported a difference between groups this may have occurred by chance. On the other hand, for some less frequent outcomes (e.g. low Apgar scores or the need for neonatal resuscitation), some findings suggested that there may have been a difference between groups but the studies often had small sample sizes, and differences between groups were not clear. In addition, we are aware that statistical and clinical significance may not be the same thing. For example, it is difficult to know what a 0.6 cm difference in scores on a 10 cm VAS means in relation to a difference in actual pain.

We were surprised by the number of studies where women's views of pain relief, or their assessments of pain in labour, were not measured at all. We were also surprised at the paucity of data on breastfeeding outcomes. Even more recent studies did not generally collect data on this important outcome, even though observational

studies have suggested that opioids are associated with sedation in babies and suppression of sucking in the minutes and hours after birth. We had also hoped to collect information on the costs associated with using opioid drugs; none of the included studies provided data on the costs incurred by health service providers.

It is known that opioids cross the placental barrier, and short-term effects such as the impact of opioids on fetal heart rate patterns and very early neurological scores have been well documented in observational and randomised studies. It is not clear that these effects have any clinical significance or lasting impact on infant well-being. It has also been suggested that exposure to opioids during labour may predispose children to serious long-term effects; however, much more research is needed to confirm or refute these findings from observational studies (Jacobson 1990; Nyberg 2000). None of the studies included in the review followed up women and babies for more than a few hours or days so we are not able to contribute to these debates.

All of the included studies examined IV or IM administration; two excluded studies examined the subcutaneous administration of opioids (Cahal 1960; De Kornfeld 1964); three studies compared opioids with TENS (Neumark 1978; Tawfik 1982; Thakur 2004). Two trials compared an opioid with no treatment (Jahani 2013; Li 1988). The lack of placebo in these two trials confound the comparison as the placebo effect from the IM/IV administration cannot be separated out from the effect of the investigated opioid. Further updates of this review will exclude such trials.

Quality of the evidence

Overall we found the evidence to be of low quality regarding the analgesic effect of opioids and satisfaction with analgesia, and poorly reported regarding adverse effects to women and babies. Risk of bias was variable in all the studies. Most studies reported post-randomisation exclusions for varying reasons such as women having an instrumental or caesarean birth, protocol violations, and birth happening within a certain time of the study drug being administered. Most studies did not give reasons for withdrawals or exclusions. Generally, study reporting was poor and assessing risk or bias was challenging.

The quality of the evidence assessed using GRADE ranged from very low to high (Summary of findings for the main comparison; Summary of findings 2), but the majority of evidence was downgraded and generally the evidence was assessed as low- or very low-quality. The reasons for downgrading included study design limitations and some heterogeneity, and for most comparisons few studies contributed data and results were frequently imprecise. Due to the large number of comparisons and small amounts of data for each, we produced one Summary of Findings table (Summary of findings for the main comparison) and one additional table (Summary of findings 2) displaying all the outcomes relating to pain for each comparison. These outcomes included maternal satisfaction with analgesia measured during labour, maternal satisfaction with analgesia in labour measured during the postnatal period, maternal pain score or pain measured in labour, additional analgesia required, and epidural.

In some studies women were not included in the analysis if they received the study drug within 30 to 60 minutes of giving birth or more than four hours before giving birth. Such exclusions are likely to introduce serious bias; we do not know whether these women had different outcomes from the rest of the sample, and it is possible that outcomes may have differed by randomisation group.

The review's primary outcomes, maternal satisfaction with analgesia reported during labour and postnatally, were reported in different ways (for example, reports of satisfaction, global assessment of pain relief) and were often poorly reported. It was not always clearly stated to whom women reported their pain levels; indeed in some cases clinicians may have made assessments. These methodological problems may mean there was serious response bias in some studies.

Potential biases in the review process

We are aware that the possibility of introducing bias was present at every stage of the reviewing process. We attempted to minimise bias in a number of ways; two review authors carried out data extraction and assessed risk of bias. Each worked independently. Nevertheless, the process of assessing risk of bias, for example, is not an exact science and includes many personal judgements.

We are also aware that publication bias is a possibility, as the review includes several small studies which reported a number of large results. Although we did attempt to assess reporting bias, lack of trial protocols meant that this assessment relied on information available in the published trial report so reporting bias was not usually apparent.

In previous updates, we may have introduced some bias by converting three-, four- and five-point categorical scales for the measurement of pain or pain relief into binary outcomes. We attempted to be consistent across studies, but this was not always possible as the wording of categories varied in different studies. We have tried to indicate in the results section, and in forest plots, what event rates in treatment groups signify.

Agreements and disagreements with other studies or reviews

The findings and recommendations of this review are similar to other reviews on this topic (Bricker 2002; NICE 2014) and to an earlier Cochrane review looking at IM opioids (Elbourne 2006). Clinical practice guidelines in the UK recommend that women should be informed of the risks of IV and IM opioids and of their limitations; NICE 2014 guidelines suggest that IM and IV opioids should be available for women to choose, women should be

informed of the alternatives, and should be made aware that parenteral opioids may have side effects (such as nausea and drowsiness) and may interfere with breastfeeding.

AUTHORS' CONCLUSIONS

Implications for practice

Though most evidence is of low or very-low quality, for healthy women with an uncomplicated pregnancy who are giving birth at 37 to 42 weeks, parenteral opioids appear to provide some relief from pain in labour but are associated with drowsiness, nausea, and vomiting in the woman. Effects on the newborn are unclear. Maternal satisfaction with opioid analgesia was largely unreported. The review needs to be examined alongside related Cochrane reviews. More research is needed to determine which analgesic intervention is most effective, and provides greatest satisfaction to women with acceptable adverse effects for mothers and their newborn.

Implications for research

The question many women would like answered is how opioids compare with other forms of pain relief available for use during labour, in terms of analgesic effectiveness and the risk of adverse effects for both women and babies. Given the paucity of useful information from the current review, it is likely that the evidence underlying this further question is also limited. It is important that this evidence is reviewed, however, so that women can be provided with information that is as complete and accurate as possible, and so that remaining gaps in knowledge can be identified and addressed through further research.

A large pragmatic randomised controlled trial (RCT) could be undertaken to compare pain relief that includes an opioid with a pain relief regimen not including an opioid, that collects data prospectively on all important prognostic factors such as co-interventions. These factors include additional analgesia and anti-emetics, labour augmentation by means of artificial rupture of membranes or intravenous (IV) infusion of oxytocin, and use of electronic fetal monitoring. Outcomes for women and their babies in the short and longer term are also required. Future studies could also be in the form of multi-armed/and/or adaptive designs to try and focus in on the most effective interventions more quickly.

Maternal outcomes that would be important to guide practice are actual pain relief and maternal satisfaction with analgesia, and important unintended effects such as nausea, vomiting and sedation. For the neonate, Apgar scores at five and 10 minutes, resuscitation including use of naloxone, neonatal intensive care unit admission, initial effective suckling and establishment of breastfeeding, sedation and irritability. Future updates of this review should include all of these maternal and neonatal outcomes.

With respect to measuring the effectiveness of an opioid for labour pain, there are a number of issues. Assessment of pain should be measured in the pause between contractions. In order to minimise response bias, it is important that maternal pain assessment be recorded by the woman herself and not by the woman's caregiver. Lastly, it is important to assess maternal satisfaction to encompass more than just the effects on pain but include other central nervous system (CNS) effects. It would be important to measure satisfaction in the short term (within 24 hours of delivery) and again several days postpartum. In addition, it is known that maintaining control in labour is important to women and this relates to pain and pain control; formal assessment of sense of control in labour would therefore be useful such as the use of the Labour Agentry Scale (Hodnett 1987).

Stratification at baseline of two important predictors of outcome should include maternal parity and spontaneous or induced labour onset.

All studies were conducted on women labouring in hospital settings exclusively. Many women labour and give birth in community settings, the proportion of which is likely to increase due to the international initiative to normalise birth, and reduce interventions associated with complications. Therefore, more research in midwifery-led units and at home would inform practitioners using opioids in these settings.

If recruitment of women to RCTs is hampered due to strong maternal preferences for pain relief, then a prospective observational study, across different care settings, which collects data on important predictors and outcomes as described for the RCT would also be informative.

ACKNOWLEDGEMENTS

We would like to thank GJ Hofmeyr and referees for their helpful feedback on early drafts of the protocol. We also thank the translators of papers assessed for inclusion in the review: Angela Cooke, Graham Dane, Sarah Dodd, John Finch, Catherine Fowler, Youngmee Hahn, Kate Kaminski, Andreas Schwab, Caroline Summers, Bunpode Suwannachat, Andrea Svobodova, Elizabeth Whiteley and Darren J Wright.

A previous version of this review forms part of a series of reviews focusing on pain management in labour that were included in a Cochrane overview of reviews (Jones 2012); contributing reviews shared a generic protocol (Jones 2011). We would like to thank Leanne Jones for her valuable help in updating this review so as to improve consistency between this and other pain management reviews.

This project was supported by the National Institute for Health Research, via Cochrane Infrastructure funding to Cochrane Pregnancy and Childbirth. The views and opinions expressed therein

are those of the authors and do not necessarily reflect those of the Systematic Reviews Programme, NIHR, NHS or the Department of Health.

As part of the pre-publication editorial process, this review has been commented on by three peers (an editor and two referees who are external to the editorial team), a member of Cochrane Pregnancy and Childbirth's international panel of consumers and the Group's Statistical Adviser.

We would like to thank Roz Ullman and Rintaro Mori who both contributed as authors on previous versions of this review. We would also like to thank Therese Dowswell, Research Associate, Cochrane Pregnancy and Childbirth, who contributed to study assessment and data extraction for this current update (2018).

REFERENCES

References to studies included in this review

Atkinson 1994 *{published data only}*
Atkinson BD, Truitt LJ, Rayburn WF, Turnbull GL, Christensen HD, Wlodaver A. Double-blind comparison of intravenous butorphanol (Stadol) and fentanyl (Sublimaze) for analgesia during labor. *American Journal of Obstetrics and Gynecology* 1994;**171**(4):993–8.

Bitsch 1980 *{published data only}*
Bitsch M, Emmrich J, Hary J, Lippach G, Rindt W. Obstetrical analgesia with tramadol [Geburtshilfliche Analgesie mit Tramadol]. *Fortschritte der Medizin* 1980;**98**(16):632–4.

Blair 2005 *{published data only}*
Blair JM, Dobson GT, Hill DA, Fee JPH. Patient-controlled analgesia for labor: a comparison of remifentanil and pethidine [abstract]. *Anesthesiology* 2001;**95**:Abstract no: A1063.
* Blair JM, Dobson GT, Hill DA, McCracken GR, Fee JPH. Patient controlled analgesia for labour: a comparison of remifentanil with pethidine. *Anaesthesia* 2005;**60**(1):22–7.

Borglin 1971 *{published data only}*
Borglin NE, Klottrup P. Pethidine and pentazocine. A double blind investigation in obstetric material. *Lakartidningen* 1971;**68 Suppl 3**:41–4.

Campbell 1961 *{published data only}*
Campbell C, Phillips OC, Frazier TM. Analgesia during labor: a comparison of pentobarbital, meperidine and morphine. Obstetrics & Gynecology 1961; Vol. 17:714–8.

De Boer 1987 *{published data only}*
De Boer F, Shortland D, Simpson RL, Clifford WA, Catley DM. A comparison of the effects of maternally administered meptazinol and pethidine on neonatal acid-base status. *British Journal of Obstetrics and Gynaecology* 1987;**94**(3):256–61.

Direkvand-Moghadam 2014 *{published data only}*
Direkvand-Moghadam A, Delpisheh A, Direkvand-Moghadam A, Fathollahi E. The effects of pethidine on the duration of active labor in nulliparous women. *Journal of Basic Research in Medical Sciences* 2014;**1**(3):60–4.

Douma 2010 *{published data only}*
* Douma MR, Verwey RA, Kam-Endtz CE, Van der Linden PD, Stienstra R. Obstetric analgesia: a comparison of patient-controlled meperidine, remifentanil, and fentanyl in labour. *British Journal of Anaesthesia* 2010;**104**(2):209–15. ISRCTN12122492. Obstetric analgesia: a comparison of patient controlled pethidine, remifentanil and fentanyl in labour. isrctn.com/ISRCTN12122492 (first received 14 February 2006).

Duncan 1969 *{published data only}*
Duncan SL, Ginsburg J, Morris NF. Comparison of pentazocine and pethidine in normal labor. *American Journal of Obstetrics and Gynecology* 1969;**105**(2):197–202.

El-Refaie 2012 *{published data only}*
El-Refaie TA, El-Said MM, Shoukry AA, Khafagy SM, El-Din AS, Badawy MM. Meperidine for uterine dystocia and its effect on duration of labor and neonatal acid-base status: a randomized clinical trial. *Journal of Obstetrics and Gynaecology Research* 2012;**38**(2):383–9.

Erskine 1985 *{published data only}*
Erskine WA, Dick A, Morrell DF, Vital M, van den Heever J. Self-administered intravenous analgesia during labour. A comparison between pentazocine and pethidine. *South African Medical Journal* 1985;**67**(19):764–7.

Fairlie 1999 *{published data only}*
Fairlie FM, Marshall L, Walker JJ. Pethidine compared with diamorphine for pain relief in labour. *American Journal of Obstetrics and Gynecology* 1992;**166**:394.
* Fairlie FM, Marshall L, Walker JJ, Elbourne D. Intramuscular opioids for maternal pain relief in labour: a randomised controlled trial comparing pethidine with

diamorphine. *British Journal of Obstetrics and Gynaecology* 1999;**106**(11):1181–7.

Fieni 2000 ***{published data only}***

Fieni S, Angeri F, Kaihura CT, Ricci L, Bedocchi L, Galanti B, et al. Evaluation of the peripartum effects of 2 analgesics: meperidine and tramadol, used in labor. *Acta Bio-Medica de l Ateneo Parmense* 2000;**71 Suppl 1**:397–400.

Frank 1987 ***{published data only}***

Frank M, McAteer EJ, Cattermole R, Loughnan B, Stafford LB, Hitchcock AM. Nalbuphine for obstetric analgesia: a comparison of nalbuphine with pethidine for pain relief in labour when administered by patient-controlled analgesia (PCA). *Anaesthesia* 1987;**42**(7):697–703.

Giannina 1995 ***{published data only}***

Giannina G, Guzman ER, Lai YL, Lake MF, Cernadas M, Vintzileos AM. Comparison of the effects of meperidine and nalbuphine on intrapartum fetal heart rate tracings. *Obstetrics & Gynecology* 1995;**86**(3):441–5.

Gillam 1958 ***{published data only}***

Gillam JS, Hunter GW, Darner CB, Thompson GR. Meperidine hydrochloride and alphaprodine hydrochloride as obstetric analgesic agents. A double blind study. *American Journal of Obstetrics and Gynecology* 1958;**75**(5):1105–10.

Grant 1970 ***{published data only}***

Grant A, Holt EM, Noble AD. A comparison between pethidine and phenazocine (Narphen) for relief of pain in labour. *Journal of Obstetrics and Gynaecology of the British Commonwealth* 1970;**77**(9):824–9.

Hamann 1972 ***{published data only}***

Hamann GO. Avacan vs fortral. A controlled double blind investigation on parturient patients. *Ugeskrift for Laeger* 1972;**134**:2261–5.

Hodgkinson 1979 ***{published data only}***

Hodgkinson R, Huff RW, Hayashi RH, Husain FJ. Double-blind comparison of maternal analgesia and neonatal neurobehaviour following intravenous butorphanol and meperidine. *Journal of International Medical Research* 1979; **7**(3):224–30.

Husslein 1987 ***{published data only}***

Husslein P, Kubista E, Egarter C. Obstetrical analgesia with tramadol - results of a prospective randomized comparison with pethidine. *Zeitschrift fur Geburtshilfe und Perinatologie* 1987;**191**:234–7.

Jackson 1983 ***{published data only}***

Jackson MB, Robson PJ. Preliminary clinical and pharmacokinetic experiences in the newborn when meptazinol is compared with pethidine as an obstetric analgesic. *Postgraduate Medical Journal* 1983;**59**(Suppl 1): 47–51.

Jahani 2013 ***{published data only}***

Jahani N, Ebrahimzadeh S, Mirzakhani K, Mazlom SR. The effect of intravenous fentanyl on pain and duration of the active phase of first stage labor. *Oman Medical Journal* 2013;**28**(5):306–10.

Kainz 1992 ***{published data only}***

Kainz C, Joura E, Obwegeser R, Plockinger B, Gruber W. Efficacy and tolerance of tramadol with or without antiemetic compared to pethidine in obstetric analgesia. *Zeitschrift fur Geburtshilfe und Perinatologie* 1992;**196**: 78–82.

Kamyabi 2003 ***{published data only}***

* Kamyabi Z, Naderi T, Ramazani A. A randomized, placebo-controlled trial of the effects of pethidine on labor pain, uterine contractions and infant Apgar score. *Annals of Saudi Medicine* 2003;**23**(5):318–20.

Kamyabi Z, Zamiri Z, Ramazani A. A randomized double-blind survey of the effects of pethidine on the relief of labour pains, length of labour, uterine contractions and infant's Apgar score. *Journal of Obstetrics and Gynaecology Research* 2002;**28**(1):47.

Kermani 2015 ***{published data only}***

Kermani S, Derogar M, Moghadam MB, Bahri N, Mahmoudian AS, Mojtabavi SJ. Comparison of the effects of SP6 acupressure and use of pethidine on the intensity of labor pain in nulliparous women. *Avicenna Journal of Phytomedicine* 2015;**5**(Suppl 1):23.

Keskin 2003 ***{published data only}***

Keskin HL, Aktepe Keskin E, Avsar AF, Tabuk M, Caglar GS. Pethidine versus tramadol for pain relief during labor. *International Journal of Gynecology & Obstetrics* 2003;**82**(1): 11–6.

Khooshideh 2009 ***{published data only}***

Khooshideh M, Shahriari A. A comparison of tramadol and pethidine analgesia on the duration of labour: a randomised clinical trial. *Australian and New Zealand Journal of Obstetrics and Gynaecology* 2009;**49**(1):59–63.

Kuti 2008 ***{published data only}***

Kuti O, Faponle AF, Adeyemi AB, Owolabi AT. Pain relief in labour: A randomized controlled trial comparing pentazocine with tramadol. *Nepal Journal of Obstetrics and Gynaecology* 2008;**3**(1):14–8.

Lalooha 2017 ***{published data only}***

Lalooha F, Barikani A, Hashemian N-B, Esmailzadehha N. Effect of pethidine (meperidine) on decreasing the duration of first and second stages of labor. *Iranian Journal of Obstetrics, Gynecology and Infertility* 2017;**19**(39):1–7.

Lardizabal 1999 ***{published data only}***

Lardizabal JL, Belizan JM, Carroli G, Gonzalez L, Campodonico L, Aguillaume CJ. A randomized trial of nalbuphine versus meperidine for analgesia during labor. *References en Gynecologie Obstetrique* 1999;**6**(3):245–8.

Levy 1971 ***{published data only}***

Levy DL. Obstetric analgesia. Pentazocine and meperidine in normal primiparous labor. *Obstetrics & Gynecology* 1971; **38**(6):907–11.

Li 1988 ***{published data only}***

Li DF, Rees GA, Rosen M. Feasibility of self-administration analgesia by the intramuscular route in labour. *European Journal of Obstetrics & Gynecology and Reproductive Biology* 1988;**27**(2):99–104.

Li 1994 *{published data only}*
Li YF, Li E, Tie LP, Weng LJ. Tramadol in labor analgesia. *Beijing Medical Journal* 1994;**16**:265–8.

Lisboa 1997 *{published data only}*
Lisboa AP, Cunha RD, Silva JC, Mamede JAV, Ennes DK. Random clinical study, comparing nalbufine (IM) and meperidine (IM) during labour - 1996. [abstract]. *Acta Obstetricia et Gynecologica Scandinavica* 1997;**76**(167):1.

Liu 2015 *{published data only}*
Liu Y, Xu M, Che X, He J, Guo D, Zhao G, et al. Effect of direct current pulse stimulating acupoints of JiaJi (T10-13) and Ciliao (BL 32) with Han's Acupoint Nerve Stimulator on labour pain in women: a randomized controlled clinical study. *Journal of Traditional Chinese Medicine* 2015;**35**(6): 620–5.

Maduska 1978 *{published data only}*
Maduska AL, Hajghassemali M. A double-blind comparison of butorphanol and meperidine in labour: maternal pain relief and effect on the newborn. *Canadian Anaesthetists Society Journal* 1978;**25**(5):398–404.

Mitterschiffthaler 1991 *{published data only}*
Mitterschiffthaler G, Huter O. Pethidin or nalbuphin for analgesia in labour?. *Geburtshilfe und Frauenheilkunde* 1991;**51**:362–5.

Mobaraki 2016 *{published data only}*
Mobaraki N, Yousefian M, Seifi S, Sakaki M. A randomized controlled trial comparing use of enthonox with pethidine for pain relief in primigravid women during the active phase of labor. *Anesthesiology and Pain Medicine* 2016;**6**(4): e37420.

Moore 1970 *{published data only}*
Moore J, Carson RM, Hunter RJ. A comparison of the effects of pentazocine and pethidine administered during labour. *Journal of Obstetrics and Gynaecology of the British Commonwealth* 1970;**77**(9):830–6.

Morley-Forster 2000 *{published data only}*
Morley-Forster PK, Reid DW, Vandeberghe H. A comparison of patient-controlled analgesia fentanyl and alfentanil for labour analgesia. *Canadian Journal of Anaesthesia* 2000;**47**(2):113–9.

Morrison 1987 *{published data only}*
Morrison CE, Dutton D, Howie H, Gilmour H. Pethidine compared with meptazinol during labour. *Anaesthesia* 1987; **42**(1):7–14.

Mowat 1970 *{published data only}*
Mowat J, Garrey MM. Comparison of pentazocine and pethidine in labour. *BMJ* 1970;**2**(5712):757–9.

Nel 1981 *{published data only}*
Nel CP, Bloch B, Rush JM. A comparison of meptazinol and pethidine for pain relief during the first stage of labour. *South African Medical Journal* 1981;**59**(25):908–10.

Nelson 2005 *{published data only}*
Nelson KE, Eisenach JC. A comparison of butorphanol and meperidine for labor analgesia [abstract]. *Anesthesiology* 2004;**101 Suppl**:Abstract no: A1221.
* Nelson KE, Eisenach JC. Intravenous butorphanol, meperidine, and their combination relieve pain and distress in women in labour. *Anesthesiology* 2005;**102**(5):1008–13.

Neumark 1978 *{published data only}*
Neumark J, Pauser G, Scherzer W. Pain relief in childbirth; an analysis of the analgesic effects of transcutaneous nerve stimulation (TNS), pethidine and placebos. *Praktische Anaesthesie, Wiederbelebung und Intensivtherapie* 1978;**13**: 13–20.

Nicholas 1982 *{published data only}*
Nicholas ADG, Robson PJ. Double-blind comparison of meptazinol and pethidine in labour. *British Journal of Obstetrics and Gynaecology* 1982;**89**(4):318–22.

O'Dwyer 1971 *{published data only}*
O'Dwyer E. A comparison of the analgesics pentazocine and pethilorfan in the relief of pain during labour. *Journal of the Irish Medical Association* 1971;**64**(408):173–6.

Olofsson 1996 *{published data only}*
Olofsson Ch, Ekblom A, Ekman-Ordeberg G, Hjelm A, Irestedt L. Lack of analgesic effect of systemically administered morphine or pethidine on labour pain. *British Journal of Obstetrics and Gynaecology* 1996;**103**(10):968–72.

Olson 1964 *{published data only}*
Olson RO, Riva HL. Evaluation of phenazocine with meperidine as an analgesic agent during labor, by the double blind method. *American Journal of Obstetrics and Gynecology* 1964;**88**:601–11.

Osler 1987 *{published data only}*
Osler M. A double-blind study comparing meptazinol and pethidine for pain relief in labour. *European Journal of Obstetrics & Gynecology and Reproductive Biology* 1987;**26** (1):15–8.

Prasertsawat 1986 *{published data only}*
Prasertsawat OP, Herabutya Y, Chaturachinda K. Obstetric analgesia: comparison between tramadol, morphine, and pethidine. *Current Therapeutic Research, Clinical and Experimental* 1986;**40**(6):1022–8.

Quilligan 1980 *{published data only}*
Quilligan EJ, Keegan KA, Donahue MJ. Double-blind comparison of intravenously injected butorphanol and meperidine in parturients. *International Journal of Gynecology & Obstetrics* 1980;**18**(5):363–7.

Rayburn 1989a *{published data only}*
Rayburn WF, Smith CV, Parriott JE, Woods RE. Randomized comparison of meperidine and fentanyl during labor. Obstetrics & Gynecology 1989; Vol. 74, issue 4: 604–6.

Refstad 1980 *{published data only}*
Refstad SO, Lindbaek E. Ventilatory depression of the newborn of women receiving pethidine or pentazocine. A

double-blind comparative trial. *British Journal of Anaesthesia* 1980;**52**(3):265–71.

Sekhavat 2009 ***{published data only}***
Sekhavat L, Behdad S. The effects of meperidine analgesia during labor on fetal heart rate. *International Journal of Biomedical Science* 2009;**5**(1):59–62.

Sheikh 1986 ***{published data only}***
Sheikh A, Tunstall ME. Comparative study of meptazinol and pethidine for the relief of pain in labour. *British Journal of Obstetrics and Gynaecology* 1986;**93**(3):264–9.

Sliom 1970 ***{published data only}***
Sliom CM. Analgesia during labour: a comparison between dihydrocodeine and pethidine. *South African Medical Journal* 1970;**44**(11):317–9.

Tawfik 1982 ***{published data only}***
Tawfik O, Badraoui MHH, El-Ridi FS. The value of transcutaneous nerve stimulation (TNS) during labour in Egyptian mothers. *Schmerz* 1982;**2**:98–105.

Thakur 2004 ***{published data only}***
Thakur R, Rekha P. Comparative study of transcutaneous electrical nerve stimulation (TENS) and tramadol hydrochloride for pain relief in labor. *Journal of Obstetrics and Gynecology of India* 2004;**54**(4):346–50.

Tharamas 1999 ***{published data only}***
Tharamas W. Buprenorphine versus meperidine for analgesia in labor in nullipara at Chon Buri Hospital. *Chon Buri Hospital Journal* 1999;**24**(2):25–34.

Tsui 2004 ***{published data only}***
Tsui MHY, Warwick D, Kee N, Ng FF, Lau TK. A double blinded placebo-controlled study of intramuscular pethidine for pain relief in the first stage of labour. *British Journal of Obstetrics and Gynaecology* 2004;**111**(7):648–55.

Viegas 1993 ***{published data only}***
Viegas OA, Khaw B, Ratnam SS. Tramadol in labour pain in primiparous patients: a prospective comparative clinical trial. *European Journal of Obstetrics & Gynecology and Reproductive Biology* 1993;**49**(3):131–5.

Volikas 2001 ***{published data only}***
Volikas I, Male D. A comparison of pethidine and remifentanil patient-controlled analgesia in labour. *International Journal of Obstetric Anesthesia* 2001;**10**(2): 86–90.

Wahab 1988 ***{published data only}***
Wahab SA, Askalani AH, Amar RA, Ramadan ME, Neweigy SB, Saleh AA. Effect of some recent analgesics on labor pain and maternal and fetal blood gases and pH. *International Journal of Gynecology & Obstetrics* 1988;**26**(1):75–80.

Wali 2012 ***{published data only}***
Wali AS, Ajaz S, Azam SI, Ariff S. Labor analgesia: Tramadol vs. Pentazocine. *Anaesthesia, Pain and Intensive Care* 2012;**16**(1):98.

Wee 2014 ***{published data only}***
Wee MY, Tuckey JP, Thomas P, Burnard S. The IDvIP trial: a two-centre randomised double-blind controlled trial comparing intramuscular diamorphine and intramuscular pethidine for labour analgesia. *BMC Pregnancy and Childbirth* 2011;**11**:51.
Wee MY, Tuckey JP, Thomas P, Burnard S, Jackson D. The IDvIP Trial: A two-centre double-blind randomised controlled trial comparing i.m. diamorphine and i.m. pethidine for labour analgesia. *International Journal of Obstetric Anesthesia* 2012;**21**:S15.
* Wee MY, Tuckey JP, Thomas PW, Burnard S. A comparison of intramuscular diamorphine and intramuscular pethidine for labour analgesia: a tow-centre randomised blinded controlled trial. *BJOG: an international journal of obstetrics and gynaecology* 2014;**121**(4):447–56.

Wheble 1988 ***{published data only}***
Wheble AM, Dawes GS, Gillmer MD, Sykes GS. A double blind quantitative study of the effects of meptazinol and pethidine on the fetal heart rate in labour. *Journal of Obstetrics and Gynaecology* 1988;**8**(3):248–52.

Wilson 1986 ***{published data only}***
* Wilson CM, McClean E, Moore J, Dundee JW. A double-blind comparison of intramuscular pethidine and nalbuphine in labour. *Anaesthesia* 1986;**41**(12):1207–13.
Wilson CM, Moore J, McClean E, Dundee JW. Maternal analgesia and neonatal neuro-behaviour following nalbuphine and pethidine (abstract). *British Journal of Clinical Pharmacology* 1986;**21**:613P.

Zafar 2016 ***{published data only}***
Zafar S, Najam Y, Arif Z, Hafeez A. A randomized controlled trial comparing Pentazocine and Chamomilla recutita for labor pain relief. *Homeopathy* 2016;**105**(1): 66–70.

Zhu 2013 ***{published data only}***
Zhu HX, Yao Y, Wu YS, Liu Y, Yan LR, Su XJ. Influence of acupoint injection with small dose of fentanyl-droperidol mixed liquor on labor analgesia and level of stress hormone in parturient. *Chinese acupuncture & moxibustion* 2013;**33** (4):342–6.

References to studies excluded from this review

Abd-El-Maeboud 2014 ***{published data only}***
Abd-El-Maeboud KH, Elbohoty AE, Mohammed WE, Elgamel HM, Ali WA. Intravenous infusion of paracetamol for intrapartum analgesia. *Journal of Obstetrics and Gynaecology Research* 2014;**40**(11):2152–7.

Abdollahi 2014 ***{published data only}***
* Abdollahi MH, Mojibian M, Pishgahi A, Mallah F, Dareshiri S, Mohammadi S, et al. Intravenous paracetamol versus intramuscular pethidine in relief of labour pain in primigravid women. *Nigerian Medical Journal : Journal of the Nigeria Medical Association* 2014;**55**(1):54–7.
IRCT201207215506N5. Intravenous paracetamol versus intramuscular pethidine in relief of labor pain in primigravid women. en.search.irct.ir/view/10319 (first received 2 February 2012).

Aiken 1971 *{published data only}*

Aiken RA, Cope E. The value of promazine and diazepam as adjuncts to pethidine in labour. Proceedings of 3rd International Congress on Psychosomatic Medicine in Obstetrics and Gynaecology; 1971; London, UK. 1971: 241–3.

Alhashemi 2011 *{published data only}*

Alhashemi JA, NCT01394731. Analgesic effects of intravenous acetaminophen on labor pain. clinicaltrials.gov/ct2/show/NCT01394731 (first received 12 July 2011).

* Alhashemi JA, Tawfeeq NA, Sadat M, Mujallid RH. Intravenous acetaminophen vs. intramuscular meperidine for labor analgesia. http://www.asaabstracts.com/strands/asaabstracts/abstractList.htm;jsessionid=0507CB47FEB444D841EEF290BF35A8BF?year=2011&index=13 (accessed 1 February 2012). 2011.

Ankumah 2016 *{published data only}*

Ankumah NA, Tsao M, Hutchinson M, Pedroza C, Mehta J, Blackwell S, et al. The comparative effectiveness of intravenous acetaminophen versus intravenous morphine for pain relief in early labor: a randomized controlled trial. *American Journal of Obstetrics and Gynecology* 2016;**214**(1 Suppl):S62, Abstract no: 89.

Balcioglu 2007 *{published data only}*

Balcioglu O, Akin S, Demir S, Aribogan A. Patient-controlled intravenous analgesia with remifentanil in nulliparous subjects in labor. *Expert Opinion on Pharmacotherapy* 2007;**8**(18):3089–96.

Balki 2007 *{published data only}*

Balki M, Kasodekar S, Dhumne S, Bernstein P, Carvalho J. Patient-controlled analgesia with background remifentanil infusion for labor pain [abstract]. *Anesthesiology* 2006;**104** (Suppl 1):13.

* Balki M, Kasodekar S, Dhumne S, Bernstein P, Carvalho JC. Remifentanil patient-controlled analgesia for labour: optimizing drug delivery regimens. *Canadian Journal of Anaesthesia* 2007;**54**(8):626–33.

Balki 2012 *{published data only}*

NCT01563939. Patient-controlled intravenous analgesia with remifentanil infusion for labour: is demand bolus required for optimal analgesia. clinicaltrials.gov/ct2/show/NCT01563939 (first received 23 March 2102).

Ballas 1976 *{published data only}*

Ballas S, Toaff ME, Toaff R. Effects of intravenous meperidine and meperidine with promethazine on uterine activity and fetal heart rate during labor. *Israel Journal of Medical Sciences* 1976;**12**(10):1141–7.

Bare 1962 *{published data only}*

Bare WW. Double-blind evaluation of hydroxyzine hydrochloride for labour and delivery. *American Journal of Obstetrics and Gynecology* 1962;**83**(1):18–21.

Bhatia 2013 *{published data only}*

Bhatia N, Makkar JK, Jain K, Jain V. Comparison of analgesic efficacy of paracetamol and tramadol for pain relief in early labour: A randomized double blind study. *Journal of Obstetric Anaesthesia and Critical Care* 2013;**3**(2):118.

Bredow 1992 *{published data only}*

Bredow V. Use of tramadol versus pethidine versus denaverine suppositories in labor--a contribution to noninvasive therapy of labor pain [Die Anwendung von Tramadol– versus Pethidin– versus Denaverin–suppositorien unter der Geburt—-ein Beitrag zur nichtinvasiven Geburtsschmerztherapie]. *Zentralblatt fur Gynakologie* 1992;**114**(11):551–4.

Brelje 1966 *{published data only}*

Brelje MC, Garcia-Bunuel R. Meperidine-hydroxyzine in obstetric analgesia. *Obstetrics & Gynecology* 1966;**27**(3): 350–4.

Brookes 2013 *{published data only}*

EUCTR2012-005257-22-GB. Remifentanil intravenous patient controlled analgesia (PCA) versus intramuscular pethidine for pain relief in labour: a randomised controlled trial - RESPITE. clinicaltrialsregister.eu/ctr-search/search?query=eudract_number:2012-005257-22 (first received 21 June 2013).

Busacca 1982 *{published data only}*

Busacca M, Gementi P, Gambini E, Lenti C, Meschi F, Vignali M. Neonatal effects of the administration of meperidine and promethazine to the mother in labor. Double blind study. *Journal of Perinatal Medicine* 1982;**10** (1):48–53.

Cahal 1960 *{published data only}*

Cahal DA, Dare JG, Keith D. A sequential trial of analgesics in labour. *Journal of Obstetrics and Gynaecology of the British Commonwealth* 1961;**63**:88–93.

Calderon 2006 *{published data only}*

Calderon E, Martinez E, Roman MD, Pernia A, Garcia-Hernandez R, Torres LM. Intravenous remifentanil delivered through an elastomeric device versus intramuscular meperidine comparative study for obstetric analgesia [Remifentalino intravenoso mediante infusor elastomerico frente a meperidina intramuscular. Estudio comparativo en analgesia obstetrica]. *Revista de la Sociedad Espanola del Dolor* 2006;**13**(7):462–7.

Callaghan 1966 *{published data only}*

Callaghan PE, Zelenik JS. Methotrimeprazine for obstetric analgesia. *American Journal of Obstetrics and Gynecology* 1966;**95**(5):636–9.

Camann 1992 *{published data only}*

Camann WR, Denney RA, Holby ED, Datta S. A comparison of intrathecal, epidural and intravenous sufentanil for labor analgesia. Anesthesiology 1992; Vol. 77, issue 5:884–7.

Castro 2004 *{published data only}*

Castro C, Tharmaratnam U, Brockhurst N, Tureanu L, Tam K, Windrim R. Patient-controlled analgesia with fentanyl provides effective analgesia for second trimester labour: a randomized controlled study. *Canadian Journal of Anaesthesia* 2004;**50**(10):1039–46.

Cavanagh 1966 *{published data only}*

Cavanagh D, Le Cart C, Cassady JC, Kiem IM. A comparison of anileridine and meperidine as obstetric

analgesia. A double-blind study of 471 patients. *American Journal of Obstetrics and Gynecology* 1966;**96**(2):213–20.

Chandnani 2013 *{published data only}*
Chandnani K, Sainee HB. Pain relief in labour: tramadol versus pentazocine. *International Journal of Reproduction, Contraception, Obstetrics and Gynecology* 2013;**2**(2):186–9.

Chang 1976 *{published data only}*
Chang A, Wood C, Humphrey M, Gilbert M, Wagstaff C. The effects of narcotics on fetal acid base status. *British Journal of Obstetrics and Gynaecology* 1976;**83**(1):56–61.

Cincadze 1978 *{published data only}*
Cincadze II, Bagdany S, Kintraia PJ, Mamtavrisvili II. Intensive fetal monitoring within obstetrical analgesia. Proceedings of 6th European Congress of Perinatal Medicine; 1978 Aug 29-Sept 1; Vienna, Austria. 1978: Abstract no: 52.

Cullhed 1961 *{published data only}*
Cullhed S, Lofstrom B. Obstetric analgesia with pethidine and scopolamine. *Lancet* 1961;**1**(7168):75–7.

Dahiya 2015 *{published data only}*
Dahiya K, Malik R. Intravenous infusion of paracetamol versus intravenous tramadol as an intrapartum analgesic in active labor. *International Journal of Gynecology and Obstetrics* 2015;**131**(Suppl 5):E215.

Dan 1991 *{published data only}*
Dan U, Barkai G, Rabinovici J, Echin A, Modan M, Mashiah S. A prospective double blind comparison between intravenous nalbuphine and pethidine administered during labor. Proceedings of 11th European Congress of Perinatal Medicine; 1988 April 10-13; Rome, Italy. 1988.
* Dan U, Rabinovici Y, Barkai G, Modan M, Etchin A, Mashiach S. Intravenous pethidine and nalbuphine during labor: a prospective double-blind comparative study. *Gynecologic and Obstetric Investigation* 1991;**32**(1):39–43.

De Kornfeld 1964 *{published data only}*
De Kornfeld TJ, Pearson JW, Lasagna L. Methotrimeprazine in the treatment of labor pain. *New England Journal of Medicine* 1964;**270**:391–4.

De Lamerens 1964 *{published data only}*
De Lamerens S, Tuttle AH, Aballi AJ. Neonatal bilirubin levels after use of phenothiazine derivatives for obstetrical analgesia. *Journal of Pediatrics* 1964;**65**:925–8.

Eames 1964 *{published data only}*
Eames GM, Pool KRS. Clinical trial of oxymorphone in labour. *BMJ* 1964;**2**:353–5.

Easton 2016 *{published data only}*
NCT02783508. Pethidine versus nitrous oxide for pain relief during labor among multiparous. a randomized controlled trial. clinicaltrials.gov/ct2/show/NCT02783508 (first received:18 May 2016).

Elbohoty 2012 *{published data only}*
Elbohoty AE, Abd-Elrazek H, Abd-El-Gawad M, Salama F, El-Shorbagy M, Abd-El-Maeboud KH. Intravenous infusion of paracetamol versus intravenous pethidine as an intrapartum analgesic in the first stage of labor. *International Journal of Gynecology and Obstetrics* 2012;**118**(1):7–10.

Elhalwagy 2017 *{published data only}*
JPRN-UMIN000026415. Intranasal Ketamine versus intramuscular Pethidine in labor pain analgesia. upload.umin.ac.jp/cgi-open-bin/ctr_e/ctr_view.cgi?recptno=R000030347 (first received 7 March 2017).

Eliot 1975 *{published data only}*
Eliot BW, Hill JG, Cole AP, Hailey DM. Continuous pethidine/diazepam infusion during labour and its effects on the newborn. *British Journal of Obstetrics and Gynaecology* 1975;**82**(2):126–31.

El-Kerdawy 2010 *{published data only}*
El-Kerdawy H, Farouk A. Labor analgesia in preeclampsia: remifentanil patient controlled intravenous analgesia versus epidural analgesia. *Middle East Journal of Anesthesiology* 2010;**20**(4):539–45.

El Kinawy 2015b *{published data only}*
El Kinawy H, NCT02549118. Efficacy of intravenous tenoxicam as an analgesic during the first stage of labor: a randomized controlled trial. clinicaltrials.gov/ct2/show/record/NCT02549118 (first received 10 September 2015).
El Kinawy H, NCT02557087. Efficacy of intravenous hyoscine butylbromide as an analgesic during the first stage of labor: a randomized controlled trial. clinicaltrials.gov/ct2/show/record/NCT02557087. NCT02557087 (first received 21 September 2015).
El Kinawy H, NCT02578251. Efficacy of intravenous paracetamol as an analgesic during the first stage of labor: a randomized controlled trial. clinicaltrials.gov/ct2/show/record/NCT02578251. NCT02578251 (first received 15 October 2015).

Evron 2005 *{published data only}*
Evron S, Glezerman M, Sadan O, Boaz M. Remifentanil patient controlled analgesia for labor pain. *Anesthesiology* 2002;**96 Suppl**:Abstract no: A1032.
* Evron S, Glezerman M, Sadan O, Boaz M, Ezri T. Remifentanil: a novel systematic analgesic for labor pain. *Anesthesia & Analgesia* 2005;**100**:233–8.
Evron S, Sadan O, Ezri T, Boaz M, Glezerman M. Remifentanil: a new systemic analgesic for labor pain and an alternative to dolestine [abstract]. *American Journal of Obstetrics and Gynecology* 2001;**185**(6 Suppl):S210.

Evron 2007 *{published data only}*
Evron S, Parameswaran R, Zipori D, Ezri T, Sadan O, Koren R. Activin beta A in term placenta and its correlation with placental inflammation in parturients having epidural or systemic meperidine analgesia: a randomized study. *Journal of Clinical Anesthesia* 2007;**19**(3):168–74.

Evron 2008 *{published data only}*
Evron S, Ezri T, Protianov M, Muzikant G, Sadan O, Herman A, et al. The effects of remifentanil or acetaminophen with epidural ropivacaine on body temperature during labor. *Journal of Anesthesia* 2008;**22**(2):105–11.

Fernandez 2015 *{published data only}*
Fernandez J, NCT02493192. Birth ball versus meperidine and haloperidol injection for pain relief during first stage of labour. clinicaltrials.gov/ct2/show/record/NCT02493192 (first received 23 June 2015).

Fleet 2015 *{published data only}*
ACTRN12609001027202. Obstetric analgesia: a comparison of intranasal or subcutaneously administered fentanyl with intramuscular administered pethidine in labour and its effects on mother and baby. anzctr.org.au/Trial/Registration/TrialReview.aspx?ACTRN=12609001027202 (first received 27 November 2009).
Fleet J, Belan I, Jones M. Women's experience of intranasal fentanyl, subcutaneous fentanyl or intramuscular pethidine for labour analgesia. *Women and Birth* 2015;**28 Suppl**:S14.
* Fleet J, Belan I, Jones MJ, Ullah S, Cyna AM. A comparison of fentanyl with pethidine for pain relief during childbirth: A randomised controlled trial. *BJOG: an international journal of obstetrics and gynaecology* 2015;**122**(7):983–92.
Fleet J, Cyna A, Belan I, Jones M, Ullah S. Fentanyl versus pethidine for pain relief during labour and childbirth: A randomised controlled trial. Australian and New Zealand College of Anaesthetists Annual Meeting; 2013 May 4-8; Melbourne, Australia. 2013.
Fleet J, Jones M, Belan I. A comparison of intranasal or subcutaneous administered fentanyl with intramuscular pethidine during childbirth: a randomised controlled trial. International Confederation of Midwives 30th Triennial Congress. Midwives: Improving Women's Health; 2014 June 1-4; Prague, Czech Republic. 2014:P105.

Freeman 2012 *{published data only}*
Freeman LM, Bloemenkamp KW, Franssen MTM, Papatsonis DNM, Hajenius PJ, van ME, et al. Remifentanil patient controlled analgesia versus epidural analgesia in labour. a multicentre randomized controlled trial. *BMC Pregnancy and Childbirth* 2012;**12**:63.

Gambling 1998 *{published data only}*
Gambling DR, Sharma SK, Ramin SM, Lucas MJ, Leveno KJ, Wiley J, et al. A randomized study of combined spinal-epidural analgesia versus intravenous meperidine during labor: impact on cesarean delivery rate. *Anesthesiology* 1998;**89**(6):1336–44.

Ginosar 2003 *{published data only}*
Ginosar Y, Columb MO, Cohen SE, Mirikatani E, Tingle MS, Ratner EF, et al. The site of action of epidural fentanyl infusions in the presence of local anesthetics: a minimum local analgesic concentration infusion study in nulliparous labor. *Anesthesia & Analgesia* 2003;**97**(5):1439–45.

Goodlin 1988 *{published data only}*
Goodlin RC. Prevention of in utero meconium aspiration by narcotic administration. Personal communication 1988.

Grandjean 1979 *{published data only}*
Grandjean H, De Mouzon J, Cabot JA, Desprats R, Pontonnier G. Peridural analgesia and by phenoperidine in normal labor. Therapeutic trial with a control series. *Archives Francaises de Pediatrie* 1979;**36**(9 Suppl): LXXV–LXXXI.

Greer 1988 *{published data only}*
Greer IA, Johnston J, Tulloch I, Walker JJ. Effect of maternal ketorolac administration on platelet function in the newborn. *European Journal of Obstetrics & Gynecology and Reproductive Biology* 1988;**29**(4):257–60.

Gupta 2016 *{published data only}*
CTRI/2013/09/003968. Intravenous paracetamol as an adjunct to patient-controlled epidural analgesia with levobupivacaine and fentanyl in labour: a randomised controlled trial. ctri.nic.in/Clinicaltrials/pdf_generate.php?trialid=6573&EncHid=&modid=&compid=%27,%276573det%27 (first received 11 September 2013).
* Gupta K, Mitra S, Kazal S, Saroa R, Ahuja V, Goel P. I.V. paracetamol as an adjunct to patient-controlled epidural analgesia with levobupivacaine and fentanyl in labour: a randomized controlled study. *British Journal of Anaesthesia* 2016;**117**(5):617–22.
Mitra S, Gupta K, Kazal S, Saroa R, Ahuja V, Goel P. Intravenous acetaminophen as an adjunct to patient-controlled epidural analgesia with levobupivacaine and fentanyl in labor: a randomized controlled study. Society for Obstetric Anesthesia and Perinatology (SOAP) 48th Annual Meeting; 2016 May 18-22; Boston USA. 2016: T–27.

Hashemiyan 2014 *{published data only}*
IRCT2014012016283N1. The effect of pethidine in shortening of first and second stage of labor. en.search.irct.ir/view/16722 (first received 14 April 2014).

Hodgkinson 1978 *{published data only}*
Hodgkinson R, Bhatt M, Grewal G, Marx GF. Neonatal neurobehavior in the first 48 hours of life: effect of the administration of meperidine with and without naloxone in the mother. Pediatrics 1978; Vol. 62, issue 3:294–8.

Isenor 1993 *{published data only}*
Isenor L, Penny-MacGillivray T. Intravenous meperidine infusion for obstetric analgesia. *Journal of Obstetric, Gynecologic and Neonatal Nursing* 1993;**22**(4):349–56.

John 2013 *{published data only}*
John C, Fyneface-Ogan S, Enyindah C. A comparison of the effect of spinal analgesia and sedo-analgesia on maternal cortisol levels during labour. 1st FIGO African Regional Conference of Gynecology and Obstetrics; 2013 Oct 2-5; Addis Ababa, Ethiopia. 2013.

Jost 2015 *{published data only}*
Jost A, Ban B, Kamenik M. Modified patient-controlled remifentanil bolus delivery regimen for labour pain. *Anaesthesia* 2013;**68**(3):245–52.
* Jost A, Blagus R, Ban B, Kamenik M. Effect-site concentration of remifentanil during patient-controlled analgesia in labour. *International Journal of Obstetric Anesthesia* 2015;**24**(3):230–6.

Kalaskar 2007 *{published data only}*
Kalaskar A, Nayak AH. Comparative evaluation of analgesic efficacy and safety of intramuscular tramadol

with pentazocine for labour analgesia: a prospective study. 31st British International Congress of Obstetrics and Gynaecology; 2007 July 4-6; London, UK. 2007:112.

Kaltreider 1967 *{published data only}*
Kaltreider DF. Premature labor and meperidine analgesia. *American Journal of Obstetrics and Gynecology* 1967;**99**(7): 989–93.

Karadjova 2016 *{published data only}*
Karadjova D, Shosholceva M, Spasovski S, Ivanov E, Sivevski A, Zlatkova M, et al. Intravenous patient controlled analgesia with remifentanil versus continuous epidural for labor analgesia. *Anesthesia & Analgesia* 2016;**123**(3 Suppl): PR199.

Kaur 2015 *{published data only}*
Kaur Makkar J, Jain K, Bhatia N, Jain V, Mal Mithrawal S. Comparison of analgesic efficacy of paracetamol and tramadol for pain relief in active labor. *Journal of Clinical Anesthesia* 2015;**27**(2):159–63.

Khooshideh 2015 *{published data only}*
Khooshideh M, Shahriari A, Sheikh M. Comparison of the effect of incremental bolus and incremental infusion regimens of remifentanil on labour pain. *Shiraz E Medical Journal* 2015;**16**(5):e25626.

Krins 1969 *{published data only}*
Krins AJ, Mitchell WR, Wood C. Effect of morphine upon maternal capillary blood oxygen and carbon dioxide tension. *Journal of Obstetrics and Gynaecology of the British Commonwealth* 1969;**76**(4):359–61.

Lallar 2015 *{published data only}*
Lallar M, Anam H, Nandal R, Singh Sunder P, Katyal S. Intravenous paracetamol infusion versus intramuscular tramadol as an intrapartum labor analgesic. *Journal of Obstetrics and Gynecology of India* 2015;**65**(1):17–22.

Li 1995 *{published data only}*
Li E, Weng L. Influence of dihydroetorphine hydrochloride and tramadol on labor pain and umbilical blood gas. *Chung-Hua Fu Chan Ko Tsa Chih [Chinese Journal of Obstetrics and Gynaecology]* 1995;**30**(6):345–8.

Logtenberg 2017 *{published data only}*
Logtenberg SLM, Oude Rengerink K, van der Post JA, Verhoeven CJ, Freeman LM, Middeldorp JM, et al. Labour pain with remifentanil patient-controlled analgesia versus epidural analgesia: a randomised equivalence trial. *BJOG: an International Journal of Obstetrics and Gynaecology* 2017; **124**(4):652–60.

MacVicar 1960 *{published data only}*
MacVicar J, Murray MH. Clinical evaluation of promazine as an adjunct to predelivery sedation. *British Medical Journal* 1960;**1**(5173):595–8.

Malkasian 1967 *{published data only}*
Malkasian GD, Smith RA, Decker DG. Comparison of hydroxyzine-meperidine and promethazine-meperidine for analgesia during labor. *Obstetrics & Gynecology* 1967;**30**(4): 568–75.

Marshalov 2012 *{published data only}*
Marshalov D, Salov I, Shifman E, Petrenko A. Influence of epidural analgesia on abdominal wall pain tension and level of abdominal pressure in labor. *Regional Anesthesia and Pain Medicine* 2012;**37**(7 Suppl):E278.

McDonald 1964 *{published data only}*
McDonald R, Shaw M, Craig C. Effect of phenothiazines and analgesics given during labour on neonatal serum bilirubin. *British Medical Journal* 1964;**1**(5384):677.

McGrath 1992 *{published data only}*
McGrath J, Chestnut D, Debruyn C. The effect of epidural bupivacaine vs intravenous nalbuphine on fetal heart rate during labor. *Anesthesiology* 1992;**77**:A983.

McInnes 2004 *{published data only}*
Hillan E. Diamorphine for pain relief in labour: a randomised controlled trial comparing intramuscular injection and patient controlled analgesia. http://controlled-trials.com (accessed 12 June 2002) 2002.
Hillan EM. Diamorphine for pain relief in labour: a randomized controlled trial comparing intramuscular injection and patient-controlled analgesia. 16th International Nursing Research Congress; 2005 14-16 July; Hawaii. 2005.
* McInnes RJ, Hillan E, Clark D, Gilmour H. Diamorphine for pain relief in labour: a randomised controlled trial comparing intramuscular injection and patient-controlled analgesia. *BJOG: an International Journal of Obstetrics & Gynaecology* 2004;**111**(10):1081–9.

McQuitty 1967 *{published data only}*
McQuitty FM. Relief of pain in labour A controlled double-blind trial comparing pethidine and various phenothiazine derivatives. *Journal of Obstetrics and Gynaecology of the British Commonwealth* 1967;**74**(6):925–8.

Moore 1974 *{published data only}*
Moore J, Ball HG. A sequential study of intravenous analgesic treatment during labour. *British Journal of Anaesthesia* 1974;**46**(5):365–72.

Morgan 2004 *{published data only}*
Morgan PJ, Palmer SK, Kung R, Halpern SH, Yee JA. Effect of intramuscular opioids on subsequent epidural analgesia [abstract]. *Canadian Journal of Anesthesia* 2004;**51**(Suppl 1):A58.

Morris 1994 *{published data only}*
Morris GF, Gore-Hickman W, Lang SA, Yip RW. Can parturients distinguish between intravenous and epidural fentanyl?. *Canadian Journal of Anaesthesia* 1994;**41**(8): 667–72.

Nafisi 2006 *{published data only}*
Nafisi S. Effects of epidural lidocaine analgesia on labor and delivery: a randomized, prospective, controlled trial. *BMC Anesthesiology* 2006;**6**:15.

Ng 2011 *{published data only}*
Ng TK, Cheng BC, Chan WS, Lam KK, Chan MT. A double-blind randomised comparison of intravenous patient-controlled remifentanil with intramuscular

pethidine for labour analgesia. *Anaesthesia* 2011;**66**(9): 796–801.

Nikkola 2000 *{published data only}*
Nikkola EM, Jahnukainen TJ, Eklad UU, Kero PO, Salonen MA. Neonatal monitoring after maternal fentanyl analgesia in labor. *Journal of Clinical Monitoring & Computing* 2000; **16**(8):597–608.

Overton 1992 *{published data only}*
Overton C, Haddad N, Williams J. Trial to study the effectiveness and suitability of sublingual diamorphine hydrochloride as an alternative in labour and to compare it with the presently available methods. Proceedings of 26th British Congress of Obstetrics and Gynaecology; 1992 July 7-10; Manchester, UK. 1992:431.

Pandole 2003 *{published data only}*
Pandole A, Akolekar R, Sardeshpande N, Kore S, Ambiye VR. A comparative study between tramadol and pethidine as a form of labour analgesia. *Bombay Hospital Journal* 2003;**45**:4.

Polley 2000 *{published data only}*
Polley LS, Columb MO, Naughton NN, Wagner DS, Dorantes DM, van de Ven JM. Effect of intravenous versus epidural fentanyl on the minimum local analgesic concentration of epidural bupivacaine in labor. *Anesthesiology* 2000;**93**(1):122–8.

Posner 1960 *{published data only}*
Posner AC. Combined pethidine and antagonists in obstetrics. *British Medical Journal* 1960;**1**:124–5.

Powe 1962 *{published data only}*
Powe CE, Kiem IM, Fromhagen C, Cavanagh D. Propiomazine hydrochloride in obstetrical analgesia. *JAMA* 1962;**181**:290–4.

Rabie 2006 *{published data only}*
Rabie ME, Negmi HH, Moustafa AM, Al Oufi H. Remifentanil by patient controlled analgesia compared with epidural analgesia for pain relief in labour [abstract]. *Regional Anesthesia and Pain Management* 2006;**31**(5 Suppl 1):52.

Rahimi 2012 *{published data only}*
IRCT201104026115N1. The effect of adding Remifentanil to Entonox in reducing labour pain in first stage of active phase of labour in parturients. en.search.irct.ir/view/5636 (first received 14 August 2012).

Ransom 1966 *{published data only}*
Ransom S. Oxymorphone as an obstetric analgesic - a clinical trial. *Anaesthesia* 1966;**21**(4):464–71.

Rayburn 1989 *{published data only}*
Rayburn W, Leuschen MP, Earl R, Woods M, Lorkovic M, Gaston-Johansson F. Intravenous meperidine during labor: a randomized comparison between nursing- and patient-controlled administration. Obstetrics & Gynecology 1989; Vol. 74, issue 5:702–6.

Rayburn 1991 *{published data only}*
Rayburn WF, Smith CV, Leuschen MP, Hoffman KA. Patient-controlled analgesia using fentanyl during labor. Proceedings of 10th Annual Meeting of Society of Perinatal Obstetricians; 1990 Jan 23-27; Houston, Texas, USA. 1990:51.
* Rayburn WF, Smith CV, Leuschen MP, Hoffman KA, Flores CS. Comparison of patient-controlled and nurse-administered analgesia using intravenous fentanyl during labor. *Anesthesiology Review* 1991;**18**(1):31–6.

Roberts 1957 *{published data only}*
Roberts H, Kane KM, Percival N, Snow P, Please NW. Effects of some analgesic drugs used in childbirth with special reference to variation in respiratory minute volume of the newborn. Lancet 1957; Vol. 1, issue 6960:128–32.

Roberts 1960 *{published data only}*
Roberts H, Kuck MAC. Use of alphaprodine and levallorphan during labour. *Canadian Medical Association Journal* 1960;**83**:1088–93.

Robinson 1980 *{published data only}*
Evans JM, David H, Rosen M, Revill SI, Robinson J, McCarthy J, et al. Patient activated intravenous narcotic. Obstetric Anaesthetists Assn Report. Anaesthesia 1976; Vol. 31:847.
* Robinson JO, Rosen M, Evans JM, Revill SI, David H, Rees GAD. Self-administered intravenous and intramuscular pethidine - a controlled trial in labour. Anaesthesia 1980; Vol. 35, issue 8:763–70.

Ron 1984 *{published data only}*
Ron M, Menashe M, Hochner-Celnikier D, Palti Z. Maternal blood pressure response to the intravenous administration of pethidine-promethazine during labor. *European Journal of Obstetrics & Gynecology and Reproductive Biology* 1984;**18**(1):25–8.

Rowley 1963 *{published data only}*
Rowley WF, Tannrikulu O, Grossman A, Hsia DY. A controlled study on effect of promethazine hydrochloride and meperidine hydrochloride upon serum bilirubin levels in the newborn infant. *Journal of Pediatrics* 1963;**62**:934–5.

Sabry 2011 *{published data only}*
NCT01290289. Analgesia in labor, a prospective parallel single blind study to compare regional analgesia (combined spinal epidural analgesia (cse), epidural analgesia (e)) and intravenous (iv) pethidine analgesia. clinicaltrials.gov/show/NCT01290289 (first received 4 February 2011).

Samanta 2013 *{published data only}*
Samanta S, Jain K, Bhardwaj N, Jain V, Singla V. Doppler velocimetric changes following labour epidural analgesia in growth restricted fetuses with impaired umbilical blood flow: A randomised controlled trial. *Journal of Obstetric Anaesthesia and Critical care* 2013;**31**(1):57.

Savage 1955 *{published data only}*
Savage D. Chlorpromazine (Largactil) as an analgesic in labour. *British Journal of Anaesthesia* 1955;**27**(7):346–53.

Sentnor 1966 *{published data only}*
* Sentnor MH, Posner NA, Kohl SG, Pomerance W. Oxymorphone re-evaluated. The addition of a respiratory

antagonist. *American Journal of Obstetrics and Gynecology* 1966;**96**(3):430–6.
Sentnor MH, Solomons E, Kohl SG. An evaluation of oxymorphone in labor. *American Journal of Obstetrics and Gynecology* 1962;**84**:956–61.

Shahriari 2007 ***{published data only}***
Shahriari A, Khooshideh M. A randomized controlled trial of intravenous remifentanil compared with intramuscular meperidine for pain relief in labor. *Journal of Medical Sciences* 2007;**7**(4):635–9.

Singh 2001 ***{published data only}***
Singh S, Mathur V, Srivastava U, Pandey DN, Gupta N. Comparative evaluation of efficacy of tramadol with pentazocine for labour analgesia and their effects on foetal outcome. *Journal of Obstetrics and Gynecology of India* 2001; **51**(2):55–7.

Solek-Pastuszka 2009 ***{published data only}***
Solek-Pastuszka J, Kepinski S, Makowski A, Celewicz Z, Zukowski M, Safranow K, et al. Patient-controlled continuous epidural analgesia vs intravenous remifentanil infusion for labour anaesthesia [Porownanie jakosci znieczulenia u rodzacych otrzymujacych remifentanil metoda analgezji dozylnej sterowanej przez pacjenta lub ciaglego znieczulenia zewnatrzoponowego]. *Anestezjologia Intensywna Terapia* 2009;**41**(2):84–8.

Soontrapa 2002 ***{published data only}***
Sookpanya S, Suntrapa S, Komwilaisak R. Effectiveness of intravenous pethidine for pain relief in the first stage of labour. *Thai Journal of Obstetrics and Gynaecology* 1999;**11** (4):272.
* Soontrapa S, Somboonporn W, Komwilaisak R, Sookpanya S, Soontrapa Sukree, Somboonporn Woraluk, et al. Effectiveness of intravenous meperidine for pain relief in the first stage of labour. *Journal of the Medical Association of Thailand* 2002;**85**(11):1169–75.

Sosa 2004 ***{published data only}***
* Sosa CG, Balaguer E, Alonso JG, Panizza R, Laborde A, Berrondo C. Meperidine for dystocia during the first stage of labor: a randomized controlled trial. *American Journal of Obstetrics and Gynecology* 2004;**191**(4):1212–8.
Sosa CG, Buekens P, Hughes JM, Balaguer E, Sotero G, Panizza R, et al. Effect of pethidine administered during the first stage of labor on the acid-base status at birth. *European Journal of Obstetrics & Gynecology and Reproductive Biology* 2006;**129**(2):135–9.

Spellacy 1966 ***{published data only}***
Spellacy WN, Shattuck CA, Loffer FD. A double-blind study of the comparative effects of meperidine with secobarbital, hydroxyzine, or a placebo on labor and delivery. *Obstetrics & Gynecology* 1966;**27**(2):290–3.

Stocki 2014 ***{published data only}***
Stocki D, Matot I, Einav S, Eventov-Friedman S, Ginosar Y, Weiniger CF. A randomized controlled trial of the efficacy and respiratory effects of patient-controlled intravenous remifentanil analgesia and patient-controlled epidural analgesia in laboring women. *Anesthesia & Analgesia* 2014; **118**(3):589–97.

Stourac 2014 ***{published data only}***
Stourac P, Suchomelova H, Stodulkova M, Huser M, Krikava I, Janku P, et al. Comparison of parturient-controlled remifentanil with epidural bupivacain and sufentanil for labour analgesia: randomised controlled trial. *Biomedical Papers: Journal of the Palacky University* 2014; **158**(2):227–32.

Suvonnakote 1986 ***{published data only}***
Suvonnakote T, Thitadilok W, Atisook R. Pain relief during labour. *Journal of the Medical Association of Thailand* 1986; **69**(11):575–9.

Taskin 1993 ***{published data only}***
Taskin O, Saade G, Belfort M, Moise K. The effect of narcotics and spasmolytics on cervical dilatation in labor: a randomized placebo-controlled study. *American Journal of Obstetrics and Gynecology* 1993;**168**:362.

Thurlow 2002 ***{published data only}***
Thurlow JA, Laxton CH, Dick A, Waterhouse P. A comparison of patient controlled analgesia (PCA) using remifentanil with intramuscular pethidine for pain relief in labour [abstract]. *International Journal of Obstetric Anesthesia* 2000;**9**:200.
* Thurlow JA, Laxton CH, Dick A, Waterhouse P, Sherman L, Goodman NW. Remifentanil by patient-controlled analgesia compared with intramuscular meperidine for pain relief in labour. *British Journal of Anaesthesia* 2002;**88**(3): 374–8.

Tomlin 1965 ***{published data only}***
Tomlin PJ. Pethidine compared with pethidine plus levallorphan and with a placebo. *British Journal of Anaesthesia* 1965;**37**:23–8.

Tournaire 1980 ***{published data only}***
Tournaire M, Catinat-Ozil D, Breart G, Scherrer P, Baron JM, Leroy B. The influence of pethidine on uterine activity and dilatation of the cervix in spontaneous labour. *Journal de Gynecologie, Obstetrique et Biologie de la Reproduction* 1980;**9**(2):261–6.

Treisser 1981 ***{published data only}***
Treisser A, Breart G, Blum F, Jouhet P, Pigne A, Barrat J. Dystocia at the onset of labour. An evaluation of the different treatments available. *Journal de Gynecologie, Obstetrique et Biologie de la Reproduction* 1981;**10**(1):91–8.

Tripti 2006 ***{published data only}***
Tripti N, Jyotsna A. Pain relief in labor tramadol versus pentazocine. *Journal of Obstetrics and Gynecology of India* 2006;**56**(5):406–9.

Vavrinkova 2005 ***{published data only}***
Vavrinkova B, Oborna L, Binder T, Horak J. Nalbuphine in obstetrical analgesia [Nalbuphine v porodnicke analgezii]. *Ceska Gynekologie* 2005;**70**(3):180–3.

Volmanen 2005 ***{published data only}***
* Volmanen P, Akural E, Raudakoski T, Ohtonen P, Alahuhta S. Comparison of remifentanil and nitrous oxide

in labour analgesia. *Acta Anaesthesiologica Scandinavica* 2005;**49**:453–8.

Volmanen P, Akural E, Raudaskoski, Alahuhta S. Comparison of maternal haemodynamic effects and respiratory indices during remifentanil and nitrous oxide labour analgesia. *International Journal of Obstetric Anesthesia* 2004;**13**(3):S19.

Volmanen 2008 ***{published data only}***

Volmanen P, Sarvela J, Akural EI, Raudaskoski T, Korttila K, Alahuhta S. Intravenous remifentanil vs. epidural levobupivacaine with fentanyl for pain relief in early labour: a randomised, controlled, double-blinded study. *Acta Anaesthesiologica Scandinavica* 2008;**52**(2):249–55.

Volmanen 2009 ***{published data only}***

Volmanen P, Akural E, Alahuhta S. In early labour, IVPCA remifentanil bolus during the contraction pause does not improve the analgesic effect but reduces sedation compared with bolus given during the uterine contraction. *European Journal of Anaesthesiology* 2009;**26**(Suppl 45):148, Abstract no: 11AP1-4.

* Volmanen PV, Akural EI, Raudaskoski T, Ranta P, Tekay A, Ohtonen P, et al. Timing of intravenous patient-controlled remifentanil bolus during early labour. Acta Anaesthesiologica Scandinavica 2011; Vol. 55, issue 4: 486–94.

Von Vorherr 1963 ***{published data only}***

Von Vorherr H. Is there a pharmacological acceleration of childbirth? [Gibt es eine medikamentose Geburtsbeschleunigung?]. *Deutsche Medizinische Wochenschrift* 1963;**88**:1426–30.

Walker 1992 ***{published data only}***

Walker JJ, Johnston J. A randomised study of non-steroidal anti-inflammatory drug ketolorac against pethidine in labour. Proceedings of 11th European Congress of Perinatal Medicine; 1988 April 10-13; Rome, Italy. 1988:163.

* Walker JJ, Johnston J, Fairlie FM, Lloyd J, Bullingham R. A comparative study of intramuscular ketorolac and pethidine in labour pain. *European Journal of Obstetrics & Gynecology and Reproductive Biology* 1992;**46**(2):87–94.

Walker JJ, Johnstone J, Lloyd J, Rocha CL. The transfer of ketorolac tromethamine from maternal to foetal blood. *European Journal of Clinical Pharmacology* 1988;**34**(5): 509–11.

Wan 1965 ***{published data only}***

Wan LS, Emich JP. Use of propiomazine hydrochloride during labor - a double-blind study on 236 patients. *Obstetrics & Gynecology* 1965;**25**:68–71.

Weissman 2006 ***{published data only}***

NCT00296751. Epidural analgesia versus iv meperidine for labor pain control. objective evaluation of the pain intensity influence on the autonomic nervous system. clinicaltrials.gov/ct2/show/record/NCT00296751 (first received 24 February 2006).

Wiener 1979 ***{published data only}***

Wiener PC, Hogg MI, Rosen M. Neonatal respiration, feeding and neurobehavioural state: effects of intrapartum bupivacaine, pethidine and pethidine reversed by naloxone. Anaesthesia 1979; Vol. 34, issue 10:996–1004.

Williams 1962 ***{published data only}***

Williams G, Cope I. An evaluation of a combination of pethidine and levallorphan ("pethilorfan"' in labour. *Medical Journal of Australia* 1962;**49**(2):499–503.

Wilson 2016 ***{published data only}***

NCT02179294. A randomised controlled trial of remifentanil intravenous patient controlled analgesia (pca) versus intramuscular pethidine for pain relief in labour. clinicaltrials.gov/ct2/show/record/NCT02179294 (first received 11 June 2014).

* Wilson M, MacArthur C, Gao Smith F, Homer L, Handley K, Daniels J. The respite trial: remifentanil intravenously administered patient-controlled analgesia (pca) versus pethidine intramuscular injection for pain relief in labour: study protocol for a randomised controlled trial. *Trials* 2016;**17**(1):591.

Wong 2005 ***{published data only}***

Scavone BM, Sullivan JT, Peaceman AM, Strauss-Hoder TP, Wong CA. Fetal heart rate and uterine contraction pattern abnormalities after combined spinal/epidural vs systemic labor analgesia [abstract]. *Anesthesiology* 2002;**96 Suppl**: Abstract no: A1049.

Sullivan JT, Scavone BM, McCarthy RJ, Wong CA. Does type of labor analgesia alter the pattern of oxytocin use? [abstract]. *Anesthesiology* 2002;**96**(Suppl 1):Abstract no: P48.

Sullivan JT, Scavone BM, McCarthy RJ, Wong CA. Neuraxial labor analgesia is associated with an altered pattern of oxytocin use [abstract]. *Anesthesiology* 2002;**96 Suppl**:Abstract no: A1039.

Wong CA, McCarthy RJ, Sullivan JT, Scavone BM, Gerber SE, Yaghmour EA. Early compared with late neuraxial analgesia in nulliparous labor induction: a randomized controlled trial. *Obstetrics & Gynecology* 2009;**113**(5): 1066–74.

* Wong CA, Scavone BM, Peaceman AM, McCarthy RJ, Sullivan JT, Diaz NT, et al. The risk of cesarean delivery with neuraxial analgesia given early versus late in labor. [See comment]. *New England Journal of Medicine* 2005;**352**(7): 655–65.

Wong CA, Scavone BM, Sullivan JT, Ebarvia MJ, McCarthy RJ. The risk of cesarean delivery with early neuraxial analgesia in nulliparous induction of labor. *Anesthesiology* 2007;**107**:Abstract no: A1204.

Wong CA, Scavone BM, Sullivan JT, Strauss-Hoder TP, McCarthy RJ. Randomized trial of neuraxial vs systemic analgesia for latent phase labor: effect on incidence of cesarean delivery [abstract]. *Anesthesiology* 2002;**96 Suppl**: Abstract no: A1047.

Wong CA, Sullivan JT, McCarthy RJ, Scavone BM, Patel R, Ebarvia MJ. Randomized trial of neuraxial vs. systemic analgesia for labor induction: effect on incidence of cesarean delivery [abstract]. *Anesthesiology* 2007;**106**(Suppl 1):21.

References to studies awaiting assessment

Mohan 2015 *{published data only}*
Mohan H, Ramappa R, Sandesh M, Akash BK. Intravenous paracetamol infusion versus intramuscular tramadol as an intrapartum labor analgesic. *International Journal of Reproduction, Contraception, Obstetrics and Gynecology* 2015; **4**(6):1726–9.

Sereshti 2013 *{published data only}*
Sereshti M, Asefi F, Shabanian M, Banaeian S. Comparing the effects of massage and intra intramuscular pethidine on pain relief in the stages of labor and the length of labor. *Iranian Journal of Obstetrics, Gynecology and Infertility* 2013; **16**(80):6–16.

References to ongoing studies

Kokki 2015 *{published data only}*
EUCTR2015-000185-59-FI. The effect of oxycodone to placental and fetal circulation during the phase I of labor and the efficacy, safety and neonatal effects of oxycodone. clinicaltrialsregister.eu/ctr-search/search?query=eudract_number:2015-000185-59 (first received 27 January 2015).

Raheja 2016 *{published data only}*
NCT02999594. Tramadol for labor analgesia in low risk women: a placebo controlled randomized trial. clinicaltrials.gov/show/NCT02999594 (first received 2 December 2016).

Reyes 2013 *{published data only}*
NCT01889979. Tramadol for labour analgesia in low risk primiparous women. double blind, randomized, controlled trial. clinicaltrials.gov/ct2/show/NCT01889979 (first received 26 June 2013).

Sahin 2012 *{published data only}*
NCT01555671. Is there any effect of meperidine on the length of duration of labor? a prospective randomized controlled trial. clinicaltrials.gov/ct2/show/NCT01555671 (first received 14 March 2012).

Shen 2008 *{published data only}*
NCT00710086. Remifentanil intravenous patient-controlled labor analgesia for nulliparous women. clinicaltrials.gov/ct2/show/NCT00710086 (first received 2 July 2008).

Additional references

Aghdas 2014
Aghdas K, Talat K, Sepideh B. Effect of immediate and continuous mother-infant skin-to-skin contact on breastfeeding self-efficacy of primiparous women: a randomised control trial. *Women & Birth: Journal of the Australian College of Midwives* 2014;**27**(1):37–40.

Anim-Somuah 2018
Anim-Somuah M, Smyth RMD, Cyna AM, Cuthbert A. Epidural versus non-epidural or no analgesia for pain management in labour. *Cochrane Database of Systematic Reviews* 2018, Issue 5. DOI: 10.1002/14651858.CD000331.pub4

Aziato 2016
Aziato L, Ohemeng HA, Omenyo CN. Experiences and perceptions of Ghanaian midwives on labour pain and religious beliefs and practices influencing their care of women in labour. *Reproductive Health* 2016;**13**(1):136.

Barragán 2011
Barragán Loayza IM, Solà I, Juandó Prats C. Biofeedback for pain management during labour. *Cochrane Database of Systematic Reviews* 2011, Issue 6. DOI: 10.1002/14651858.CD006168.pub2

Bohren 2017
Bohren MA, Hofmeyr GJ, Sakala C, Fukuzawa RK, Cuthbert A. Continuous support for women during childbirth. *Cochrane Database of Systematic Reviews* 2017, Issue 7. DOI: 10.1002/14651858.CD003766

Bricker 2002
Bricker L, Lavender T. Parenteral opioids for labor pain relief: a systematic review. *American Journal of Obstetrics and Gynecology* 2002;**186**(5 Suppl):S94–S109.

Brimdyr 2015
Brimdyr K, Cadwell K, Widstroem AM, Svensson K, Neumann M, Hart EA, et al. The association between common labor drugs and suckling when skin-to-skin during the first hour after birth. *Birth* 2015;**42**(4):319-28.

Carberry 2013
Carberry AE, Raynes-Greenow CH, Turner RM, Jeffery HE. Breastfeeding within the first hour compared to more than one hour reduces risk of early-onset feeding problems in term neonates: a cross-sectional study. *Breastfeeding Medicine* 2013;**8**(6):513–4.

Cluett 2009
Cluett ER, Burns E. Immersion in water in labour and birth. *Cochrane Database of Systematic Reviews* 2009, Issue 2. DOI: 10.1002/14651858.CD000111.pub3

Cook 2012
Cook K, Loomis C. The impact of choice and control on women's childbirth experiences. *Journal of Perinatal Education* 2012;**21**(3):158-68.

Deeks 2001
Deeks JJ, Altman DG, Bradburn MJ. Statistical methods for examining heterogeneity and combining results from several studies in meta-analysis. In: Egger M, Davey Smith G, Altman DG editor(s). *Systematic reviews in health care: meta-analysis in context*. London: BMJ Books, 2001.

Derry 2012
Derry S, Straube S, Moore RA, Hancock H, Collins SL. Intracutaneous or subcutaneous sterile water injection compared with blinded controls for pain management in labour. *Cochrane Database of Systematic Reviews* 2012, Issue 1. DOI: 10.1002/14651858.CD009107.pub2

Dowswell 2009
Dowswell T, Bedwell C, Lavender T, Neilson JP. Transcutaneous electrical nerve stimulation (TENS) for pain relief in labour. *Cochrane Database of Systematic Reviews* 2009, Issue 2. DOI: 10.1002/14651858.CD007214.pub2

Edmond 2006
Edmond KM, Zandoh C, Quigley MA, Amenga-Etego S, Owusu-Agyei S, Kirkwood BR. Delayed breastfeeding initiation increases risk of neonatal mortality. *Pediatrics* 2006;**117**(3):e380–6.

Eisenach 2010
Eisenach J. Neurophysiology of labour pain. European Society of Anaesthesiology lecture 2010.

Elbourne 2006
Elbourne D, Wiseman RA. Types of intra-muscular opioids for maternal pain relief in labour. *Cochrane Database of Systematic Reviews* 2006, Issue 3. DOI: 10.1002/14651858.CD001237.pub2

Fleet 2017
Fleet JA, Jones M, Belan I. The influence of intrapartum opioid use on breastfeeding experience at 6 weeks post partum: A secondary analysis. *Midwifery* 2017;**50**:106–9.

Genesi 1998a
Genesi L, Niescierowicz R. Neuroendocrinology and birth 1: stress. *British Journal of Midwifery* 1998;**6**(10):659–64.

Genesi 1998b
Genesi L, Niescierowicz R. Neuroendocrinology and birth 2: the role of oxytocin. *British Journal of Midwifery* 1998;**6**(12):791–6.

Green 2003
Green JM, Baston HA. Feeling in control during labour: concepts, correlates, and consequences. *Birth* 2003;**30**(4):235–47.

Hawkins 2003
Hawkins J. Obstetric analgesia and anaesthesia. In: Scott JR, Gibbs RS, Karlan BY, Haney AF editor(s). *Darnforth's Obstetrics and Gynaecology*. 9th Edition. London: Lippincott, Williams and Wilkins, 2003.

Higgins 2011a
Higgins JPT, Green S, editors. Cochrane Handbook for Systematic Reviews of Interventions Version 5.1.0 [updated March 2011]. The Cochrane Collaboration, 2011. Available from www.cochrane-handbook.org.

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

Hodnett 1987
Hodnett ED, Simmons-Tropea DA. The labour agentry scale: Psychometric properties of an instrument measuring control during childbirth. *Research in Nursing and Health* 1987;**10**(5):301-10.

Hodnett 2002
Hodnett ED. Pain and women's satisfaction with the experience of childbirth: a systematic review. *American Journal of Obstetrics and Gynecology* 2002;**186**(5 Suppl Nature):S160–S172.

Hodnett 2012
Hodnett ED, Downe S, Walsh D. Alternative versus conventional institutional settings for birth. *Cochrane Database of Systematic Reviews* 2012, Issue 8. DOI: 10.1002/14651858.CD000012.pub4

Hogg 1977
Hogg MI, Wiener PC, Rosen M, Mapleson WW. Urinary excretion and metabolism of pethidine and norpethidine in the newborn. *British Journal of Anaesthesia* 1977;**49**(9):891–9.

Jacobson 1990
Jacobson B, Nyberg K, Grönbladh L, Eklund G, Bygdeman M, Ryberg U. Opiate addiction in adult offspring through possible imprinting after obstetric treatment. *BMJ* 1990;**301**(6760):1067–70.

Jones 2011
Jones L, Dou L, Dowswell T, Alfirevic Z, Neilson JP. Pain management for women in labour: generic protocol. *Cochrane Database of Systematic Reviews* 2011, Issue 6. DOI: 10.1002/14651858.CD009167

Jones 2012
Jones L, Othman M, Dowswell T, Alfirevic Z, Gates S, Newburn M, et al. Pain management for women in labour: an overview of systematic reviews. *Cochrane Database of Systematic Reviews* 2012, Issue 3. DOI: 10.1002/14651858.CD009234.pub2

Jordan 2005
Jordan S, Emery S, Bradshaw C, Watkins A, Friswell W. The impact of intrapartum analgesia on infant feeding. *BJOG: an international journal of obstetrics and gynaecology* 2005;**112**(7):927–34.

Klomp 2012
Klomp T, van Poppel M, Jones L, Lazet J, Di Nisio M, Lagro-Janssen ALM. Inhaled analgesia for pain management in labour. *Cochrane Database of Systematic Reviews* 2012, Issue 9. DOI: 10.1002/14651858.CD009351.pub2

Klomp 2014
Klomp T, Mannien J, de Jonge A, Hutton EK, Lagro-Janssen ALM. What do midwives need to know about approaches of women towards labour pain management? A qualitative interview study into expectations of management of labour pain for pregnant women receiving midwife-led care in the Netherlands. *Midwifery* 2014;**30**(4):432–8.

Lally 2014
Lally JE, Thomson RG, MacPhail S, Exley C. Pain relief in labour: a qualitative study to determine how to support women to make decisions about pain relief in labour. *BMC Pregnancy & Childbirth* 2014;**14**:6.

Lamm 2007
Lamm C, Batson CD, Decety J. The neural substrate of human empathy: effects of perspective-taking and cognitive appraisal. *Journal of Cognitive Neuroscience* 2007;**19**(1):42–58.

Lang 2006
Lang AJ, Sorrell JT, Rodgers CS, Lebeck MM. Anxiety sensitivity as a predictor of labor pain. *European Journal of Pain* 2006;**10**(3):263–70.

Lawrence 2013
Lawrence A, Lewis L, Hofmeyr GJ, Styles C. Maternal positions and mobility during first stage labour. *Cochrane Database of Systematic Reviews* 2013, Issue 10. DOI: 10.1002/14651858.CD003934.pub4

Leap 2004
Leap N, Anderson T. The role of pain in normal birth and the empowerment of women. Chapter 2. In: Downe, S editor(s). *Normal Childbirth: Evidence and Debate*. Churchill Livingstone, 2004.

Lee 2004
Lee K, Ho KM. Obstetric regional analgesia services in New Zealand: a national survey. *New Zealand Medical Journal* 2004;**117**(1206):U1177.

Lind 2014
Lind JN, Perrine CG, Li R. Relationship between use of labor pain medications and delayed onset of lactation. *Journal of Human Lactation* 2014;**30**(2):167–73.

Lowe 2002
Lowe NK. The nature of labor pain. *American Journal of Obstetrics and Gynecology* 2002;**186**(5 Suppl Nature): S16–S24.

Madden 2016
Madden K, Middleton P, Cyna AM, Matthewson M, Jones L. Hypnosis for pain management during labour and childbirth. *Cochrane Database of Systematic Reviews* 2016, Issue 5. DOI: 10.1002/14651858.CD009356.pub3

MHRA 2007
The Medicines and Healthcare products Regulatory Agency (MHRA). Midwives: Prescribing. http://www.mhra.gov.uk/Howweregulate/Medicines/Availabilityprescribingsellingandsupplyingofmedicines/ExemptionsfromMedicinesActrestrictions/Midwives/index.htm (accessed 5 May 2010) 2007.

Moore 2016
Moore ER, Bergman N, Anderson GC, Medley N. Early skin-to-skin contact for mothers and their healthy newborn infants. *Cochrane Database of Systematic Reviews* 2016, Issue 11. DOI: 10.1002/14651858.CD003519.pub4

NICE 2014
National Institute for Health and Care Excellence (NICE). *NICE Clinical Guideline CG190. Intrapartum Care for Healthy Women and Babies*. London: NICE, 2014.

Nissen 1995
Nissen E, Lilja G, Matthiesen AS, Ransjo-Arvidsson AB, Uvnas-Moberg K, Widstrom AM. Effects of maternal pethidine on infants' developing breast feeding behaviour. *Acta Paediatrica* 1995;**84**(2):140–5.

Novikova 2011
Novikova N, Cluver C. Local anaesthetic nerve block for pain management in labour. *Cochrane Database of Systematic Reviews* 2011, Issue 7. DOI: 10.1002/14651858.CD009200

Nyberg 2000
Nyberg K, Buka SL, Lipsitt LP. Perinatal medication as a potential risk factor for adult drug abuse in a North American cohort. *Epidemiology* 2000;**11**(6):715–6.

Othman 2012
Othman M, Jones L, Neilson JP. Non-opioid drugs for pain management in labour. *Cochrane Database of Systematic Reviews* 2012, Issue 7. DOI: 10.1002/14651858.CD009223.pub2

Ransjo-Arvidson 2001
Ransjo-Arvidson AB, Matthiesen AS, Lilja G, Nissen E, Widstrom AM, Uvnas-Moberg K. Maternal analgesia during labor disturbs newborn behavior: effects on breastfeeding, temperature, and crying. *Birth* 2001;**28**(1): 5–12.

Redshaw 2007
Redshaw M, Rowe R, Hockley C, Brocklehurst P. *Recorded Delivery: a National Survey of Women's Experience of Maternity Care 2006*. Oxford: National Perintal Epidemiology Unit, University of Oxford, 2007.

Redshaw 2015
Redshaw M, Henderson J. *Safely Delivered: a National Survey of Women's Experience of Maternity Care 2014*. Oxford: The National Perinatal Epidemiology Unit, University of Oxford, 2015.

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

Reynolds 2002
Reynolds F, Sharma SK, Seed PT. Analgesia in labour and fetal acid-base balance: a meta-analysis comparing epidural with systemic opioid analgesia. *BJOG: an international journal of obstetrics and gynaecology* 2002;**109**(12):1344-53.

Righard 1990
Righard L, Alade MO. Effect of delivery room routines on success of first breast-feed. *Lancet* 1990;**336**(8723):1105–7.

Sandall 2016
Sandall J, Soltani H, Gates S, Shennan A, Devane D. Midwife-led continuity models versus other models of care for childbearing women. *Cochrane Database of Systematic Reviews* 2016, Issue 4. DOI: 10.1002/14651858.CD004667.pub5

Saravanakumar 2007
Saravanakumar K, Garstang JS, Hasan K. Intravenous patient-controlled analgesia for labour: a survey of UK practice. *International Journal of Obstetric Anesthesia* 2007; **16**(3):221–5.

Simmons 2012
Simmons SW, Taghizadeh N, Dennis AT, Hughes D, Cyna AM. Combined spinal-epidural versus epidural analgesia in

labour. *Cochrane Database of Systematic Reviews* 2012, Issue 10. DOI: 10.1002/14651858.CD003401.pub3

Smith 2011a
Smith CA, Collins CT, Crowther CA. Aromatherapy for pain management in labour. *Cochrane Database of Systematic Reviews* 2011, Issue 7. DOI: 10.1002/14651858.CD009215

Smith 2011b
Smith CA, Collins CT, Crowther CA, Levett KM. Acupuncture or acupressure for pain management in labour. *Cochrane Database of Systematic Reviews* 2011, Issue 7. DOI: 10.1002/14651858.CD009232

Smith 2018a
Smith CA, Levett KM, Collins CT, Armour M, Dahlen HG, Suganuma M. Relaxation techniques for pain management in labour. *Cochrane Database of Systematic Reviews* 2018, Issue 3. DOI: 10.1002/14651858.CD009514.pub2

Smith 2018b
Smith CA, Levett KM, Collins CT, Dahlen HG, Ee CC, Suganuma M. Massage, reflexology and other manual methods for pain management in labour. *Cochrane Database of Systematic Reviews* 2018, Issue 3. DOI: 10.1002/14651858.CD009290.pub3

Solt 2002
Solt I, Ganadry S, Weiner Z. The effect of meperidine and promethazine on fetal heart rate indices during the active phase of labor. *Israel Medical Association Journal* 2002;**4**(3): 178–80.

Sosa 2006
Sosa CG, Balaguer E, Alonso JG, Panizza R, et al. Effect of pethidine administered during the first stage of labor on the acid-base status at birth. *European Journal of Obstetrics & Gynecology and Reproductive Biology* 2006;**129**(2):135-9.

Trout 2004
Trout KK. The neuromatrix theory of pain: implications for selected nonpharmacologic methods of pain relief for labor. *Journal of Midwifery and Womens Health* 2004;**49**(6):482–8.

Tveit 2009
Tveit T O, Halvorsen A, Rosland J H. Analgesia for labour: a survey of Norwegian practice - with a focus on parenteral opioids. *Acta Anaesthesiologica Scandinavica* 2009;**53**(6): 794–9.

Victora 2016
Victora CG, Bahl R, Barros JD, França GV, Horton S Krasevec J, et al. Breastfeeding in the 21st century: epidemiology, mechanisms, and lifelong effect. *Lancet* 2016;**387**(6736):475-90.

Widstrom 2011
Widstrom AM, Lilja G, Aaltomaa-Michalias P, Dahllof A, Lintula M, Nissen E. Newborn behaviour to locate the breast when skin-to-skin: a possible method for enabling early self-regulation. *Acta Paediatrica* 2011;**100**(1):79–85.

Williams 2013
Williams AC, Morris J, Stevens K, Gessler S, Cella M, Baxter J. What influences midwives in estimating labour pain?. *European Journal of Pain* 2013;**17**(1):86–93.

Wong 2009
Wong C. Advances in labor analgesia. *International Journal of Women's Health* 2009;**1**:139–54.

References to other published versions of this review

Ullman 2008
Ullman R, Dowswell T, Mori R. Parenteral opioids for maternal pain relief in labour. *Cochrane Database of Systematic Reviews* 2008, Issue 4. DOI: 10.1002/14651858.CD007396

Ullman 2010
Ullman R, Smith LA, Burns E, Mori R, Dowswell T. Parenteral opioids for maternal pain management in labour. *Cochrane Database of Systematic Reviews* 2010, Issue 9. DOI: 10.1002/14651858.CD007396.pub2

* *Indicates the major publication for the study*

CHARACTERISTICS OF STUDIES

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

Atkinson 1994

Methods	RCT 2-arm parallel-group design
Participants	Setting: (not clear) hospital in Oklahoma, USA 100 women in early active labour (with regular contractions and cervical dilatation 3 cm to 4 cm); at term (at or > 37 weeks' gestation); no medical or obstetric complications or evidence of fetal distress; requesting a "pain shot" rather than an epidural (all women were offered epidural)
Interventions	Both groups had continuous electronic fetal monitoring and intrauterine pressure catheters Experimental: IV fentanyl 50 µg to 100 µg every 1 to 2 hrs to a max of 5 doses Control: IV butorphanol 1 mg to 2 mg every 1 to 2 hrs to a max 5 doses (Doses of drugs were approximately equivalent in both arms of the trial.)
Outcomes	Maternal uterine activity; adverse effects and side effects (including vomiting and sedation); pain scored using 10-point VAS (0 = no pain, 10 = excruciating pain) scores were recorded by nurses; Apgar scores at 1 and 5 mins; infant neurological exam 2 to 4 hrs and 24 to 36 hrs after birth
Notes	Start and end date: December 1992 - June 1993 Power calculation: unclear Baseline imbalances between groups: unclear Funding source: not specified Conflicts of interest: not specified

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Computer-generated randomisation schedule
Allocation concealment (selection bias)	Low risk	Pharmacy prepared identical unlabelled, coded syringes
Blinding of participants and personnel (performance bias) All outcomes	Low risk	Identical syringes. Described as double-blind.
Blinding of outcome assessment (detection bias) All outcomes	Low risk	Outcome assessors reported as blinded

Atkinson 1994 (*Continued*)

Incomplete outcome data (attrition bias) All outcomes	Unclear risk	It was not clear at what point women were randomised.155 women enrolled; 24 decided to have an epidural and were excluded (it was not clear whether or not this was after randomisation); 19 women delivered within 1 hr of first dose and 12 did not request analgesia and were not included in the analysis. Data available for 100 women; if loss occurred after randomisation this represents a very high level of attrition
Selective reporting (reporting bias)	Unclear risk	Unclear
Other bias	Low risk	None apparent

Bitsch 1980

Methods	RCT, 2-arm parallel groups
Participants	Setting: hospital, Germany 45 women, in labour, cephalic presentation
Interventions	Experimental: IM tramadol 50 mg (N = 23) Control: IM pethidine 50 mg (N = 22)
Outcomes	Primary outcome: maternal analgesia. Pain assessed as good, not good relief 5 to 10 mins after injection Secondary outcomes: maternal side effects and fetal heart changes
Notes	German language paper, translation obtained. Tramadol 100 mg plus antiemetic arm not extracted If additional analgesia required, repeat doses could be administered within < 1 hr Tramadol: could have up to 3 repeat doses, 50 mg Pethidine: could have up to 3 repeat doses, 25 mg Start and end date: August 1978 - December 1978 Power calculation: unclear Baseline imbalances between groups: unclear Funding source: unclear Conflicts of interest: unclear

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

Bitsch 1980 (*Continued*)

Blinding of participants and personnel (performance bias) All outcomes	Unclear risk	Not reported
Blinding of outcome assessment (detection bias) All outcomes	Low risk	Assessor was described as unaware of treatment assignment.
Incomplete outcome data (attrition bias) All outcomes	High risk	Women not having a normal birth were excluded from analyses. No information on pain relief was available for 7/45 women
Selective reporting (reporting bias)	Unclear risk	Unclear
Other bias	Unclear risk	Unclear

Blair 2005

Methods	RCT, 2-arm parallel groups
Participants	Setting: Belfast hospital, UK 40 women (healthy and well) in labour, ASA I or II Exclusion criteria: women planning to have epidural analgesia, with pre-eclampsia, multiple pregnancy, premature labour, allergy to study medications
Interventions	Experimental: PCA remifentanil 40 µg with lock-out of 2 mins Control: PCA pethidine 15 mg with lock-out of 10 mins Nitrous oxide was available to all women and women were free to choose an epidural at any stage
Outcomes	Maternal sedation score (1 to 5 fully awake to unrousable); VAS 0 to 10 for pain and satisfaction with pain relief; nausea; anxiety; Apgar scores at 1 min and 5 mins; infant neurological adaptive capacity score (2 hrs and 24 hrs after birth)
Notes	VAS scores were reported as median with inter-quartile range. We were not able to enter data into RevMan tables but have described findings briefly in the text Start and end date: not reported. Power calculation: "prospective power calculation showed that a sample size of 20 would give 85% power for detecting a difference of 20 mm on the VAS for overall pain, with SD 21.2 from previous work" Baseline imbalances between groups: "The two groups were similar as to characteristics and duration, stage of labour and use of PCA" Funding source: not specified Conflicts of interest: not declared

Risk of bias

Bias	**Authors' judgement**	**Support for judgement**

Blair 2005 (*Continued*)

Random sequence generation (selection bias)	Unclear risk	Quote: "women were randomly allocated."
Allocation concealment (selection bias)	Unclear risk	Not clear when randomisation occurred or how it was carried out
Blinding of participants and personnel (performance bias) All outcomes	Unclear risk	Described as double-blind study
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	It was reported that for some outcomes assessment was blinded
Incomplete outcome data (attrition bias) All outcomes	Low risk	40 women were randomised, 1 women was not included in the analysis because of a "protocol violation". 1 woman that withdrew from the study was included in the analysis
Selective reporting (reporting bias)	Unclear risk	Unclear
Other bias	Low risk	No baseline imbalance apparent

Borglin 1971

Methods	RCT, 2-arm parallel groups
Participants	Hospital setting 199 women: in labour, at term gestation, following normal pregnancy No inclusion or exclusion criteria reported
Interventions	Experimental: IM pentazocine 20 mg to 40 mg (N = 91) Control: IM pethidine 50 mg to 100 mg (N = 89)
Outcomes	Primary: analgesic and sedative effects. Pain assessed at time of birth or when second injection administered, as very good, good, moderate or none Secondary: maternal and neonatal side effects
Notes	If additional analgesia required opioid repeated once after 3 or > hrs of first injection. Actual dose received by women not reported Start and end date: unclear Power calculation: unclear Baseline imbalances between groups: unclear Funding source: not specified Conflicts of interest: not specified
Risk of bias	

Borglin 1971 (*Continued*)

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Not reported
Allocation concealment (selection bias)	Unclear risk	Ampoules numbered and in random order
Blinding of participants and personnel (performance bias) All outcomes	Unclear risk	Reported as double-blind, but no description of how achieved. Identical volume but appearance not described
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	Not reported
Incomplete outcome data (attrition bias) All outcomes	Low risk	All participants analysed, but missing data for some outcome
Selective reporting (reporting bias)	Unclear risk	Unclear
Other bias	Low risk	Balanced at baseline for age, parity, blood pressure, pulse, frequency contractions, FHR, augmented labour, intensity of labour, membranes intact or ruptured

Campbell 1961

Methods	RCT, 3-arm parallel-group design
Participants	Setting: hospital in Baltimore, USA 212 women randomised (141 included in the analyses in this review) Inclusion criteria: women admitted to hospital for planned vaginal birth, at term, requesting analgesia (birth under regional anaesthesia) Exclusions: imminent birth, allergy to any study medication or requiring birth under general anaesthesia
Interventions	Interventions at 3 cm to 4 cm dilatation for primiparous, and 4 cm to 5 cm for multiparous women Group 1: pentobarbital IV (initial dose 200 mg) dosage varied Group 2: pethidine IV (initial dose 100 mg), (69 women) Group 3: morphine IV (initial dose 8 mg), (72 women) All 3 groups also received 0.4 mg of scopolamine. If further analgesia was required, women were given a half of the initial dose and 0.2 mg of scopolamine. If more than 2 additional doses were required analgesia was at the discretion of the attending doctor In this review we have included groups 2 and 3 only in the analyses; pentobarbital (a barbiturate) is no longer used for pain relief in labour

Campbell 1961 (*Continued*)

Outcomes	Length of labour, amount of analgesia required, obstetric complications and neonatal condition (Apgar score at 1 min). Maternal perceptions were recorded 3 days after birth (satisfaction and amnesia). A focus of this paper was the perception of staff on whether women were "manageable". Unmanageable women were those who were "possibly dangerous to others or themselves, perhaps by leaving her bed". Staff had the option of removing unmanageable women from the study and prescribing whatever medication was deemed suitable
Notes	All women included delivered under regional anaesthesia. Start and end date: not reported Power calculation: not specified Baseline imbalances between groups: unclear Funding source: not specified Conflicts of interest: not specified

Risk of bias

Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Unclear risk	Quote: "in a random manner."
Allocation concealment (selection bias)	Low risk	Coded vials containing study drugs were provided by pharmacy
Blinding of participants and personnel (performance bias) All outcomes	Low risk	Quote: "None of the personnel concerned with the administration of the drugs or the evaluation of the patients' reaction had access to the master list at any time."
Blinding of outcome assessment (detection bias) All outcomes	Low risk	Quote: "None of the personnel concerned with the administration of the drugs or the evaluation of the patients' reaction had access to the master list at any time."
Incomplete outcome data (attrition bias) All outcomes	Unclear risk	All women appear to be accounted for in the analysis and there were few missing data. The data regarding babies were less clear, denominators were not provided
Selective reporting (reporting bias)	High risk	Results were not provided for babies. There was a statement in the text "there were few infant complications in the neonatal period; none of these appeared related to the drugs"
Other bias	Unclear risk	Baseline characteristics described as similar.

De Boer 1987

Methods	RCT, 2-arm parallel groups
Participants	Setting: hospital, UK 46 women (20 primiparous and 14 multiparous women included in the analyses). Uncomplicated pregnancy Exclusions: first stage of labour > 12 hr, second stage > 1 hr, body weight < 45 kg, multiple pregnancy, non-vertex presentation, preterm or postmature labour, previous caesarean section, birthweight outside the 5th and 95th centiles for gestational age, congenital fetal abnormality
Interventions	Experimental: IM meptazinol 1.5 mg/kg body weight plus 10 mg metoclopramide hydrochloride (N = 17) Control: IM pethidine 1.5 mg/kg body weight plus 10 mg metoclopramide hydrochloride (N = 17)
Outcomes	Neonatal acid-base balance. Maternal pH pre injection, repeated at head crowning, neonatal pH at 10 and 60 mins PN
Notes	If additional analgesia required opioid repeated > 3-hourly. Actual dose received by women not reported Start and end date: not reported Power calculation: not specified Baseline imbalances between groups: unclear Funding source: not specified Conflicts of interest: not specified

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	States double-blind but not described.
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	States double-blind but not described.
Incomplete outcome data (attrition bias) All outcomes	High risk	12 women excluded from analysis, reasons for all exclusions not explained
Selective reporting (reporting bias)	High risk	Reasons why some participant data excluded not explained. 3/12 excluded because problem with pH analyser (meptazinol group)

De Boer 1987 (*Continued*)

Other bias	Low risk	No baseline imbalances

Direkvand-Moghadam 2014

Methods	Randomised clinical trial using individual randomisation.
Participants	Setting: hospital in Iran 90 women randomised: nulli-parous, aged between 18 and 35 years, singleton pregnancy, spontaneous active labour, cervical dilation between 4 cm and 5 cm, gestational age between 38 and 40 weeks, normal FHR tracings, intact membranes, and vertex presentation Exclusion criteria: elective labour induction, emergency caesarean delivery, known cephalopelvic disproportion, diagnosed pre eclampsia, chorioamnionitis, pyelonephritis, maternal cardiac, renal disease, intrauterine growth restriction and cervical dilation greater than 5 cm
Interventions	Experimental group: pethidine 50 mg IM - no further detail given. Not clear if it was given as requested or to all women or whether women could request a subsequent dose. (N = 45) Control group: normal saline IV same volume as pethidine. (N = 45) Amniotomy was performed by a trained midwife when cervical dilation reached 5 cm if the membranes had not ruptured spontaneously
Outcomes	Mode of birth Duration of active phase
Notes	Start and end date: December 2012 to March 2014 Funding: not stated CoI: reported no conflicts of interest

Risk of bias

Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Low risk	Randomisation was carried out in the obstetric triage unit using a random-number chart
Allocation concealment (selection bias)	Unclear risk	Method of concealment not described.
Blinding of participants and personnel (performance bias) All outcomes	High risk	Equal volumes of normal saline and pethidine given but by different routes. Likely that caregiver would realise allocation. Participants likely to be aware of treatment
Blinding of outcome assessment (detection bias) All outcomes	High risk	Labour outcomes were collected by caregiver.

Direkvand-Moghadam 2014 (*Continued*)

Incomplete outcome data (attrition bias) All outcomes	Unclear risk	Reported that none of the 90 enrolled women withdrew for any reason. Data reported for all women. However not all data are reported in absolute numbers and denominators and results are not clear for Apgar scores or neonatal admission to intensive care
Selective reporting (reporting bias)	Unclear risk	Protocol not available. Outcomes are not clearly pre-specified. It was not clear which outcomes the power calculation related to. Important outcomes were not reported
Other bias	Unclear risk	Similar baseline characteristics. Generally poorly reported.

Douma 2010

Methods	RCT, 3-arm parallel groups
Participants	Setting: the Netherlands, Department of Obstetrics and Gynaecology 180 enrolled, 159 completed the study. Inclusion criteria: healthy ASA physical status I or II term parturients in an active stage of labour, with singleton cephalic presentation, without prior administration of opioid analgesics Exclusion criteria: obesity (BMI $\geq$ 40 kg m^{-2}), opioid allergy, substance abuse history, and high-risk patients (pre-eclampsia, severe asthma, insulin-dependent diabetes mellitus, hepatic insufficiency, or renal failure)
Interventions	1. Remifentanil, patient controlled IV, 40 µg loading dose, remifentanil 40 µg per bolus with a lockout of 2 mins and max dose limit of 1200 µg h^{-1} 2. Meperidine, patient controlled IV, 49.5 mg loading dose and 5 mg bolus with lockout of 10 mins and max dose limit of 200 mg 3. Fentanyl, patient controlled IV, 50 µg loading dose and 20 µg bolus with lockout of 5 mins and a max dose limit of 240 µg h^{-1}
Outcomes	Outcomes: pain scores (VAS) every hr; sedation score (1 awake, 2 sleepy, 3 eyes closed, 4 eyes closed but rousable, 5 unrousable; overall satisfaction on 10-point scale 2 hrs after delivery; side effects - nausea,vomiting, itching; Apgar scores at 1 min, 5 mins; cord blood gas analysis; NACS scores at 15 mins and 2 hrs after delivery; oxytocin use; instrumental delivery; CS; spontaneous delivery
Notes	Quote: "All women received similar instructions on how to use the PCA device: all parturients were instructed to press the bolus button whenever they needed pain relief." Start and end date: not reported Power calculation: 'For sample size calculation, we hypothesized that average pain scores in the remifentanil or fentanyl group would differ at least 10% from the meperidine

Douma 2010 (*Continued*)

	group. Assuming an SD of 15 mm based on the previous studies, we calculated a sample size of 60 parturients per group for a power of 0.95 and a two-sided a level of 0.05 to detect this difference' Baseline imbalances between groups: 'The characteristics of the parturients did not differ statistically.' Funding source: Bronovo Research Fund Conflicts of interest: not specified

Risk of bias

Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Low risk	Quote: "Established using a computer generated random sequence in numbered envelopes."
Allocation concealment (selection bias)	Low risk	Quote: "Study medication was prepared and blinded by hospital pharmacy."
Blinding of participants and personnel (performance bias) All outcomes	Low risk	Quote: "Observants and medical personnel attending to the parturient were unaware of the drug assignment."
Blinding of outcome assessment (detection bias) All outcomes	Low risk	Quote: "with exception of baseline data, all observations and measurements were made by blinded observers."
Incomplete outcome data (attrition bias) All outcomes	Low risk	180 enrolled, 159 completed the study: 52 R group; 53 M group; 54 F group; 21 excluded because delivered within 1 hr after randomisation Quote: "Data analysis was per-protocol."
Selective reporting (reporting bias)	Unclear risk	All outcomes discussed in methods appear to have been reported upon within results. However, the study protocol was not evaluated
Other bias	Low risk	Baseline characteristics similar

Duncan 1969

Methods	RCT, 2-arm parallel groups
Participants	Setting: hospital, UK 200 women. 66% primips, 34% multips, > 35 weeks' gestation. Singleton, uncomplicated pregnancy Exclusions: toxaemia, chronic medical disease, isoimmunisation, obstetric complication

Duncan 1969 (*Continued*)

Interventions	Experimental: IM pentazocine 48 mg (N = 100) Control: IM pethidine 120 mg (N = 100) Nalorphine hydrobromide + methylphenidate given if opioid administered within 2/24 of second stage diagnosis and, or fetal distress
Outcomes	Primary outcome: analgesic effects: pain assessed at time of injection and every 30 mins for 4 hrs. Severe or moderate pain. Pain relief complete, partial or none Secondary outcomes: maternal: vomiting, blood pressure and pulse. Neonatal: Apgar at 1 min in babies born within 4 hrs of opioid
Notes	If additional analgesia required opioid repeated after 4 hrs. As inclusion criteria > 35 weeks' gestation, may include preterm infants Start and end date: not reported Power calculation: not specified Baseline imbalances between groups: the 100 women given each drug was comparable in respect of age, parity, height, last antenatal weight and blood pressure, attendance at preparation classes, and infant weight Funding source: drug - Pentazocine was supplied by Bayer products Conflicts of interest: not specified

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	States "double blind" but does not report how achieved.
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	States "double blind" but does not report how achieved.
Incomplete outcome data (attrition bias) All outcomes	High risk	200 women randomised. Exclusion of women from analyses if inadequacy of records, reached second stage before analgesic assessment, operative birth or another intervention. Exclusion of babies from Apgar analysis if additional analgesia given, GA, antidote given to mother pre-birth or clinical explanation for depressed baby. Denominators for outcomes not clear
Selective reporting (reporting bias)	Unclear risk	Unclear

Duncan 1969 (*Continued*)

Other bias	Unclear risk	Balanced at baseline for age, parity, height, weight, blood pressure, attendance at antenatal classes and infant weight

El-Refaie 2012

Methods	RCT, 2-arm parallel groups
Participants	Setting: Ain Shams University Maternity Hospital, Egypt 240 women randomised Inclusion criteria: healthy, nulliparous, women aged between 18 and 30 years, at term (37-42 weeks of gestation) with a single fetus in vertex presentation, and diagnosed with prolonged labour due to uterine dystocia during the first stage of labour with a cervical dilatation of 4 cm to 6 cm. (Uterine dystocia was defined as crossing of the alert line on the partogram without abnormal fetal presentation or cephalopelvic disproportion.) Exclusion criteria: meperidine allergy, any contraindication for vaginal delivery, labour induction, use of oxytocin or any type of analgesia prior to randomisation, maternal request of pain relief, fetal death, or evidence of fetal distress
Interventions	Experimental: Meperidine - single dose of 50 mg meperidine in 10 mL of isotonic saline by slow intravenous administration over 2 mins (50 mg pethidine, 2-mL solution; Misr Pharmaceutics, Cairo, Egypt) (N = 120) Control: placebo - 10 mL of isotonic saline supplied in identical vials. (N = 120)
Outcomes	Primary outcomes: (i) duration of labour (from the time of the beginning of the intervention to the time of expulsion of the fetal head) and (ii) neonatal acid-base balance in arterial and venous. umbilical cord blood samples at birth. Secondary outcomes: severity of labour pain, as assessed by the 10-cm visual analogue scale (VAS) score (0 defined as no pain) before the intervention and 15, 30, and 60 mins after drug or placebo administration, and during the second stage of labour; maternal adverse effects; requirement for oxytocin augmentation after intervention; mode of delivery; and Apgar score at 1 and 5 mins
Notes	When labour crossed the alert line on partograph, women were randomised and oxytocin commenced Start and end date: July 2007 and October 2009 Power calculation: 'The sample size was calculated using a power of 80%, an alpha of 0.05, expected 60-min reduction in the length of labour, and assumed standard deviation of 158 mins based on a previous report of the length of labor in a population of women similar to our population. A sample size of 220 women was calculated to be necessary on the basis of these assumptions.' Baseline imbalances between groups: 'There were no significant differences between the two groups with regard to maternal age, body mass index, gestational age at delivery, cervical dilatation and length before intervention, and VAS score before drug or placebo administration' Funding source: not reported Conflicts of interest: not reported

El-Refaie 2012 (*Continued*)

Risk of bias		
Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Low risk	Computer-generated sequence
Allocation concealment (selection bias)	Low risk	Randomisation codes were placed in sequentially-numbered, opaque, sealed envelopes to be opened at time of enrolment by a nurse who prepared the study drug and had no further involvement with the care of the participants
Blinding of participants and personnel (performance bias) All outcomes	Low risk	The study is described as double-blind, placebo trial. If the neonatologists needed to know the administered intervention to manage a neonatal side effect, they would call a nurse to obtain such information
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	Not reported
Incomplete outcome data (attrition bias) All outcomes	Low risk	There was no loss to follow-up and all women reportedly received their allocated intervention
Selective reporting (reporting bias)	Unclear risk	All outcomes described in methods appear to be reported.
Other bias	Unclear risk	Similar baseline characteristics. Some lack of clarity in results, e.g. unclear if labour durations include women who had a caesarean

Erskine 1985

Methods	RCT 2-arm parallel-group design
Participants	Setting: Cape Town, South Africa 29 women in established labour, not clear how many primips, mean age 24 years, women were expected to have a vaginal birth and have no antenatal medical or obstetric problems
Interventions	Experimental: pethidine, IV PCA 10-min lock out, 0.3 mg per kg Control: pentazocine, IV PCA 10-min lock out, 0.15 mg per kg
Outcomes	Pain relief in labour (assessed by midwife); pain relief (measured immediately after labour (10 cm VAS) and 24 hrs postpartum from mother); satisfaction with pain relief; maternal and neonatal serum samples; Apgar score at 1 min and 5 mins; infant weight; neurobehavioural examination on 1st and 5th day

Erskine 1985 (*Continued*)

Notes	The study also included a non-randomised control group; we have not included this group in the analysis Start and end date: not reported Power calculation: not specified Baseline imbalances between groups: unclear Funding source: not specified Conflicts of interest: not specified

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Random number table
Allocation concealment (selection bias)	Unclear risk	Not described
Blinding of participants and personnel (performance bias) All outcomes	Unclear risk	It was reported that women were attended by the same midwife throughout labour who was not informed what medication women received. It is not clear whether this blinding was achieved for all staff
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	Outcome assessors of neonatal outcomes were reported to be blind to group allocation
Incomplete outcome data (attrition bias) All outcomes	Unclear risk	Overall attrition not clear, there were some missing data for some outcomes. Denominators were not provided in all of the results tables
Selective reporting (reporting bias)	Unclear risk	Unclear
Other bias	Unclear risk	No baseline imbalance apparent

Fairlie 1999

Methods	RCT 2-arm parallel-group design
Participants	Setting: hospital, UK 161 women randomised, data available for 133 women. 52% primips, 48% multips, cx at least 3 cm dilated, 37 or > weeks' gestation in spontaneous or induced labour (induction by amniotomy and IV infusion oxytocin)
Interventions	Experimental: IM diamorphine 7.5 mg (primips), 5 mg (multips) plus 12.5 mg prochlorperazine (N = 65) Control: IM pethidine 150 mg (primips), 100 mg (multips) plus 12.5 mg prochlorperazine (N = 68)

Fairlie 1999 (*Continued*)

Outcomes	Primary outcome: maternal pain at 1 hr VAS (0-100), pain intensity (0 = no pain, 1 = mild pain, 2 = moderate pain, 3 = severe pain), pain relief (0 = none, 1 = slight, 2 = moderate, 3 = good, 4 = complete) Secondary outcomes: maternal: vomiting, sedation, global analgesia assessment at 24 hr (good or poor). Neonatal: Apgar at 1 min and 5 mins, resuscitation, naloxone administration, SCBU admission, significant morbidity (seizures, respiratory distress, intraventricular haemorrhage, necrotising enterocolitis)
Notes	Second dose at maternal request: her choice of drug or epidural. Stratified by maternal parity. Trial stopped early after recruitment of 150 women. Planned sample size was 200 women Start and end date: May 1990 - February 1992 Power calculation: not specified Baseline imbalances between groups: unclear Funding source: not specified Conflicts of interest: not specified

Risk of bias

Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Unclear risk	Block sizes of 6
Allocation concealment (selection bias)	Low risk	Coded drug containers, randomisation code not broken until analysis
Blinding of participants and personnel (performance bias) All outcomes	Low risk	States double-blind, drug containers identical in appearance
Blinding of outcome assessment (detection bias) All outcomes	Low risk	It was stated that the randomisation code was not broken until the analysis stage
Incomplete outcome data (attrition bias) All outcomes	High risk	28 (17%) excluded as delivered within 1 hr of administration of study drug
Selective reporting (reporting bias)	Unclear risk	Unclear
Other bias	Low risk	Balanced at baseline

Fieni 2000

Methods	RCT 2-arm parallel-group design
Participants	Italy: hospital care setting 40 women. Full-term pregnancy, cx ≥ 4 cm, in spontaneous active labour and requiring analgesia
Interventions	Experimental: IM tramadol 100 mg (N = 20) Control: IM pethidine 75 mg (N = 20)
Outcomes	Primary outcome: maternal pain relief and acceptability. Pain assessed hourly up to 5 hrs, VAS 1-3 Secondary outcomes: maternal: observations (pulse, BP, respiratory rate, arterial oxygen saturation). Neonatal: Apgar at 1 min and 5 mins. Umbilcal cord pH
Notes	Second dose of study drug allowed after 2 hrs as required. Italian language, translation obtained. Data were presented in a way in which we were not able to incorporate them into data tables in RevMan Start and end date: unclear Power calculation: unclear Baseline imbalances between groups: unclear Funding source: unclear Conflicts of interest: unclear

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Computer generated
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
Incomplete outcome data (attrition bias) All outcomes	Unclear risk	Unclear how many women analysed as only percentages reported
Selective reporting (reporting bias)	Unclear risk	Unclear
Other bias	High risk	No baseline characteristics table - unclear re maternal parity Likely response bias as no information on whom women reported to about their pain post injection

Frank 1987

Methods	RCT 2-arm parallel-group design
Participants	Setting: London hospital, UK 60 healthy women at term (38-42 weeks) requiring pain relief in labour Women requesting epidural, that had already received opioid analgesia, were receiving treatment for depression or where the fetus was at risk were excluded
Interventions	Experimental: (30 women) nalbuphine, 3 mg with 3 mg increments to a max of 18 mg per hr; lockout time 10 mins (total max dose = 42 mg) Control: (30 women) pethidine, 15 mg, 15 mg increments to a max of 90 mg per hr; lockout time 10 mins (total max dose = 210 mg) Entonox ® was available to women in both groups but was withheld for 30 mins for analgesia assessment. Analgesia was stopped in the 2nd stage if there were side effects or if the woman requested an alternative method
Outcomes	Pain (measured on 5-point scale from 1- no pain to 5 - very severe); pain relief (assessed 1 day after birth; pain relief rated as good or excellent and women saying they would use the same method again); sedation (1 awake, 3 asleep); neuro-behavioural assessment 6 to 10 hrs after birth; FHR
Notes	Start and end date: not reported Power calculation: not specified Baseline imbalances between groups: unclear Funding source: Dupont (UK) Ltd Conflicts of interest: not specified

Risk of bias

Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Unclear risk	Quote: "randomly allocated."
Allocation concealment (selection bias)	Unclear risk	Described as double-blind but allocation concealment was not described
Blinding of participants and personnel (performance bias) All outcomes	Unclear risk	Very little information. Described as double-blind.
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	Unclear
Incomplete outcome data (attrition bias) All outcomes	Unclear risk	There were some outcome data for all but one of the women randomised, but there were high levels of missing data for some neonatal outcomes (e.g. neurological infant assessments 40/60 babies available for analysis)

Frank 1987 (*Continued*)

Selective reporting (reporting bias)	Unclear risk	Unclear
Other bias	Unclear risk	There was some baseline imbalance; 6/30 in the nalbuphine group were multiparous compared with 12/30 in the pethidine group. The authors report that they took this into account in the analysis. In this review data have not been adjusted for baseline imbalance

Giannina 1995

Methods	RCT, 2-arm parallel groups
Participants	New Jersey USA, hospital setting, 1994 28 women in labour (36 randomised) with uncomplicated pregnancies, singleton, vertex presentation, at term (37 to 41 weeks), 4 cm or less cervical dilatation, at least 3 contractions in 10 mins, no known maternal or fetal conditions that would affect FHR tracings, fetal reactive, no medications that would affect FHR in the previous 2 weeks Exclusions criteria: meconium staining, pregnancy-induced hypertension, fetal tachy- or brady-cardia, arrhythmias or decelerations, chorioamnionitis, FGR, abnormal placenta, maternal fever, fetal chromosomal disorder of structural abnormality
Interventions	Experimental: IV nalbuphine10 mg Control: IV pethidine 50 mg Both groups had continuous fetal monitoring for 1 hr following medication
Outcomes	FHR (accelerations, high and low variation); Apgar scores < 8 at 1 min and 5 mins; mode of birth; cord pH < 7.15
Notes	Start and end date: March 1994 - August 1994. Power calculation: 'Using the normal reference ranges for long-term variation and acceleration of ten beats per minute for a 15-second duration, the study would require 28 women to achieve a power of 90% to detect a change from values at the 50th percentiles to values below the fifth percentile at an alpha error of 0.05.' Baseline imbalances between groups: there was statistical difference between the groups Funding source: not specified Conflicts of interest: not specified

Risk of bias

Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Low risk	Computer-generated random number table
Allocation concealment (selection bias)	Low risk	Sequentially-numbered, sealed envelopes

Giannina 1995 (*Continued*)

Blinding of participants and personnel (performance bias) All outcomes	Unclear risk	Not specified
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	Not specified
Incomplete outcome data (attrition bias) All outcomes	Unclear risk	36 women were enrolled. 8 women did not have sufficient FHR tracings and were not included in the analysis (22% attrition)
Selective reporting (reporting bias)	Unclear risk	Unclear
Other bias	Low risk	No apparent baseline imbalance

Gillam 1958

Methods	RCT, 2-arm parallel-group design
Participants	Setting: hospital in USA 500 women admitted to hospital in labour. Little information provided
Interventions	Experimental: (185 women) alphaprodine (Nisentil), initial dose 40 mg IV, subsequent doses IM Control: (210 women) pethidine, initial dose 100 mg IV, subsequent doses IM Both groups received scopolamine. Analgesia was for the first stage of labour, birth was carried out "with rare exception" under "saddle block or pudendal block terminal anesthesia"
Outcomes	Pain relief (rated just before leaving the room for childbirth); side effects and length of labour
Notes	Start and end date: not reported Power calculation: not reported Baseline imbalances between groups: unclear Funding source: not reported Conflicts of interest: not reported

Risk of bias

Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Unclear risk	No information
Allocation concealment (selection bias)	Low risk	Coded drug containers

Gillam 1958 (*Continued*)

Blinding of participants and personnel (performance bias) All outcomes	Low risk	Drugs were prepared by pharmacy in coded containers and the codes were not revealed until after birth
Blinding of outcome assessment (detection bias) All outcomes	Low risk	Drugs were prepared by pharmacy in coded containers and the codes were not revealed until after birth
Incomplete outcome data (attrition bias) All outcomes	High risk	500 women were randomised, 55 women received no analgesia and were excluded, 22 women received more than 1 dose of opioid (not necessarily the same drug) and were excluded, 21 women who were in preterm labour or had a CS were excluded and 1 woman was excluded because she was sensitive to study medication. Data available for 395 women (21% attrition)
Selective reporting (reporting bias)	Unclear risk	Unclear
Other bias	Unclear risk	Study medication was for pain relief in the first stage of labour, most women received a pudendal block for birth so outcomes relating to birth may not be attributable to study medication alone

Grant 1970

Methods	RCT 2-arm parallel-group design
Participants	Setting: hospital, UK 212 women in spontaneous or induced labour with cephalic presentation at > 36 weeks' gestation. Recruited to the trial at 36 week antenatal clinic visit
Interventions	Experimental: IM phenazocine 3 mg (N = 107) Control: IM pethidine 150 mg (N = 105)
Outcomes	Primary outcome: maternal analgesia assessed in labour as poor, fair, good, very good. Pain relief also assessed in postnatal questionnaire within 36 hrs of birth Secondary outcomes: maternal: amnesia, restlessness, anxiety, vomiting. Neonatal: Apgar at 1 min and 5 mins
Notes	Epidural available if further analgesia required. Start and end date: not reported Power calculation: not reported Baseline imbalances between groups: 'There was no significant difference between the two groups with respect to age, parity, height, weight, pelvic size, incidence of induced labour or cervical dilation at the time of first dose of analgesia' Funding source: Smith and Nephew (Pharmaceutics) Ltd provided the marked drug ampoules

Grant 1970 (*Continued*)

	Conflicts of interest: not reported

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Not reported
Allocation concealment (selection bias)	Low risk	Code kept by hospital pharmacist and remained unbroken until trial completed
Blinding of participants and personnel (performance bias) All outcomes	Low risk	States double-blind, coded ampoules but no further description given
Blinding of outcome assessment (detection bias) All outcomes	Low risk	Code kept by hospital pharmacist and remained unbroken until trial completed
Incomplete outcome data (attrition bias) All outcomes	Unclear risk	212 women randomised. Number of women analysed is not reported
Selective reporting (reporting bias)	Unclear risk	MW assessed maternal side effects in labour.
Other bias	Unclear risk	Although baseline characteristics described as similar - proportion of primips to multips not provided. Balanced for age, parity, height, weight, cx dilatation PN maternal recollection of pain within 36 hr and unclear to whom women reported ratings

Hamann 1972

Methods	RCT. 2-arm parallel-group design
Participants	185 randomised. analysis for 160 women in labour. Inclusion criteria: primiparous, no pregnancy complications. Exclusions: women with hypertension or pre-eclampsia. It appeared that women who had any complications during birth (e.g. CS) were excluded after randomisation
Interventions	Intervention group: Avacan ® 25 mg IM (a spasmolytic) Control group: Fortral ® 20 mg IM (pentazocine)
Outcomes	Number of requests for analgesia, infant birthweight, Apgar score (at birth)

Hamann 1972 (*Continued*)

Notes	Data extraction was done from translation notes. Start and end date: June 1969 - January 1971 Power calculation: unclear Baseline imbalances between groups: unclear Funding source: unclear Conflicts of interest: unclear

Risk of bias

Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Low risk	Table of random numbers
Allocation concealment (selection bias)	Unclear risk	Described as a double-blind trial but methods were not described
Blinding of participants and personnel (performance bias) All outcomes	Unclear risk	Described as double-blind.
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	Unclear
Incomplete outcome data (attrition bias) All outcomes	High risk	185 women approached, 25 were excluded and results suggest that any women who had CS were excluded from the analysis along with women who had long labours (> 24 hrs) or where no injections were given
Selective reporting (reporting bias)	Unclear risk	Unclear
Other bias	Unclear risk	Assessment of risk of bias done using translation notes.

Hodgkinson 1979

Methods	RCT 4-arm parallel-group design
Participants	Setting not clear, USA 200 women admitted to hospital in the 1st stage of normal labour, mean age 24 years, women received medication if they complained of moderate or severe pain
Interventions	Experimental: (100 women) (i) IV butorphanol 1 mg (67 women) (ii) IV butorphanol 2 mg (33 women) Control: (100 women) (i) IV pethidine 40 mg (68 women) (ii) IV pethidine 80 mg (32 women)

Hodgkinson 1979 (*Continued*)

Outcomes	Pain intensity (graphs with hourly readings); pain relief (4-point scale); neuro-behavioural assessment 1 day after birth (Scanlon scale)
Notes	Start and end date: not reported Power calculation: not reported Baseline imbalances between groups: unclear Funding source: not reported Conflicts of interest: not reported

Risk of bias

Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Unclear risk	No information
Allocation concealment (selection bias)	Unclear risk	No information. Described as "double-blind".
Blinding of participants and personnel (performance bias) All outcomes	Unclear risk	Described as double-blind but little detail of methods of allocation concealment or blinding
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	Described as double-blind but little detail of methods of allocation concealment or blinding
Incomplete outcome data (attrition bias) All outcomes	Low risk	No loss to follow-up apparent
Selective reporting (reporting bias)	Unclear risk	Unclear
Other bias	Unclear risk	Very little information on study methods.

Husslein 1987

Methods	RCT 2-arm parallel-group design
Participants	Setting: hospital, Austria 40 women with no pregnancy complications, in spontaneous and induced labour, cx 3 cm to 5 cm dilated. 72.5% primips, 27.5% multips
Interventions	Experimental: IM tramadol 100 mg (N = 20) Control: IM pethidine 100 mg (N = 20)
Outcomes	Primary: pain relief, assessed 10, 30, 60, 120 mins after injection using VAS 0-100, 0 = pain free to 100 strongest pain experienced Secondary: side effects, augmentation and type of birth.

Husslein 1987 (*Continued*)

Notes	Not stated in 1 dose only Start and end date: unclear Power calculation: unclear Baseline imbalances between groups: unclear Funding source: unclear Conflicts of interest: unclear

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	Blinding not described
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	Blinding not described
Incomplete outcome data (attrition bias) All outcomes	Low risk	All women analysed
Selective reporting (reporting bias)	Unclear risk	Unclear
Other bias	Unclear risk	Baseline characteristics stated as similar

Jackson 1983

Methods	RCT 2-arm parallel-group design
Participants	Setting: hospital, UK 100 women in labour at term gestation with uncomplicated pregnancy
Interventions	Experimental: Meptazinol 1.8 mg/kg body weight (N = 50) Control: pethidine 1.8 mg/kg body weight (N = 50) All participants received promethazine 12.5 mg with first injection
Outcomes	Primary: newborn effects: Apgar score at 1 min and 3 mins
Notes	If additional analgesia required, a repeat injection could be administered 3-hourly 6/50 women from each arm received a second dose at a 3-hourly interval Start and end date: not reported Power calculation: not reported

Jackson 1983 (*Continued*)

	Baseline imbalances between groups: unclear Funding source: not reported Conflicts of interest: not reported

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	States double-blind but method not described
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	States double-blind but method not described
Incomplete outcome data (attrition bias) All outcomes	High risk	5 babies excluded from analysis due to heart defects and fetal distress
Selective reporting (reporting bias)	Unclear risk	Unclear
Other bias	Unclear risk	Balanced for parity, weight and size of baby at baseline.

Jahani 2013

Methods	RCT 2-arm parallel-group design
Participants	Setting: Maternity Unit, Tamin Ejtemai Hospital, Iran 70 women randomised Inclusion criteria: multiparous pregnant women (gravida 2-7); term singleton pregnancy; cephalic presentation; low-risk pregnancy with no history of drug tolerance (addiction) , medical or mental diseases Exclusion criteria: respiratory rate < 8 or maternal bradycardia (pulse rate less than 60) and severe congenital anomalies in neonate after birth
Interventions	Experimental: Fentanyl - 50 mcg fentanyl was prescribed in 2 doses with an interval of 1 hr after being diluted in 4 cc normal saline (total volume 5 cc - 25 μg/5 mL during 10 mins infusion and repeated second dose an hr later 25 μg/5 mL) at zero and 60 mins Control: no analgesia
Outcomes	Outcomes: pain score, blood pressure, heart rate, FHR and maternal respiratory rate, duration of labour, maternal side effects drowsiness, dizziness, nausea/vomiting, respiratory

	depression, hypotension (BP < 90 mmHg or less than < 20% of baseline), bradycardia (HR < 60 beats min-1), and pruritus.Neonatal outcomes included Apgar scores at 1 min and 5 mins and resuscitation efforts (if any)
Notes	Power calculation: 'based on results from a pilot study on 10 parturients (and mean duration of the active phase), effect size was obtained at 0.4 hours with power 80% and confidence level of 95%, the sample size was then calculated to be 70 parturients' Baseline imbalances between groups: 'There was no statistically significant difference in mean age between the two groups. There were no significant differences in gravidity, parity, fetal heart rate, contraction duration or HR between the two groups' Funding source: not reported Conflicts of interest: not reported

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	A coin was tossed to determine the participants comprising the control and case groups (35 women per group). It was not reported if this was at the point of randomisation but no information on allocation concealment
Allocation concealment (selection bias)	High risk	Coin toss to determine group. If this was at the point of randomisation this is a high-risk method. There was no indication of allocation concealment
Blinding of participants and personnel (performance bias) All outcomes	High risk	Not feasible
Blinding of outcome assessment (detection bias) All outcomes	High risk	Outcome assessor likely to be aware of allocation.
Incomplete outcome data (attrition bias) All outcomes	Unclear risk	No reported loss to follow-up, no denominators given in tables and no details of women requesting further analgesia and changing groups. Not clear if there was loss to follow-up or not
Selective reporting (reporting bias)	High risk	Protocol not seen, outcomes listed in methods but are not well reported. Apgar results described narratively, resuscitation measures not mentioned
Other bias	Low risk	Baseline characteristics were balanced across groups.

Kainz 1992

Methods	RCT 3-arm parallel-group design
Participants	Setting: hospital, Germany 66 women. 38-41 weeks' gestation, free of complications, in active labour and requiring analgesia, excluded if analgesia received within 4 hrs of randomisation Parity: not reported
Interventions	Experimental: IM tramadol 100 mg (N = 20); IM tramadol 100 mg + triflupromazine 10 mg (N = 25) Control: IM pethidine 50 mg + triflupromazine 10 mg (N = 21) Unclear if single or multiple doses administered, and if additional analgesia administered
Outcomes	Maternal outcomes: maternal pain intensity VAS (0 to 10 cm) 30, 60, 120 and 180 mins, vomiting, drowsiness, BP, HR, cardiotocogram
Notes	Tramadol 100 mg only group (A) not included in our analyses. German language, translation obtained Start and end date: unclear Power calculation: unclear Baseline imbalances between groups: unclear Funding source: unclear Conflicts of interest: unclear

Risk of bias

Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Low risk	"zulfallszahlentafel" coincidence number table.
Allocation concealment (selection bias)	Unclear risk	Not reported
Blinding of participants and personnel (performance bias) All outcomes	Unclear risk	Stated as double-blind but methods not described
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	Stated as double-blind but methods not described
Incomplete outcome data (attrition bias) All outcomes	Unclear risk	2/66 women excluded due to giving birth within 1 hr of study drug administration
Selective reporting (reporting bias)	Unclear risk	Unclear
Other bias	Unclear risk	Unclear

Kamyabi 2003

Methods	RCT 2-arm parallel-group design
Participants	Setting: hospital in Iran 88 primiparous women in spontaneous labour, gestation ≥ 37 weeks, and cervix 5 cm dilated Excluded if high-risk pregnancy, narcotic addiction.
Interventions	Experimental: IM (placebo) normal saline 1.5 mL (N = 44) Control: IM pethidine 75 mg (N = 44)
Outcomes	Primary: analgesic effect. Pain assessed pre and post injection using Likert Scale VAS: 10 cm line, 0% = minimum effect, 100% = maximum effect Secondary: side effects on uterine contractions (contraction duration and interval recorded 3 times 15 to 60 mins post injection) and neonatal Apgar score at 1 min and 5 mins
Notes	Timing of maternal pain assessment not reported. Start and end date: not reported Power calculation: the required number of women was based on a pilot study and considering a power of 90%, d 7%, and error 5%, 44 women were needed in each group Baseline imbalances between groups: unclear Funding source: not reported Conflicts of interest: not reported

Risk of bias

Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Unclear risk	States 'divided randomly'.
Allocation concealment (selection bias)	Unclear risk	Not reported
Blinding of participants and personnel (performance bias) All outcomes	Low risk	Study agents were of identical volume and appearance
Blinding of outcome assessment (detection bias) All outcomes	Low risk	Study agents were of identical volume and appearance
Incomplete outcome data (attrition bias) All outcomes	Unclear risk	Number of participants analysed and planned analysis not reported
Selective reporting (reporting bias)	Unclear risk	Unclear
Other bias	Unclear risk	The number of women allocated to each group is not reported and unclear if there are baseline imbalances in prognostic factors

Kermani 2015

Methods	RCT, individual randomisation - difficult to assess abstract only
Participants	Setting: not clear, Iran 48 women with term pregnancies in active labour. Exclusion criteria: not stated
Interventions	Experimental group: pethidine (n = not clear) route and dose not stated Control group: acupressure (n = not clear) acupressure at spleen point 6 (SP6)
Outcomes	No data - abstract only
Notes	Dates of study: not stated Funding: not stated Conflicts of interest: not stated 15th June 2017 - email to 2nd author. Awaiting response.

Risk of bias

Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Unclear risk	Quote: "Subjects were randomly selected and divided". No further description
Allocation concealment (selection bias)	Unclear risk	Method not described
Blinding of participants and personnel (performance bias) All outcomes	High risk	Not mentioned but not possible to blind intervention
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	Outcomes probably assessed by caregiver
Incomplete outcome data (attrition bias) All outcomes	Unclear risk	Unclear due to lack of information in abstract
Selective reporting (reporting bias)	Unclear risk	Unable to assess
Other bias	Unclear risk	Unable to assess

Keskin 2003

Methods	RCT 2-arm parallel-group design
Participants	Setting: hospital, Turkey 59 primiparous women with uncomplicated pregnancy at term gestation, in labour with cervix 3 cm to 5 cm dilated and reporting a pain score 4 - 5 according to Wong-Baker

Keskin 2003 (*Continued*)

	Faces Pain Rating Scales with 0 = no pain, 5 = most intense pain Exclusions: maternal medical disorders, history of drug or alcohol abuse
Interventions	Experimental: IM tramadol 100 mg, single dose (N = 30) Control: IM pethidine 100 mg, single dose (N = 29)
Outcomes	Primary: analgesic effect assessed 30, 60 and 120 mins following injection using Wong-Baker Faces Pain Rating Scales with 0 = no pain, 5 = most intense pain Secondary: side effects: nausea, vomiting, drowsiness, fatigue and neonatal effects (Apgar score at 1 min and 5 mins)
Notes	Start and end date: not reported Power calculation: not reported Baseline imbalances between groups: unclear Funding sources: not reported Conflicts of interest: not reported

Risk of bias

Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Unclear risk	Not reported. "randomly divided into two groups".
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	Outcome assessor unaware of treatment group
Incomplete outcome data (attrition bias) All outcomes	High risk	Losses to follow-up not explained and no ITT analysis.
Selective reporting (reporting bias)	Unclear risk	Unclear
Other bias	Unclear risk	Unclear

Khooshideh 2009

Methods	RCT 2-arm parallel-group design
Participants	Setting: hospital, Iran 160 women. Free of complications, spontaneous and induced onset, cx 4 cm dilated, in active labour and requiring analgesia. Women excluded if cx dilated > 5 cm

Khooshideh 2009 (*Continued*)

	Parity: not reported
Interventions	Experimental: IM tramadol 100 mg (N = 80) Control: IM pethidine 50 mg (N = 80) 2nd dose on maternal request after 4 hrs but pethidine withheld if cx dilated > 8 cm and tramadol given instead
Outcomes	Maternal outcomes: maternal pain intensity VAS (0 to 10 cm) 10 mins , 30 mins and 1-hourly intervals until birth, maternal satisfaction 24 hrs postpartum 5-point scale (excellent, very good, good, fair, poor), drowsiness, nausea, vomiting. Neonatal outcomes: Apgar score at 1 min and 5 mins, naloxone administration, respiratory depression
Notes	Start and end date: 2004 Power calculation: based on the assumption that a difference of 30 mins in duration of labour would be clinically significant, 53 women was needed in each group 80% power on a 5% significance (α = 0.05, β = 0.2) Baseline imbalances between groups: 'The two groups were comparable regarding age, parity, height, weight, period of gestation, fetal weight, cervical dilatation at initiation of analgesia and need for oxytocin use' Funding source: not specified Conflicts of interest: not specified

Risk of bias

Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Low risk	Computer-generated codes
Allocation concealment (selection bias)	Low risk	Sequentially-numbered, sealed opaque envelopes
Blinding of participants and personnel (performance bias) All outcomes	Unclear risk	Drugs administered by clinician blind to group allocation, but does not state how this was achieved
Blinding of outcome assessment (detection bias) All outcomes	Low risk	Women fed back their maternal pain score to anaesthetist.
Incomplete outcome data (attrition bias) All outcomes	Low risk	Flow chart addresses all data.
Selective reporting (reporting bias)	Unclear risk	Unclear
Other bias	Unclear risk	Baseline characteristics similar

Kuti 2008

Methods	Reported to be randomised clinical trial. Individual women randomised
Participants	Setting: labour ward of Wesley Guild Hospital, Ilesa Nigeria 100 women who were admitted in active spontaneous labour at term with uncomplicated singleton pregnancies requesting analgesia Exclusion criteria: mothers with chronic medical diseases.
Interventions	Experimental group: IM injection of Pentazocine 30 mg (Laborate Pharmaceuticals, India) (N = 50, 44 following exclusions) Control group: IM tramadol 100 mg.(P.T Interbat, Indonesia) (n = 50, 42 following exclusions)
Outcomes	Satisfaction with analgesia Pain in labour Mode of birth Maternal side effects Neonatal admission to special care Apgar scores
Notes	Start and end dates: June 2005 - May 2006 Funding and COI: not reported

Risk of bias

Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Low risk	Computer-generated random numbers in blocks of 4
Allocation concealment (selection bias)	Low risk	Randomisation codes were placed in sequentially-numbered, opaque, sealed envelope. Envelope was opened when the woman requested pain relief and the drug administered by the randomising midwife
Blinding of participants and personnel (performance bias) All outcomes	Low risk	It is reported that the trial is double-blind. When each woman requested pain relief, the next numbered envelope was opened and the appropriate drug administered by the randomising midwife. Not clear if this midwife cared for woman in labour. Both given IM so women should be unaware
Blinding of outcome assessment (detection bias) All outcomes	Low risk	The labour ward resident doctor, unaware of the type of injection given, recorded the clinical data and assess the analgesic efficacy

Kuti 2008 (*Continued*)

Incomplete outcome data (attrition bias) All outcomes	Unclear risk	14 women (6 in the pentazocine group and 8 in the tramadol group) delivered within 1 hr of drug administration and were therefore excluded from further analysis. Outcome data are available for the remaining women in the respective groups. Giving birth within the hr, the drug administered could have affected the neonate
Selective reporting (reporting bias)	Unclear risk	All essential outcomes are reported. Protocol not seen.
Other bias	Unclear risk	Women had similar characteristics at trial entry. Some lack of clarity in reporting outcomes

Lalooha 2017

Methods	Reported to be randomised clinical trial. Individual women randomised
Participants	Setting: hospital in Iran 120 women randomised, nulliparous women with term singleton pregnancy who had induction of labour (reasons for and methods of induction not stated in abstract) Exclusion criteria: not stated
Interventions	Experimental group: single dose of 50 mg IV pethidine at 4 cm dilatation (it was not clear whether this was at maternal request or whether all women received it) (N = 60) Control group: IV normal saline (placebo) (N = 60)
Outcomes	Duration of labour
Notes	Start and end dates: unclear Conflict of interest: not stated Funding not stated Translation requested 15th June 2017 - no data used in this review

Risk of bias

Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Unclear risk	No information "randomly assigned"
Allocation concealment (selection bias)	Unclear risk	No information "randomly assigned"
Blinding of participants and personnel (performance bias) All outcomes	Low risk	Participants: placebo-controlled trial. Caregiver: placebo-controlled trial. Staff may have been aware of allocation if there

Lalooha 2017 (*Continued*)

		was sedation or other side effects
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	Not clear when group assignment revealed and staff providing care recorded outcomes
Incomplete outcome data (attrition bias) All outcomes	Unclear risk	120 women included. No information on dropouts or missing data. Not clear
Selective reporting (reporting bias)	Unclear risk	This was a very brief abstract. Key outcomes not reported.
Other bias	Unclear risk	Assessment from abstract. Full paper in Arabic. Very little information on methods. Full translation requested

Lardizabal 1999

Methods	RCT 2-arm parallel-group design
Participants	Argentina: 2 hospitals 310 women of mixed parity, in labour 37-42 weeks' gestation with cervix 4 cm to 6 cm dilated, cephalic presentation and requiring analgesia Exclusions: maternal medical condition, evidence of fetal distress, previous caesarean section
Interventions	Experimental: IM nalbuphine 20 mg, single dose (N = 152) Control: IM pethidine 100 mg, single dose (N = 158)
Outcomes	Primary: neonatal Apgar score < 7 at 1 min Secondary: maternal pain assessed using VAS pre-injection, and 30 mins and 120 mins afterwards (severe pain 75 or >), nausea, vomiting and type of birth. Neonatal side effects: condition over first 24 hrs, admission to neonatal intensive care nursery
Notes	Stratified by hospital. Start and end date: June 1991 - September 1993 Power calculation: based on previous literature, mean incidence of low Apgar score was 12% in women receiving meperidine and 3% in women receiving nalbuphine, α = 0.05, β = 0.20, 152 women in each group is needed for a 75% relative risk reduction in the primary endpoint Baseline imbalances between groups: the groups were balanced across various prognostic variables such as age, nulliparity, weeks of gestation, maternal weight, cervical dilatation at randomisation, uterine activity, number of women with induced labour, severe pain, nausea, vomiting, dizziness, and dry mouth Funding source: not reported Conflicts of interest: not reported
Risk of bias	

Lardizabal 1999 (*Continued*)

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Computer-generated code
Allocation concealment (selection bias)	Low risk	Coded ampoules, sealed and prepared by independent pharmacist and identical in appearance
Blinding of participants and personnel (performance bias) All outcomes	Low risk	Identical ampoules
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	Not reported
Incomplete outcome data (attrition bias) All outcomes	Low risk	Few losses to follow-up
Selective reporting (reporting bias)	Unclear risk	Not mentioned if women reported pain to their caregiver
Other bias	Unclear risk	Data analyst unaware of coding. Balanced at baseline.

Levy 1971

Methods	RCT 2-arm parallel-group design
Participants	USA: hospital setting 93 primiparous women in labour, uncomplicated pregnancy at 37 or more weeks' gestation and in pain described as moderate or severe
Interventions	Experimental: IM pentazocine 60 mg (N = 38) Control: IM pethidine 100 mg (N = 45)
Outcomes	Primary: pain relief assessed at 1 hr, as good or poor. Secondary: maternal side effects, nausea or vomiting, labour progress. Neonatal Apgar score at 1 min and 5 mins
Notes	If additional analgesia was required, a second injection could be administered at the discretion of medic. Not stated if IOL onset included Start and end date: not reported Power calculation: not reported Baseline imbalances between groups: unclear Funding sources: Sterling drug company and NIH Grant RR 00404 Conflicts of interest: not reported

Levy 1971 (*Continued*)

Risk of bias		
Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Unclear risk	Not reported
Allocation concealment (selection bias)	Unclear risk	Identical vials with code number but no further information given
Blinding of participants and personnel (performance bias) All outcomes	Low risk	Identical vials with code number
Blinding of outcome assessment (detection bias) All outcomes	Low risk	No-one involved with the immediate care of the woman knew the drug identity
Incomplete outcome data (attrition bias) All outcomes	High risk	83/93 women analysed and reasons for missing data not reported
Selective reporting (reporting bias)	Unclear risk	Unclear
Other bias	Unclear risk	Unclear how many women randomised to each group and balance at baseline unclear

Li 1988

Methods	(Feasibility study) RCT, 2-arm parallel-group design
Participants	10 primiparous women in labour requesting pain relief, and who had no made any request for alternative analgesia
Interventions	Intervention group: meptazinol (PCA IM) up to 600 mg (75 mg per mL) Comparison group: pethidine (PCA IM) up to 400 mg (50 mg per mL) Doses described as equivalent. Nitrous oxide available to women in both groups
Outcomes	Pain, drowsiness and nausea on a 100 mm VAS (0 = no pain) during labour and also rated on the day after birth; Apgar score and neonatal weight gain over 3 days
Notes	Feasibility study focusing on PCA IM administration of opioids Start and end date: not reported Power calculation: not reported Baseline imbalances between groups: unclear Funding sources: not reported Conflicts of interest: not reported

Li 1988 (*Continued*)

Risk of bias		
Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Unclear risk	Not described, "randomly allocated".
Allocation concealment (selection bias)	Unclear risk	Described as a double-blind comparison but methods not described
Blinding of participants and personnel (performance bias) All outcomes	Unclear risk	Described as a double-blind comparison but methods not described
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	Described as a double-blind comparison but methods not described
Incomplete outcome data (attrition bias) All outcomes	Low risk	10 women randomised and all accounted for in the analysis.
Selective reporting (reporting bias)	Unclear risk	Unclear
Other bias	Unclear risk	No baseline imbalance apparent.

Li 1994

Methods	RCT. 2-arm parallel groups.
Participants	Setting: Beijing hospital, China 60 women in early labour (cervical dilatation 2 cm to 3 cm) at term, with singleton pregnancy, vertex presentation, with no pregnancy complications
Interventions	Intervention group: 100 mg IM tramadol Comparison group: no analgesia
Outcomes	Analgesic effect (not clear when measured); satisfactory, some effect or no effect
Notes	Data extraction from translation notes. Start and end date: August 1993 - October 1993 Power calculation: unclear Baseline imbalances between groups: unclear Funding sources: unclear Conflicts of interest: unclear
Risk of bias	

Li 1994 (*Continued*)

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Women were divided "at random" into groups.
Allocation concealment (selection bias)	Unclear risk	Not described
Blinding of participants and personnel (performance bias) All outcomes	High risk	Women in the control arm received no treatment.
Blinding of outcome assessment (detection bias) All outcomes	High risk	Women in the control arm received no treatment.
Incomplete outcome data (attrition bias) All outcomes	Unclear risk	Denominators not clear. No apparent loss to follow-up.
Selective reporting (reporting bias)	Unclear risk	Unclear
Other bias	Unclear risk	It was not clear whether or not women in the comparison group were given any analgesia or whether they requested any

Lisboa 1997

Methods	RCT 2-arm parallel-group design
Participants	Setting: hospital, Brazil 56 women No information in abstract about participant inclusion criteria or characteristics
Interventions	Experimental: IM nalbuphine 10 mg Control: IM pethidine 100 mg
Outcomes	Analgesia and side effects. Neonatal: Apgar score
Notes	Abstract only: insufficient information about participants. Not reported if > 1 dose given or anti-emetic. Start and end date: not reported Power calculation: not reported Baseline imbalances between groups: not reported Funding sources: not reported Conflicts of interest: not reported
Risk of bias	

Lisboa 1997 (*Continued*)

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Described as "randomly selected" but not explained how.
Allocation concealment (selection bias)	Unclear risk	Not mentioned
Blinding of participants and personnel (performance bias) All outcomes	Unclear risk	Not mentioned
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	Not mentioned
Incomplete outcome data (attrition bias) All outcomes	Unclear risk	Not mentioned
Selective reporting (reporting bias)	Unclear risk	Impossible to decipher.
Other bias	Unclear risk	Impossible to decipher.

Liu 2015

Methods	Randomised controlled trial with individual randomisation.
Participants	Setting: Beijing Obstetrics and Gynecology Hospital, China. 120 women randomised who had no previous poor obstetrical outcome; no experience in Han's Acupoint Nerve Stimulator and TENS for other reasons; term pregnancy (> 37 weeks of gestation); at active phase of the first stage of labour with cervical dilatation 3 cm Exclusion criteria: had the history of experimental drug allergy; had been diagnosed with other diseases such as preoperative presence of maternal mental, neurological diseases, affecting evaluation of pains and disease conditions; had combined with gestational hypertension, gestational diabetes, gestational thyroid diseases; had taken analgesic drugs or with a history of long-term use of analgesic drugs; had used diazepam, piperazine hydrochloride or other sedative, analgesic drugs in the stages of labour; were overweight or low pregnancy weight, BMI < 18.5 or BMI > 25 kg/m2; were not agreeable to receive painless labour and not sign the informed consent form
Interventions	Experimental group 1: HANS (Han's acupoint nerve stimulator) group (N = 30) received DC pulse stimulus at acupoints of Jiaji points (T 10-L 3) and Ciliao (BL 32)The stimulus was 100 Hz with a burst frequency of 2 Hz (dense dispersed waveform) The intensity was 15 mA to 30 mA. The pulse duration was used for 30 mins Experimental group 2: PCIA (Patient-controlled intravenous analgesia) group (N = 30) IV infused ondansetron 8 mg; 5 mins later, 1.5 mg/kg tramadol injection was slowly dripped, connected to Baxter AP II electronic pump with 50 mL of 0.70% tramadol + ondansetron 8 mg, background infusion 2 mL/hr, PCA dose of 2 mL, lockout interval

	of 10 mins Experimental group 3: PCEA (patient-controlled epidural analgesia) group (N = 30) L2-3 combined spinal- epidural puncture, intrathecal injection of 3 mg ropivacaine, epidural catheter connected to Baxter AP electronic pump, with 100 mL 0.1% ropivacaine and 50 ug sufentanil, background infusion 5 mL, PCA dose of 5 mL, lockout interval of 10 mins when the cervix was fully dilated (10 cm). N =30 All treatments were stopped at the point of complete cervical dilatation Control group (N = 30) did not receive analgesia. Only experimental groups 1 and 2 are included in this review as per methods
Outcomes	**Outcomes** Mode of birth Maternal side effects Oxytocin use Neonatal asphyxia Pain scores Duration of labour Apgar (mean, SD)
Notes	Trial dates: August 2010 - November 2013 Funding: The Scientific Achievement and Appropriate Technology Extension Project of Beijing Municipal Commission of Health and Family Planning (TG-2014-12) Conflict of interest: not reported 120 women were randomised, so the number of women in each group should be 30, this is what reported in tables 1-4, but different in trial profile

Risk of bias

Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Low risk	Random number table method
Allocation concealment (selection bias)	Unclear risk	Not reported
Blinding of participants and personnel (performance bias) All outcomes	High risk	It is not feasible to implement blinding.
Blinding of outcome assessment (detection bias) All outcomes	High risk	It is not feasible to implement blinding.
Incomplete outcome data (attrition bias) All outcomes	Unclear risk	No reports of loss to follow-up or women requesting other analgesia and changing groups. Not clear if women in the control group requested analgesia at all. Denominators given in the tables are lower than in flowchart

Liu 2015 (*Continued*)

Selective reporting (reporting bias)	Unclear risk	All outcomes from methods are reported. Protocol not seen.
Other bias	Unclear risk	There was no statistical difference in the basic information between 4 groups (P> 0. 05). Generally reporting is unclear.

Maduska 1978

Methods	RCT 2-arm parallel-group design
Participants	Setting: hospital, USA 80 women at term gestation, in spontaneous and induced labour with moderate to severe pain Exclusions: drug abuse history, systemic disease and women who planned to breastfeed their babies
Interventions	Experimental: IM butorphanol 1 or 2 mg (N = 40) Control: IM pethidine 40 or 80 mg (N = 40)
Outcomes	Primary: pain intensity assessed 30 and 60 mins post injection. Described as 1 = slight relief, 2 = moderate relief, 3 = good relief, 4 = complete relief. Maternal satisfaction of overall drug effect assessed postnatally as 1 = poor, 2 = fair, 3 = very good, 4 = excellent Secondary: neonatal Apgar score at 1 and 5 mins, resuscitation. Maternal nausea and vomiting
Notes	If additional analgesia was required, a second dose of original drug could be administered Maternal parity not reported but different drug dosage depending on parity Almost all (77/80) participants were non-Caucasion and all were delivered with local or regional anaesthesia Start and end date: not reported Power calculation: not reported Baseline imbalances between groups: Quote: "There was little difference among test groups with respect to type of labour, age, sex, type of delivery, and anaesthetic agent administered. Butorphanol 1 mg group slightly lower mean body weight." Funding source: Bristol laboratories, Syracuse, New York Conflicts of interest: not reported

Risk of bias

Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Unclear risk	Not reported
Allocation concealment (selection bias)	Low risk	Drugs in consecutively-numbered, identical vials prepared by independent laboratory

Maduska 1978 (*Continued*)

Blinding of participants and personnel (performance bias) All outcomes	Low risk	States double-blind, drugs in identical vials.
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	Not reported
Incomplete outcome data (attrition bias) All outcomes	Low risk	All women analysed.
Selective reporting (reporting bias)	Unclear risk	Unclear
Other bias	Unclear risk	Balanced at baseline for type of labour, weight, age, type of birth and anaesthetic agent

Mitterschiffthaler 1991

Methods	RCT 2-arm parallel-group design
Participants	Setting: Germany 40 women. Term pregnancy, cx dilated 2 cm to 3 cm, spontaneous labour onset, in active labour and requiring analgesia Parity: not reported
Interventions	Experimental: IM nalbuphine 0.1 mg/kg (N = 20) Control: IM pethidine 0.8 mg/kg (N = 20) States dosing was 'on demand'. Unclear if single or multiple doses administered, and if additional analgesia administered
Outcomes	Maternal outcomes: maternal pain relief VAS (0 cm to 20 cm) 30, 60, 90 and 120 mins, opinion of pain relief 12 hrs postpartum, sedation 4-point scale (awake, tired, sleeping but will wake if spoken to, sleeping but will wake if shaken, asleep not possible to wake up) 30, 60, 90 and 120 mins, 'side effects', blood pressure, heart rate, CTG. Neonatal outcomes: Apgar score at 10 mins, respiratory depression
Notes	German language - translation obtained Start and end date: unclear Power calculation: unclear Baseline imbalances between groups: unclear Funding source: unclear Conflicts of interest: unclear

Risk of bias

Bias	**Authors' judgement**	**Support for judgement**

Mitterschiffthaler 1991 (*Continued*)

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
Incomplete outcome data (attrition bias) All outcomes	High risk	4/40 women excluded due to insufficient pain relief.
Selective reporting (reporting bias)	Unclear risk	Unclear
Other bias	Unclear risk	Unclear

Mobaraki 2016

Methods	Randomised clinical trial, individually randomised
Participants	Setting: hospital in Iran. 100 women randomised in spontaneous labour pain along with appropriate maternal and fetal indications for vaginal delivery Exclusion criteria: presence of a personality disorder, an addiction, a complicated pregnancy, diabetes mellitus, macrosomia, chronic obstructive pulmonary disease, an unconfident fetal heart rate, valvular heart disease, an upper respiratory tract infection or sinus obstruction, a history of asthma, and contraindications for Entonox and pethidine usage
Interventions	Experimental group: pethidine (50 women) The pethidine group received an intramuscular injection of 0.5 mg/kg of pethidine. If a patient's pain rated higher than 5 VAS, 0.25 mg/kg of pethidine was injected. Not clear if pethidine was limited to 2 doses Control group: Entonox (50 women) Patients were taught to use an Entonox face mask at the beginning of uterine contractions and to continue deep inspirations at times when there was pain and cramps. Use of Entonox could be started or cut at any moment during labour according to the needs and preferences of the woman
Outcomes	Pain scores after analgesia. Duration of first and second stage of labour.
Notes	Dates: 2015 Funding: Ardabil Medical Sciences University Conflict of interest: not stated

Mobaraki 2016 (*Continued*)

Risk of bias		
Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Unclear risk	By using random numbers, the participants were randomly allocated into 2 groups. Equal groups and no further detail
Allocation concealment (selection bias)	Unclear risk	Not described
Blinding of participants and personnel (performance bias) All outcomes	High risk	Infeasible to blind.
Blinding of outcome assessment (detection bias) All outcomes	High risk	Not mentioned, but likely to be caregiver carrying out assessment
Incomplete outcome data (attrition bias) All outcomes	Unclear risk	No loss to follow-up reported, and no denominators given in results tables. Demographic data do not add up to total number of participants. Difficult to assess due to reporting. Also not clear if anyone changed intervention
Selective reporting (reporting bias)	Unclear risk	No protocol seen and few outcomes prespecified in the methods
Other bias	Unclear risk	Parity is not reported in each group. There were 16/50 under 20 year olds in the Entonox group and 9/50 in the pethidine group. These could be more likely to be nulliparous

Moore 1970

Methods	RCT 2-arm parallel-group design
Participants	Setting: hospital, UK 206 mixed parity healthy women, in spontaneous or induced labour, at > 35 weeks' gestation, cephalic presentation and in pain described as severe, moderate or slight
Interventions	Experimental: IM pentazocine 40 mg (N = 73) Control: IM pethidine 100 mg or 50 mg (N = 133)
Outcomes	Primary: pain intensity assessed at 30, 60 and 90 mins post injection, described as severe, moderate or slight. Asked at 12 to 24 hr postnatal if drug had helped Secondary: neonatal Apgar score at 1 min and 5 mins, maternal side effects of nausea or

Moore 1970 (*Continued*)

	vomiting
Notes	If additional analgesia required, a maximum of 3 further doses of study drug could be administered at 2- to 3-hourly intervals. Women could also use nitrous oxide and some had a paracervical block > 35 weeks' gestation therefore preterm babies may be included Start and end date: not reported Power calculation: not reported Baseline imbalances between groups: the age, physical and obstetric characteristics were similar between groups except in fetal presentation Funding source: not reported Conflicts of interest: not reported

Risk of bias

Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Unclear risk	Not reported
Allocation concealment (selection bias)	Unclear risk	Coded ampoules but no further information given.
Blinding of participants and personnel (performance bias) All outcomes	Unclear risk	States double-blind. Coded ampoules but not stated if identical in appearance
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	States double-blind. Coded ampoules but not stated if identical in appearance
Incomplete outcome data (attrition bias) All outcomes	High risk	29/206 excluded because delivered or had paracervical block.
Selective reporting (reporting bias)	Unclear risk	Unclear
Other bias	Unclear risk	Unclear

Morley-Forster 2000

Methods	RCT, 2-arm parallel-group design
Participants	Setting: labour ward of a university health centre in Canada 23 women randomised when they requested analgesia, 83% primips, gestational age > 32 weeks, weight < 100 kg or > 50 kg, able to speak English, no history of opioid abuse and normal FHR tracing (Women recruited to the study had medical contraindications to epidural although it was no specified what these were.)

Morley-Forster 2000 (*Continued*)

Interventions	Experimental: fentanyl, PCA 10 mcg per mL, initial bolus dose 1 mL, basal infusion rate of 2 mL per hr with PCA bolus 2 mL Control: alfentanil, PCA 100 micro g per mL, initial bolus dose 1 mL, basal infusion rate of 2 mL per hr with PCA bolus 2 mL Doses described as equivalent. Drugs were discontinued in both groups when the attending midwife estimated that birth was likely to take place within 15 mins
Outcomes	Pain (rated on a 100 mm VAS, recorded at baseline and every 30 mins thereafter); sedation (nurse rated hourly); side effects; satisfaction with pain relief (good, adequate, inadequate); Apgar scores at 5 and 10 mins; cord blood gases; naloxone dose; neonatal neuro-behavioural score at 4 and 24 hrs
Notes	Start and end date: not reported Power calculation: not reported Baseline imbalances between groups: quote: "The two groups were similar in age, weight, gestational age, parity, inductions, type of delivery, baseline pain scores, rate of cervical dilatation, duration of PCA use. The only difference was that the opioid dose- to delivery time was shorter in the alfentanil group." Funding sources: not reported Conflicts of interest: not reported

Risk of bias

Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Low risk	Randomisation schedule prepared by pharmacy.
Allocation concealment (selection bias)	Low risk	Plain, numbered vials prepared by pharmacy.
Blinding of participants and personnel (performance bias) All outcomes	Low risk	Plain vials prepared by pharmacy.
Blinding of outcome assessment (detection bias) All outcomes	Low risk	Stated that assessment was carried out by staff blind to group assignment
Incomplete outcome data (attrition bias) All outcomes	Unclear risk	25 women were randomised. 2 did not follow the protocol and were not followed up. There were missing data for some variables
Selective reporting (reporting bias)	Unclear risk	Unclear
Other bias	Unclear risk	Small sample size and the onset of analgesia varied.

Morrison 1987

Methods	RCT 2-arm parallel-group design
Participants	Setting: hospital, UK 1100 women. 37-42 weeks' gestation, in active labour and requiring analgesia Parity: 44% primips, 56% multips.
Interventions	Experimental: IM meptazinol 100 mg ≤ 70 kg, 150 mg > 70 kg (N = 513) Control: IM pethidine 1100 mg ≤ 70 kg, 150 mg > 70 kg (N = 522) Second dose, epidural or inhalation analgesia at maternal request
Outcomes	Maternal outcomes: maternal pain at 30, 60, 90 and 120 mins VAS (0 to 100 mm), nausea, vomiting, sleepiness, use of supplementary analgesia, method of birth, opinion of analgesic effect assessed 3-5 days postpartum (rated excellent, good, poor but just able to cope, no effect and required additional analgesia). Neonatal outcomes: Apgar at 1 min and 5 mins, resuscitation, naloxone administration, fetal distress, type of feeding
Notes	Start and end date: not reported Power calculation: not reported Baseline imbalances between groups: 'The groups were comparable with regard to age, maternal weight, parity and gestation' Funding source: not reported Conflicts of interest: not reported

Risk of bias

Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Unclear risk	Not reported
Allocation concealment (selection bias)	Low risk	Coded drug containers prepared at a site remote from the trial
Blinding of participants and personnel (performance bias) All outcomes	Low risk	States double-blind and used coded drug containers.
Blinding of outcome assessment (detection bias) All outcomes	Low risk	States double-blind and used coded drug containers.
Incomplete outcome data (attrition bias) All outcomes	High risk	65 women excluded due to clerical errors or administration of wrong drug
Selective reporting (reporting bias)	Unclear risk	Unclear
Other bias	Unclear risk	Women were balanced at baseline for age, weight, parity and gestation

Mowat 1970

Methods	RCT 2-arm parallel-group design
Participants	Setting: hospital, UK 94 women. > 35 weeks' gestation, age ≥ 18 years, excluded if diabetic, history of renal or hepatic impairment or taking monoamine oxidase inhibitors, in active labour and requiring analgesia Parity: ≤ 3
Interventions	Experimental: IM pentazocine 60 ≤ mg (N = 46) Control: IM pethidine 15 ≤ 0 mg (N = 48) Up to 3 injections > 3 hrs apart at maternal request.
Outcomes	Maternal outcomes: satisfied with analgesia, nausea, vomiting, sleepiness, use of additional analgesia (study drug), method of birth. Neonatal outcomes: Apgar at 1 min and 5 mins
Notes	Data for some outcomes available after first dose. Start and end date: not reported Power calculation: not reported Baseline imbalances between groups: the groups were similar with respect to age, and number of previous pregnancies Funding source: Sterling Winthrop Research Division supplied the drugs Conflicts of interest: not reported

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	States double-blind but how achieved not reported.
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	States double-blind but how achieved not reported.
Incomplete outcome data (attrition bias) All outcomes	High risk	Exclusions from most analyses.
Selective reporting (reporting bias)	Unclear risk	Unclear
Other bias	Low risk	Balanced at baseline for age, parity, induced labour onset.

Nel 1981

Methods	RCT 2-arm parallel-group design
Participants	Setting: hospital, South Africa 75 women. Healthy with no clinically detectable abnormality, in active labour, spontaneous and induced, and requiring analgesia. Excluded if history of hypersensitivity to any drug, previous caesarean, preterm labour, cardiac, pulmonary or renal disease and significant hypertension Parity: mixed
Interventions	Experimental: IM meptazinol 100 mg (N = 37) Control: IM pethidine 100 mg (N = 38) No concomitant analgesia given, metoclopramide 10 mg as required for nausea
Outcomes	Maternal outcomes: pain at 1 hr 5-point VAS scale, drug-related side effects. Neonatal outcomes: Apgar at 1 min and 5 mins, paediatrician assessment at 24 hrs
Notes	Start and end date: not reported Power calculation: not reported Baseline imbalances between groups: unclear Funding source: not reported Conflicts of interest: not reported

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	States double-blind but does not describe how blinding achieved
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	States double-blind but does not describe how blinding achieved
Incomplete outcome data (attrition bias) All outcomes	High risk	Number of women randomised not reported only number analysed, not same numbers analysed for all outcomes
Selective reporting (reporting bias)	Unclear risk	Unclear
Other bias	Unclear risk	Women requiring caesarean or epidural were excluded from further study, unclear if this is pre- or post-randomisation

Nelson 2005

Methods	RCT, 3-arm parallel-group design
Participants	Setting: hospital in North Carolina USA. 45 healthy women with singleton pregnancies requesting analgesia Women with allergies to the study medication, those that had already had medication and those taking opioids for chronic conditions were excluded, along with those with any signs of fetal distress
Interventions	Experimental: (15 women) IV butorphanol, 1 mg bolus Control: (15 women) IV pethidine, 50 mg bolus (A second control group received IV pethidine 25 mg plus 0.5 mg butorphanol; this group has not been included in the analyses in this review.)
Outcomes	Pain (measured on a 0 -10 numerical rating scale); sedation and nausea, Apgar scores at 1 min and 5 mins
Notes	Results for pain outcomes were reported on bar charts and are difficult to interpret. We have not included these results in the analyses in this review Start and end date: not reported Power calculation: 'the study was powered based on the increased variability in pain' Baseline imbalances between groups: 'Groups did not differ in demographic or labor characteristics' Funding source: National Institutes of Health, Bethesda, Maryland (grant No. NS41386) Conflicts of interest: not reported

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Quote: "computer generated balanced block design". Block size not stated
Allocation concealment (selection bias)	Unclear risk	Study described as double-blind but not details on allocation concealment provided
Blinding of participants and personnel (performance bias) All outcomes	Low risk	Quote: "drug was prepared by an anaesthesiologist not involved with the treatment of the patient or obtaining study measures". Described as double-blind
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	Not described
Incomplete outcome data (attrition bias) All outcomes	High risk	It was not clear how many women were randomised. Any women undergoing ARM, commencing oxytocin or requesting epidural were excluded after randomisation and were replaced Quote: "their randomization was re-entered for an-

Nelson 2005 (*Continued*)

		other patient". Women who reached 10 cm dilation within 1 hr of drug administration were also excluded from the analysis
Selective reporting (reporting bias)	Unclear risk	Unclear
Other bias	Unclear risk	Unclear

Neumark 1978

Methods	Randomised trial (methods unclear)
Participants	30 women Inclusion criteria: Quote: "co-operative patients" with no drug dependency. Various ages and social groups Exclusion criteria: unclear
Interventions	5 study groups: 1. TENS group - TENS to lower back (10 women); 2. 50 mg IV pethidine (5 women); 3. placebo TENS (no current) (5 women); 4. "Wrong" TENS (electrodes applied to wrong positions) (5 women); 5. no analgesia or intervention (5 women).
Outcomes	Pain intensity (grades 1 - 6 - no pain, light, bearable, heavy, very heavy, unbearable) over 70-min period. Satisfaction with analgesia 1 day after the birth "Reaction of the subjects the day after the birth to analgesia - rated as "good", "inadequate analgesia" or "none" - table 2. Progress in labour
Notes	Paper in German. Translation notes used for data extraction. We were unable to use the data from this paper in the review. We had intended comparing outcomes for women receiving IV pethidine versus no treatment. The only outcome reported in the paper was the amount of relief obtained from the analgesia and no outcomes were reported for the control group (no treatment). 5 women received pethidine and 5 women no treatment. It was reported that 2/5 women receiving pethidine had "good relief", 3 had insufficient or no relief. All women in the control group were reported as having an increase in pain Results - categories for pain relief (good, insufficient, none) do not correspond with pain scale - 6 perceptions reported in the translation Start and end date: not reported Power calculation: unclear Baseline imbalances between groups: unclear Funding source: unclear Conflicts of interest: unclear

Risk of bias

Bias	**Authors' judgement**	**Support for judgement**

Neumark 1978 (*Continued*)

Random sequence generation (selection bias)	Unclear risk	Not described - "randomly divided".
Allocation concealment (selection bias)	Unclear risk	Not described
Blinding of participants and personnel (performance bias) All outcomes	Unclear risk	1 group received no treatment. TENS groups - 1 without current and 1 where it was applied to wrong positions were blinded to the TENS intervention. Pethidine group presumably were not blinded. blinding of personnel is unclear
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	Not clear
Incomplete outcome data (attrition bias) All outcomes	Unclear risk	1 woman was lost to follow-up.
Selective reporting (reporting bias)	Unclear risk	Small study and results were difficult to interpret.
Other bias	Unclear risk	Translation, so difficult to evaluate other bias.

Nicholas 1982

Methods	RCT 2-arm parallel-group design
Participants	Setting: hospital, UK 450 women. Healthy women with no obstetric complications, full-term pregnancy, in active labour and requiring analgesia. Excluded if history of hypersensitivity to any drug, previous caesarean, preterm labour, cardiac, pulmonary or renal disease and significant hypertension Parity: not reported
Interventions	Experimental: IM meptazinol (N = 186 analysed). Control: IM pethidine (N = 172 analysed). Both given according to body weight. 75 mg if 38 kg to 50 kg, 100 mg if 51 kg to 69 kg or 150 mg if 70-85 kg. Each patient received up to 2 injections of study drug, and if analgesia still inadequate epidural given
Outcomes	Maternal outcomes: maternal assessment of pain relief at 15, 30, 45, 60, 90 and 120 mins (rated none, poor, satisfactory, good, very good or complete), type of birth, epidural, sleepiness, nausea and vomiting. Neonatal outcomes: Apgar at 1 min and 5 mins, apnoea, resuscitation, and lethargy, muscle tone, irritability success of feeding within first 24-hr period
Notes	Does not report number randomised to each group. Start and end date:not reported Power calculation: not reported

Nicholas 1982 (*Continued*)

	Baseline imbalances between groups: not reported Funding source: not reported Conflicts of interest: not reported

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	States double-blind but does not describe methods used.
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	States double-blind but does not describe methods used.
Incomplete outcome data (attrition bias) All outcomes	High risk	79.5% follow-up but no ITT analysis.
Selective reporting (reporting bias)	Unclear risk	Unclear
Other bias	Unclear risk	Unclear

O'Dwyer 1971

Methods	RCT 2-arm parallel-group design
Participants	Setting: hospital, UK 100 women. Age > 18 years, > 35 weeks' gestation, uncomplicated singleton, vaginal birth expected, in active labour and requiring analgesia Parity: 9% primips, 76% multips, 15% grand multips.
Interventions	Experimental: IM pentazocine 30 mg (N = 48 analysed) Control: IM Pethilorfan ®100 mg (N = 50 analysed) Second injection possible after 2 hr, each patient could receive up to 4 injections of study drug, and nitrous oxide or trilene to supplement analgesia if required
Outcomes	Maternal outcomes: maternal assessment of pain relief (numbers obtaining or not obtaining pain relief), type of birth, additional analgesia required (study drug). Neonatal outcomes: Apgar at 1 min and 5 mins, naloxone administration

O'Dwyer 1971 (*Continued*)

Notes	Does not state actual number randomised to each group. Start and end date: not reported Power calculation: not reported Baseline imbalances between groups: the group was balanced in most of the variables such as age, number of previous pregnancies, and cervical dilatation Funding source: not reported Conflicts of interest: not reported

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	States double-blind but does not describe methods used.
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	States double-blind but does not describe methods used.
Incomplete outcome data (attrition bias) All outcomes	High risk	31/98 excluded from primary outcome as delivered within 1 hr of administration of study drug, and 16 babies excluded from Apgar assessment as study drug administered more than 4 hrs before birth
Selective reporting (reporting bias)	Unclear risk	Unclear
Other bias	Unclear risk	Balanced at baseline for age, parity, contractions and vital signs

Olofsson 1996

Methods	RCT 2-arm parallel-group design
Participants	Setting: hospital, Stockholm, Sweden 20 healthy nulliparous women in active labour after spontaneous rupture of the membranes, cephalic presentation. No exclusion criteria specified
Interventions	Experimental: 0.05 mg/kg IV morphine up to 3 doses (max 0.15 mg/kg body weight) Control: 0.5 mg/kg IV pethidine up to 3 doses (max 1.5 mg/kg body weight) Both groups had continuous FHR monitoring.

Olofsson 1996 (*Continued*)

Outcomes	Sedation rates; CS, nausea and vomiting.
Notes	Start and end date: not reported Power calculation: not reported Baseline imbalances between groups: the demographic variables were balanced between the groups Funding source: Karolinska Institute foundations and the Swedish Medical Research Council Conflicts of interest: not reported

Risk of bias

Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Unclear risk	Quote: "assigned at random."
Allocation concealment (selection bias)	Low risk	Coded ampoules provided by pharmacy.
Blinding of participants and personnel (performance bias) All outcomes	Low risk	Described as double-blind; pharmacy provided identical coded ampoules
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	Unclear
Incomplete outcome data (attrition bias) All outcomes	Low risk	No apparent loss to follow-up.
Selective reporting (reporting bias)	Unclear risk	Unclear
Other bias	Unclear risk	Small sample and no clear information that groups were comparable at baseline. Range of cervical dilations at recruitment between 4 cm and 9 cm

Olson 1964

Methods	RCT, 2-arm parallel-group design
Participants	Setting: Washington, USA 194 women in established labour. Analgesia was given at approximately 4 cm to 5 cm cervical dilatation
Interventions	Experimental: IV phenazocine 1 mg Control: IV pethidine 50 mg Both groups received promethazine 50 mg, and for both groups "birth was accomplished under pudendal nerve block anaesthesia with terminal self-administered trichloroethy-

Olson 1964 (*Continued*)

	lene"
Outcomes	Pain relief (recorded by women on the first postpartum day); nausea and vomiting; adverse effects; progress in labour; Apgar scores at 1 min and 5 mins
Notes	Start and end date: not reported Power calculation: not reported Baseline imbalances between groups: unclear Funding source: not reported Conflicts of interest: not reported

Risk of bias

Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Unclear risk	Not described
Allocation concealment (selection bias)	Low risk	Drugs were prepared by pharmacy in identical coded vials and the code was not broken by the pharmacist until the study had been completed
Blinding of participants and personnel (performance bias) All outcomes	Unclear risk	Drugs in identical vials.Pharmacy prepared identical coded drugs
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	Unclear
Incomplete outcome data (attrition bias) All outcomes	Low risk	Missing data for some outcomes (approximately 5% for maternal postpartum outcomes, and 10% for nurse recorded evaluations in labour)
Selective reporting (reporting bias)	Unclear risk	None apparent, protocol not seen.
Other bias	Low risk	None apparent

Osler 1987

Methods	RCT 2-arm parallel-group design
Participants	Setting: hospital, Denmark 199 women. Spontaneous or induced labour onset, in active labour and requiring analgesia Parity: 78% nullips, 22% multips

Osler 1987 (*Continued*)

Interventions	Experimental: IM meptazinol 100 mg (N = 100). Control: IM pethidine 750 mg (N = 99). Each patient could receive up to 3 injections of study drug with an interval of not less than 2 hrs between doses
Outcomes	Maternal outcomes: maternal assessment of pain relief 5, 15, 30, 60, 90, 120 mins (rated complete, good, satisfactory, unsatisfactory), type of birth, additional analgesia required, epidural, adverse effects. Neonatal outcomes: Apgar at 1 min and 5 mins, neonatal distress, admission to SCBU
Notes	Start and end date: not reported Power calculation: not reported Baseline imbalances between groups: 'There were no differences between the two groups in age, body weight or height, or number of previous deliveries Funding source: not reported Conflicts of interest: not reported

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	Described as double-blind but no methods described.
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	Described as double blind but no methods described.
Incomplete outcome data (attrition bias) All outcomes	Low risk	All women analysed.
Selective reporting (reporting bias)	Unclear risk	Unclear
Other bias	Unclear risk	No baseline imbalance in age, weight, height or number of previous deliveries

Prasertsawat 1986

Methods	RCT 3-arm parallel-group design
Participants	Setting: hospital, Thailand 135 women. 37 to 42 weeks' gestation, cx ≥ 3 cm, in active labour and requiring analgesia Parity: not reported
Interventions	Experimental: IM tramadol 100 mg (N = 45); IM morphine 100 mg (N = 45). Control: IM pethidine 100 mg (N = 45). Second injection possible after 1 hr of half original study dose, each participant could receive maximum of 2 doses
Outcomes	Maternal outcomes: pain severity/relief 30 mins, 1, 2, 3, and 4 hrs (rated good, satisfactory, no response), drowsiness, nausea, vomiting. Neonatal outcomes: Apgar at 1 min and 5 mins, neonatal resuscitation
Notes	Start and end date: 1 February 1986 - 28 February 1986 Power calculation: not reported Baseline imbalances between groups: unclear Funding sources: not reported Conflicts of interest: not reported

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	States blind but does not describe the method.
Blinding of outcome assessment (detection bias) All outcomes	Low risk	Medical students unaware of group allocation assessed outcome
Incomplete outcome data (attrition bias) All outcomes	Low risk	All participants analysed.
Selective reporting (reporting bias)	Unclear risk	Unclear
Other bias	Low risk	Age and maternal weight balanced at baseline.

Quilligan 1980

Methods	RCT, 2-arm parallel-group design
Participants	Setting not clear (hospital in USA) 100 women in good health in active labour, with no addiction to or tolerance to drugs and complaining of moderate to severe pain. Women who "planned to nurse" were excluded
Interventions	Experimental: (50 women) IV butorphanol 1 mg to 2 mg (44 women had an initial dose of 1 mg and 6 an initial dose of 2 mg, after 1 hr or more a 2nd dose was given if requested) Control: (50 women) IV pethidine 40 mg to 80 mg (45 women had an initial dose of 40 mg and 5 an initial dose of 80 mg, a 2nd dose was given after 1 hr or more if requested)
Outcomes	Pain (5-point scale 0 - no pain, 4 - very severe pain); pain relief (5-point scale 0 - none, 4 - complete relief); FHR; Apgar scores at 1 min and 5 mins
Notes	Start and end date: not reported Power calculation: not reported Baseline imbalances between groups: unclear Funding sources: not reported Conflicts of interest: not reported

Risk of bias

Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Unclear risk	Not described
Allocation concealment (selection bias)	Unclear risk	Not described
Blinding of participants and personnel (performance bias) All outcomes	Unclear risk	Described as double-blind study but no details provided.
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	Unclear
Incomplete outcome data (attrition bias) All outcomes	Unclear risk	Outcome data were available for all women randomised.
Selective reporting (reporting bias)	Unclear risk	Unclear
Other bias	Unclear risk	No baseline imbalance was apparent although 8 women in the butorphanol group were induced compared with 1 woman in the pethidine group

Rayburn 1989a

Methods	RCT. 2-arm parallel groups
Participants	Setting: Nebraska university hospital, USA 105 women in early active labour (3 cm to 4 cm cervical dilation); at or beyond 37 weeks' gestation with no medical or obstetric complications, with no signs of fetal distress and requesting narcotic analgesia rather than an epidural. (Intervention group: 55% nulliparous, 71% non-white race, mean age 23 years; control group: 48% nulliparous, 70% non-white race, mean age 23 years.)
Interventions	Experimental: (49 women) IV fentanyl 50 µg to 100 µg per hr Control: (56 women) IV pethidine 25 mg to 50 mg per hr
Outcomes	Pain (measured on 10-point VAS recorded by labour ward nurses); nausea and vomiting; sedation; itching; FHR changes
Notes	Women were recruited only between 8 am and 3 pm on weekdays. Start and end date: January 1988 - August 1988 Power calculation: not reported Baseline imbalances between groups: 'There were no statistically significant differences in maternal demographic characteristics and need for oxytocin augmentation.' Funding source: not reported Conflicts of interest: not reported

Risk of bias

Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Low risk	Pharmacy randomisation table.
Allocation concealment (selection bias)	Unclear risk	Not described
Blinding of participants and personnel (performance bias) All outcomes	High risk	Staff not blinded to group allocation.
Blinding of outcome assessment (detection bias) All outcomes	High risk	Staff not blinded to group allocation.
Incomplete outcome data (attrition bias) All outcomes	Low risk	All women randomised seem to be included in the results.
Selective reporting (reporting bias)	Unclear risk	Unclear
Other bias	Unclear risk	Women were recruited only on weekdays between 8am and 3pm so may not represent the population attending the study hospital

Refstad 1980

Methods	RCT, 2-arm parallel-group design
Participants	Setting: hospital, Norway 85 women. Healthy women at term, expected to have a normal birth in active labour and requiring analgesia Parity: not reported
Interventions	Experimental: IM pentazocine 45 mg (N = 43) Control: IM pethidine 100 mg (N = 42) Half dose repeated after 1 hr if required and further full dose after 3 hrs if labour prolonged. All women received promazine 25 mg IM before 1st injection, nitrous oxide or pudendal block or both allowed at end of 2nd stage
Outcomes	Maternal outcomes: pain relief at 1 hr (0 = no pain, 1 = slight pain, 2 = moderate pain, 3 = severe pain), type of birth, additional analgesia required. Neonatal outcomes: Apgar at 1 min and 5 mins, naloxone administration, FHR changes
Notes	Start and end date: not reported Power calculation: not reported Baseline imbalances between groups: unclear Funding source: Sterling-Winthrop company supplied trial drugs Conflicts of interest: not reported

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 blinding
Blinding of outcome assessment (detection bias) All outcomes	High risk	No blinding
Incomplete outcome data (attrition bias) All outcomes	High risk	25/85 women excluded from analysis as delivered within 1 hr of 1st dose of study drug
Selective reporting (reporting bias)	Unclear risk	Unclear
Other bias	Unclear risk	Nitrous oxide or pudendal block permitted during second stage

Sekhavat 2009

Methods	Reported to be a randomised clinical trial with individual randomisation
Participants	Setting: hospital in Iran 150 women Healthy women, with singleton cephalic presentation pregnancy in spontaneous labour, 3 cm or more cervical dilatation requesting analgesia Exclusion criteria: pethidine allergy, contraindication to vaginal delivery, fetal death or distress, fetal congenital heart malformation or obstetric complications such as antepartum haemorrhage
Interventions	Experimental group: pethidine IM 50 mg, with 25 mg after 4 hrs if women requested. (N = 75) Control group: placebo, IM saline. (N = 75) Women in both groups received routine care which included FHR surveillance and 2-hourly vaginal examinations, with a protocol for oxytocin augmentation for delay
Outcomes	Apgar scores Fetal heart rate changes Oxytocin administration
Notes	Start and end date: October 2004 to September 2005 It was reported that the study was not supported by any pharmaceutical company Conflicts of interest: not reported

Risk of bias

Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Unclear risk	It was reported that women were allocated "randomly (using a randomized consecutive numbered chart)". It was not clear whether the chart had random numbers or that numbers were ordered consecutively
Allocation concealment (selection bias)	Unclear risk	Method not described
Blinding of participants and personnel (performance bias) All outcomes	Low risk	Participants: study was placebo controlled. Caregiver: study was placebo controlled - staff may have been aware of allocation as some women received no analgesia
Blinding of outcome assessment (detection bias) All outcomes	Low risk	Reported to be blind to allocation
Incomplete outcome data (attrition bias) All outcomes	Unclear risk	150 women were randomised, 75 in each group. There was no mention of dropouts or any missing data

Sekhavat 2009 (*Continued*)

Selective reporting (reporting bias)	High risk	There was little information. The outcome reported were FHR only. Mode of birth was not reported, some outcomes were reported to be "no different" but raw data were not reported. No protocol available. No power calculation
Other bias	Unclear risk	There was little information on methods so it was not possible to assess whether other risk of bias was present

Sheikh 1986

Methods	RCT, 2-arm parallel-group design
Participants	Setting: hospital, UK 205 women. Healthy women 38 to 41 weeks' gestation, uncomplicated pregnancy, spontaneous or induced labour onset, in active labour and requiring analgesia. Excluded if epidural or forceps birth likely Parity: mixed
Interventions	Experimental: IM meptazinol 100 mg (N = 98) Control: IM pethidine 100 mg (N = 99) Additional doses of test drug allowed at intervals no less than 2 hrs if required to a maximum of 3 doses. All women could receive nitrous oxide if required and prochlorperazine 12.5 mg IM for nausea and vomiting. Epidural at midwife discretion
Outcomes	Maternal outcomes: pain intensity 30 mins and then hourly intervals until birth (rated none, mild, moderate, severe), pain relief (rated none, slight, moderate, strong or complete), type of birth, additional analgesia required, nausea and vomiting. Neonatal outcomes: Apgar at 1 min and 5 mins, resuscitation. Within 72 hrs postpartum feeding problems, irritability and muscle tone
Notes	Start and end date: not reported Power calculation: not reported Baseline imbalances between groups: both the groups were balanced for age, body weight, and parity Funding sources: Wyeth laboratories supplied the coded ampoules of the trial drugs Conflicts of interest: not reported

Risk of bias

Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Unclear risk	Not reported

Sheikh 1986 (*Continued*)

Allocation concealment (selection bias)	Low risk	Coded ampoules kept at a site remote from trial.
Blinding of participants and personnel (performance bias) All outcomes	Low risk	Described as double-blind, used coded ampoules and states that identity of drug unknown
Blinding of outcome assessment (detection bias) All outcomes	Low risk	Blind outcome assessor for all bar 15% of women.
Incomplete outcome data (attrition bias) All outcomes	Low risk	8 women excluded from analysis as delivered within 30 mins of administration
Selective reporting (reporting bias)	Unclear risk	Unclear
Other bias	Unclear risk	Balanced at baseline for age and weight, but imbalance in parity. 43/98 multip meptazinol group versus 34/99 in pethidine group

Sliom 1970

Methods	RCT, 3-arm parallel-group design
Participants	Setting: hospital, South Africa 196 women. Healthy women at term, uncomplicated labour, in active labour expected to deliver in next 4 hrs and requiring analgesia. Excluded if likely to deliver within 30 mins and had received analgesia within previous 6 hrs Parity: mixed
Interventions	Experimental: IM dihydrocodeine 50 mg (N = 80) Control: IM pethidine 100 mg (N = 58), placebo (saline) (N = 58) Single dose of study drug.
Outcomes	Maternal outcomes: pain relief at 1 hr (rated good, fair, poor), sedation (rated drowsy, alert but calm, restless), nausea, vomiting. Neonatal outcomes: Modified Apgar at 1 min and 5 mins (minus colour)
Notes	Women excluded after randomisation if delivered more than 4 hrs after injection of study drug Start and end date: not reported Power calculation: not reported Baseline imbalances between groups: all the groups were balanced for age, race, and parity Funding sources: BDH (South Africa) Pty Ltd supplied dihydrocodeine bitartrate Conflicts of interest: not reported
Risk of bias	

Sliom 1970 (*Continued*)

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	States double-blind. Not reported how blinding was achieved.
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	States double-blind. Not reported how blinding was achieved.
Incomplete outcome data (attrition bias) All outcomes	Unclear risk	Number of women randomised not reported, authors only report the number of women analysed
Selective reporting (reporting bias)	Unclear risk	Unclear
Other bias	Unclear risk	Unequal number of women in each treatment group due to post-randomisation exclusions. Exclusions included women who delivered < 30 mins or > 4 hrs after administration of study agents

Tawfik 1982

Methods	RCT: methods not clear
Participants	Setting: Egypt 90 primiparous women with normal presentation and position and expected to deliver normally
Interventions	Intervention: pethidine 50 mg IM 4- to 5-hourly Comparison: TENS applied to back. The position arranged to suit the mother and moved to lower abdomen if preferred Both groups were given 10 mg diazepam IM. Both groups had artificial rupture of membranes at 5 cm and oxytocin augmentation
Outcomes	Pain intensity (scored as being: severe = 3; moderate = 2; mild = 1) - only measured before intervention; pain relief scored (complete = 4, excellent = 3, good = 2, slight (satisfactory) = 1) at 30 mins, 5 cm and at full cervical dilatation; patient's opinion on the technique - satisfaction (during whole period of delivery), scored as (excellent = 3, good = 2, satisfactory = 1); Apgar score; side effects (drowsiness, nausea, vomiting)
Notes	Start and end date: Funding sources: Conflicts of interest:

Tawfik 1982 (*Continued*)

Risk of bias		
Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Unclear risk	"Randomly divided between 2 groups."
Allocation concealment (selection bias)	Unclear risk	No information provided.
Blinding of participants and personnel (performance bias) All outcomes	High risk	Not reported - but not feasible with nature of interventions
Blinding of outcome assessment (detection bias) All outcomes	High risk	Not reported - but not feasible with nature of interventions
Incomplete outcome data (attrition bias) All outcomes	Low risk	No apparent loss to follow-up.
Selective reporting (reporting bias)	Unclear risk	All outcomes described within the methods are reported upon within the results. However, the study protocol was not evaluated
Other bias	Unclear risk	Unbalanced groups; 35 in the intervention group and 55 in the comparison group

Thakur 2004

Methods	RCT
Participants	Setting: Indore, India 300 women in established labour attending for care in a hospital in India. The participants were described as being predominantly from low socio-economic groups and from urban areas Inclusion criteria: term pregnancy (37 to 42 weeks), vertex presentation, cervical dilatation 3 cm or more with contractions Exclusion criteria: previous uterine scar, malpresentation, multiple pregnancy, cephalopelvic disproportion, antepartum haemorrhage, pre-eclampsia or other medical disorders
Interventions	Interventions group: TENS to back Comparison group 1: 100 mg IM tramadol Comparison group 2: no intervention
Outcomes	Maternal pain score measured on a verbal response scale during labour "degree of analgesia" (degree of pain relief: no relief, mild relief, moderate relief, complete relief - dichotomised as a percentage); mean time for onset and duration of analgesia; duration of stages of labour; mode of delivery (normal, forceps, CS); mean Apgar score of neonates;

Thakur 2004 (*Continued*)

	side effects for mothers
Notes	Start and end date: not reported in translation. Funding sources: not reported in translation. Conflicts of interest: not reported in translation.

Risk of bias

Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Unclear risk	Described as "randomly allocated" but groups were of identical size with identical numbers of primiparous and multiparous women in each group
Allocation concealment (selection bias)	Unclear risk	Method of randomisation not described.
Blinding of participants and personnel (performance bias) All outcomes	High risk	No blinding reported - but not possible due to nature of intervention
Blinding of outcome assessment (detection bias) All outcomes	High risk	No blinding reported - but not possible due to nature of intervention
Incomplete outcome data (attrition bias) All outcomes	Low risk	Apparently there was no loss to follow-up.
Selective reporting (reporting bias)	Unclear risk	All outcomes described within the methods are reported upon within the results. However, the study protocol was not evaluated
Other bias	Unclear risk	Groups were unusually similar and it was not clear that there had been stratification to achieve such balanced groups

Tharamas 1999

Methods	RCT. 2-arm parallel groups
Participants	200 nulliparous women in labour. Inclusion criteria: at term (37 to 42 weeks) spontaneous labour, in active labour, vertex presentation Exclusions: age < 16 or > 35, weight < 50 kg or > 75 kg, infant birthweight estimated < 2500 g or > 4000 g, medical or surgical complication or unable to understand VAS
Interventions	Intervention group: IM buprenorphine 300 µg Comparison group: IM pethidine 75 mg
Outcomes	Analgesic effect at 1, 2, 3, 4 hrs, side effects (nausea, drowsiness, use of antidote)

Tharamas 1999 (*Continued*)

Notes	Data extraction from translation notes. Start and end date: January 1996 - December 1996 Power calculation: unclear Baseline imbalances between groups: unclear Funding source: unclear Conflicts of interest: unclear

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Random number table
Allocation concealment (selection bias)	Unclear risk	Not described
Blinding of participants and personnel (performance bias) All outcomes	Unclear risk	Treatment described as blinded.
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	Unclear
Incomplete outcome data (attrition bias) All outcomes	Unclear risk	Denominators in tables not clear.
Selective reporting (reporting bias)	Unclear risk	Unclear
Other bias	Unclear risk	Unclear

Tsui 2004

Methods	RCT, 2-arm parallel-group design
Participants	Setting: hospital, Hong Kong 50 women. Healthy women in early active labour and requiring analgesia. Uncomplicated singleton term pregnancy, cephalic presentation. Spontaneous and induced labour onset. Excluded if epidural already requested Parity: 3:2 nullip:multip ratio
Interventions	Experimental: IM pethidine 100 mg (N = 25) Control: placebo (saline) (N = 25) Single dose of study drug. Rescue analgesia allowed after 30 mins nitrous oxide or epidural for women in pethidine group and pethidine for women in placebo group

Tsui 2004 (*Continued*)

Outcomes	Maternal outcomes: pain intensity at 15 mins and 30 mins VAS (0 to 100), maternal assessment of sedation at 15 mins and 30 mins VAS (0 to 100), type of birth, additional analgesia required, vomiting, maternal satisfaction at 30 mins 5-point scale (1 = totally dissatisfied to 5 = very satisfied). Neonatal outcomes: Apgar at 1 min and 5 mins, resuscitation and admission to SCBU
Notes	Study terminated after 50 women recruited as interim analysis demonstrated benefit for pethidine. Stratified by parity Start and end date: September 2000 to May 2001. Power calculation: Using published and unpublished data, a sample size of 56 women per group was needed to have 90% power at 5% significant level to detect a mean difference of 13 mm in VAS pain score between groups Baseline imbalances between groups: Table 1 provides this information, but it is unclear if the groups were balanced or not Funding source: not reported Conflicts of interest: not reported

Risk of bias

Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Low risk	Computer generated in blocks of 10.
Allocation concealment (selection bias)	Low risk	Sequentially-numbered, opaque sealed envelopes.
Blinding of participants and personnel (performance bias) All outcomes	Low risk	States double-blind and women blind to contents of syringe.
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	States double-blind and women blind to contents of syringe. No further detail given
Incomplete outcome data (attrition bias) All outcomes	Low risk	All women accounted for in the analysis.
Selective reporting (reporting bias)	Unclear risk	Unclear
Other bias	High risk	20/25 women in pethidine group versus 12/25 women in placebo group had labour induced which may affect maternal and neonatal outcomes

Viegas 1993

Methods	RCT, 3-arm parallel-group design
Participants	Setting: hospital, Singapore 90 women. Women aged 18 to 35 years in active labour and requiring analgesia, cx 3 cm to 5 cm, uncomplicated term pregnancy with uncomplicated birth expected, spontaneous or induced labour onset. Excluded if preterm labour Parity: 100% nullips
Interventions	Experimental: IM tramadol 50 mg (N = 30), tramadol 100 mg (N = 30) Control: IM pethidine 75 mg (N = 30) Single dose of study drug.
Outcomes	Maternal outcomes: pain relief at 10, 20, 30, 45 mins and 1 hr 4-point scale (0 = none, 1 = insufficient, 2 = sufficient, 3 = complete pain relief), type of birth, drowsiness, nausea, vomiting. Neonatal outcomes: Apgar at 1 min and 5 mins, resuscitation and admission to SCBU
Notes	Start and end date: not reported Power calculation: not reported Baseline imbalances between groups: Table 1 suggests that the groups were balanced Funding source: not reported Conflicts of interest: not reported

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	Low risk	States double-blind, identical syringes prepared separately from clinical observer
Blinding of outcome assessment (detection bias) All outcomes	Low risk	States double-blind, identical syringes prepared separately from clinical observer
Incomplete outcome data (attrition bias) All outcomes	Low risk	All participants analysed.
Selective reporting (reporting bias)	Unclear risk	Unclear
Other bias	Unclear risk	Unclear

Volikas 2001

Methods	RCT, 2-arm parallel-group design
Participants	Setting: hospital in Surrey, UK 17 healthy women 36 to 40 weeks' gestation requesting pethidine for pain relief in labour, ASA I or II. Women with a contraindication to pethidine or remifentanil or requesting epidural were excluded
Interventions	Experimental: IV PCA remifentanil, 0.5 µg bolus per kg (based on antenatal booking weight) with 2 mins lock-out, no hourly max Control: IV PCA pethidine, 10 mg bolus, 5 mins lock-out, 100 mg hourly max All women were given 10 mg metoclopramide IV over 8 hrs.
Outcomes	Maternal: pain on 10 cm VAS recorded hourly; nausea recorded on a 10 cm VAS; itching; BP pulse and resps Neonate: 1 min and 5 mins Apgar scores.
Notes	Start and end date: not reported Power calculation: 'Power analysis (β = 0.2) revealed that 17 women would be required in each group, assuming 10 mm change in visual analogue pain score to be clinically significant.' Baseline imbalances between groups: the groups were balanced for baseline characteristics Funding source: not reported Conflicts of interest: not reported

Risk of bias

Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Unclear risk	Not described "randomly allocated".
Allocation concealment (selection bias)	Low risk	Quote: "by selecting the next in a series of sealed envelopes prepared by pharmacy."
Blinding of participants and personnel (performance bias) All outcomes	Low risk	Women were described as blinded. Quote: "One investigator selected the envelope and prepared the PCA pump. the pump was covered so that the other investigator, the observer, was unable to see which drug the woman was receiving."
Blinding of outcome assessment (detection bias) All outcomes	Low risk	Quote: "One investigator selected the envelope and prepared the PCA pump. the pump was covered so that the other investigator, the observer, was unable to see which drug the woman was receiving."
Incomplete outcome data (attrition bias) All outcomes	Low risk	No loss to follow-up apparent although for some outcomes it was not clear what the denominators were

Volikas 2001 (*Continued*)

Selective reporting (reporting bias)	Unclear risk	Unclear
Other bias	Low risk	None apparent

Wahab 1988

Methods	RCT. 4-arm parallel groups Start and end date: May 1984 to November 1985
Participants	Setting: hospital in Cairo, Egypt 80 multiparous women at term (39 to 41 weeks), 19 to 27 years (parity 2 to 6), in the first stage of labour following uncomplicated pregnancies, spontaneous labour Women with respiratory or cardiac disease were excluded.
Interventions	Group 1: IM nalbuphine 0.13 mg/kg Group 2: IM butorphanol 0.16 mg/kg Group 3: IM pentazocine 0.4 mg/kg Group 4: IM placebo
Outcomes	Pain relief 0 = complete relief, 3 = no relief. Apgar score at 1 min and 5 mins. Maternal and fetal blood gases
Notes	Data were reported as means and have not been included in data tables. We describe findings briefly in the text Start and end date: May 1984 - September 1985 Power calculation: not reported Baseline imbalances between groups: the groups were balanced for baseline characteristics Funding source: not reported Conflicts of interest: not reported

Risk of bias

Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Unclear risk	Not described "randomly divided".
Allocation concealment (selection bias)	Unclear risk	Not described "four equal groups".
Blinding of participants and personnel (performance bias) All outcomes	Unclear risk	Unclear
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	Unclear

Wahab 1988 (*Continued*)

Incomplete outcome data (attrition bias) All outcomes	Unclear risk	Unclear
Selective reporting (reporting bias)	Unclear risk	Not clear when randomisation took place and denominators in tables not clear
Other bias	Unclear risk	The equal division into groups suggests that there may not have been true random allocation

Wali 2012

Methods	Double-blind randomised trial
Participants	231 women with term, singleton pregnancy in cephalic position in the active stage of labour
Interventions	IM 100 mg tramadol (114 women) versus IM 30 mg pentazocine (117 women)
Outcomes	Pain at 30 and 60 mins, maternal satisfaction, side effects, neonatal outcomes
Notes	No raw data were reported in this brief abstract. We have contacted the author for more information (27th June 2017). No data are included in the analyses

Risk of bias

Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Unclear risk	Not described
Allocation concealment (selection bias)	Unclear risk	Not described
Blinding of participants and personnel (performance bias) All outcomes	Low risk	Reported to be double-blind.
Blinding of outcome assessment (detection bias) All outcomes	Low risk	Reported to be double-blind.
Incomplete outcome data (attrition bias) All outcomes	Unclear risk	Insufficient information to assess (not clear how many women were randomised or if there were missing data)
Selective reporting (reporting bias)	Unclear risk	Brief abstract so unable to assess.
Other bias	Unclear risk	Unable to assess. The trial author has been contacted to provide more information on methods

Wee 2014

Methods	Prospective, parallel-arm 2-centre RCT. Block randomisation. Blocks of 2 to 10. Women randomised individually
Participants	Setting: 2 large hospitals in the UK. 484 women Nulliparous and multiparous women aged 16 years or older who had given written informed consent, who were in active labour defined as regular uterine contractions of at least 2 in 10 mins, with a singleton pregnancy, cervical dilatation of at least 3 cm, with gestation of 37to 42 weeks, and weight between 60 kg and 120 kg. The weight eligibility criterion was reduced from 70 kg to 60 kg with a substantial amendment in June 2009 approximately 3 months after the start of recruitment Exclusion criteria: allergy or previous adverse reaction to opioids or opioid dependency, use of parenteral opioids within the previous 24 hrs or presence of severe systemic disease
Interventions	Experimental group 1: diamorphine 7.5 mg group Given into the muscles of the gluteus or lateral thigh by the midwife looking after the women from the trial syringes provided by the research midwife. IM. (244 women) Experimental group 2: pethidine 150 mg group Given into the muscles of the gluteus or lateral thigh by the midwife looking after the women from the trial syringes provided by the research midwife. IM. (240 women) A maximum of 2 doses of opioid were given with a minimum interval of 2 hrs if the women requested additional analgesia. Women also received metoclopramide 10 mg with the first dose. Regional analgesia or Entonox were available as rescue analgesia
Outcomes	Satisfaction with analgesia Severe pain Mode of birth Additional analgesia required Naloxone admin Neonatal resuscitation Admission to special care Breastfeeding problems Apgar scores Abnormal CTG Umbilical cord gases
Notes	Dates of study: not stated Funding: independent research funded by the National Institute for Health Research (NIHR) under its Research for Patient Benefit (RfPB) Programme (Grant Reference Number PB-PG-0407-13170) with additional support costs funded by the Western Comprehensive Local Research Network. The views expressed are those of the authors and not necessarily those of the NHS, the NIHR or the Department of Health Conflict of interest: all authors have completed the Unified Competing Interest form and there are no competing interests. 3 authors received travel expenses for meetings in relation to the trial

Risk of bias

Bias	Authors' judgement	Support for judgement

Wee 2014 (*Continued*)

Random sequence generation (selection bias)	Low risk	The trial statistician provided the computer-generated block randomisation using block sizes between 2 and 10 to ensure approximately equal group sizes, and stratified by centre
Allocation concealment (selection bias)	Low risk	The pharmacies of both trial centres prepared batches of 2 identical syringes labelled only with the trial number to conceal group allocation and to ensure that if 2 doses were given, the same opioid was given both times
Blinding of participants and personnel (performance bias) All outcomes	Low risk	Women, researchers, maternity unit staff and trial statistician were blinded to allocation. The actual identities of the 2 groups were not revealed until after full analysis and discussion of the results
Blinding of outcome assessment (detection bias) All outcomes	Low risk	Women, researchers, maternity unit staff and trial statistician were blinded to allocation. The actual identities of the 2 groups were not revealed until after full analysis and discussion of the results
Incomplete outcome data (attrition bias) All outcomes	Unclear risk	No loss to follow-up reported except Quote: "from the 60-minute measurement onwards there was significantly more missing data in the pethidine group than the diamorphine group (for example 19% versus 10% at 60 minutes, 53% versus 34% at 120 minutes). The difference in quantity of missing data was largely because the women in the pethidine group tended to deliver earlier.". The study recruited over their target recruitment to account for the missing data ITT analysis adhered to. Not all denominators reported in tables
Selective reporting (reporting bias)	Low risk	All outcomes reported as per protocol
Other bias	Low risk	Similar baseline characteristics

Wheble 1988

Methods	RCT, 2-arm parallel-group design
Participants	Setting: hospital, UK 47 women. Women in active labour and requiring analgesia, 37 to 42 weeks' gestation, singleton pregnancies with no known disorders, spontaneous or induced labour onset Parity: mixed
Interventions	Experimental: IM meptazinol (N = 17). Control: IM pethidine (N = 17). Study dose dependent on woman's weight: 100 mg if weight < 70 kg, 150 mg if weight ≥ 70 kg. Additional analgesia at discretion of caregiver, either 2nd dose of study drug, epidural or nitrous oxide, metoclopramide as required for nausea and vomiting
Outcomes	Maternal outcomes: type of birth, additional analgesia, epidural. Neonatal outcomes: Apgar at 1 min and 5 mins, FHR changes
Notes	Open non-randomised control arm Start and end date: not reported Power calculation: not reported Baseline imbalances between groups: unclear Funding source: Medical Research Council and Wyeth Research (UK) Conflicts of interest: not reported

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	Described as double-blind but methods not described.
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	Described as double-blind but methods not described.
Incomplete outcome data (attrition bias) All outcomes	Low risk	All patients analysed in an ITT analysis.
Selective reporting (reporting bias)	Unclear risk	Unclear
Other bias	Unclear risk	Balanced at baseline for height, weight, age, socioeconomic group, gestation, cervical dilation, parity and smoking

Wilson 1986

Methods	RCT, 2-arm parallel-group design
Participants	Setting: hospital, UK 80 women. Healthy women in active labour and requiring analgesia, ≥ 38 weeks' gestation, uncomplicated pregnancy Parity: 4 or less
Interventions	Experimental: IM nalbuphine 20 mg (N = 37). Control: IM pethidine 100 mg (N = 35). Additional doses of test drug allowed at intervals no less than 2 hrs if required to a maximum of 3 doses. Epidural if analgesia inadequate at discretion of caregiver and subsequently removed from trial
Outcomes	Maternal outcomes: pain intensity at peak of contraction at 30, 60 and 90 mins (rated very severe, severe, moderate, slight) and with VAS (0 to 100), type of birth, sleepiness, nausea and vomiting. Neonatal outcomes: Apgar at 1 min and 5 mins, naloxone administration, Scanlon score (neuro-behavioural score) at 2 to 4 hrs and 24 hrs
Notes	Start and end date: not reported Power calculation: not reported Baseline imbalances between groups: unclear Funding source: not reported Conflicts of interest: not reported

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	Low risk	States double-blind and study drugs were dispensed in coded ampoules
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	Not reported
Incomplete outcome data (attrition bias) All outcomes	High risk	8/80 excluded from analyses due to inadequate pain relief.
Selective reporting (reporting bias)	Unclear risk	Unclear
Other bias	Unclear risk	Does not report actual number randomised per group. Broadly comparable at baseline with respect to physical and obstetric characteristics

Zafar 2016

Methods	RCT with individual randomisation.
Participants	Setting: Islamic International Medical college trust - Rawalpindi (Punjab province) and Islamabad, Pakistan 150 women in early labour (3 cm to 6 cm) (spontaneous or induced) with uncomplicated singleton term pregnancy and cephalic presentation Exclusion criteria: women, who requested for other forms of analgesia, had a complicated pregnancy (e.g. pre-eclampsia, antepartum haemorrhage)/pre-existing medical disease, had any contraindication to vaginal delivery, or contraindication to opioids
Interventions	Experimental group 1 (n = 50) (conventional group) received a single intramuscular injection of 1 mL of pentazocine (30 mg) and oral placebo Experimental group 2 (n = 50) (homeopathy group) received 1 mL of saline injection and oral homeopathic medicine prescribed by a qualified homeopath. The homeopathic medicine used was*Chamomilla recutita* with strength of 1 M, manufactured by William Schwabe Karlsruhe (Schwabe) and origin was from Germany. It was used in a dose of 3 drops. This medicine comes in a dilution of ₋30, ₋200 and 1 M Control group (n = 50) (placebo group) received oral placebo and 1 mL of saline injection
Outcomes	Mode of birth Side effects Pain intensity Duration of labour
Notes	Start and end dates: August 2008 to September 2009 Funding: the funding for this project was provided by the Higher Education Commission Pakistan Conflict of interest: not reported

Risk of bias

Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Low risk	Randomisation codes were generated through computer.
Allocation concealment (selection bias)	Low risk	Randomisation codes were placed in sequential numbers in sealed envelopes. Women were asked to pick from a shuffled deck of cards with a number that was assigned to an envelope. The selected envelope containing the treatment was opened up by a health worker who prepared the study drugs and had no further involvement with women's assessment
Blinding of participants and personnel (performance bias) All outcomes	Low risk	The study drugs and the placebo were dispensed in similar packing to ensure blinding of patients as well as dispensers Caregiver: a health worker, who was blinded to

Zafar 2016 (*Continued*)

		the contents of the drug injected the medicine and dispensed oral preparation of small, white sugar pellets
Blinding of outcome assessment (detection bias) All outcomes	Low risk	Not mentioned though if caregiver recorded outcomes, assessors were blinded
Incomplete outcome data (attrition bias) All outcomes	Unclear risk	1 women in placebo group opted for epidural and was withdrawn from the study 3 women form conventional group, 8 women from homeopathy group, and 8 women from placebo group were lost to follow-up. It is reported that 'the missing values were observed as some women delivered before any pain assessment or the observations were not recorded.' There were no further reasons provided
Selective reporting (reporting bias)	Unclear risk	All essential outcomes are reported, protocol not seen and outcomes not clearly specified in text
Other bias	Unclear risk	The baseline demographic characteristics, age, weight and height, were similar in the 3 groups. However *Camomilla* group had fewer primips, and fewer > para 3. Denominators not clearly specified. Abstract reports 99 women randomised, full-text reports 150 before exclusions

Zhu 2013

Methods	Randomised trial with individual randomisation.
Participants	150 full-term primiparous women intending to have normal vaginal birth No exclusion criteria (abstract only)
Interventions	Group 1 (50 women): fentanyl-droperidol mixed liquor via acupoint injection at different time stages: BL 23 in active phase and BL 32 in second stage Group 2 (50 women): fentanyl-droperidol mixed liquor via subcutaneous injection Group 3 (50 women): NaCl 0.9% via subcutaneous injection
Outcomes	VAS score level or norepinephrine Blood pressure
Notes	Dates: not in abstract Funding: not reported Conflict of interest: not reported ABSTRACT ONLY - no data. Full text in Chinese

Zhu 2013 (*Continued*)

Risk of bias		
Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Unclear risk	"Randomly divided". Method not described
Allocation concealment (selection bias)	Unclear risk	Method not described
Blinding of participants and personnel (performance bias) All outcomes	High risk	Women receiving the subcutaneous injections may have been blinded, unlikely that blinding would have been maintained for staff
Blinding of outcome assessment (detection bias) All outcomes	High risk	Not mentioned, likely to have outcomes collected by staff.
Incomplete outcome data (attrition bias) All outcomes	Unclear risk	Unable to assess - abstract only
Selective reporting (reporting bias)	Unclear risk	Unable to assess - abstract only
Other bias	Unclear risk	Unable to assess - abstract only

ARM: artificial rupture of the membranes
ASA: American Society of Anesthesiologists Classification
BMI: body mass index
BP: blood pressure
CS: caesarean section
CTG: cardiotocograph
cx: cervix
FGR: fetal growth restriction
FHR: fetal heart rate
GA: gestational age
HR: heart rate
IM: intramuscular
IOL: induction of labour
ITT: intention-to-treat
hr(s): hour(s)
IV: intravenous
min(s): minute(s)
multips: multiparous women
MW: midwife
NACS: Neurologic and Adaptive Capacity Score
nullips: nulliparous women
PCA: patient controlled analgesia
PN: postnatal

primips: primiparous women
RCT: randomised controlled trial
resps: respirations
SC: subcutaneous
SCBU: special care baby unit
SD: standard deviation
TENS: transcutaneous electrical nerve stimulation
VAS: visual analogue scale

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

Study	Reason for exclusion
Abd-El-Maeboud 2014	The intervention was IV paracetamol, which is not an opiate.
Abdollahi 2014	IM pethidine was compared with IV paracetamol. The comparison of opiates with non-opioid drugs is not a relevant comparison for this review
Aiken 1971	This study compares the use of diazepam versus a placebo. Both groups had pethidine
Alhashemi 2011	IM pethidine was compared with IV paracetamol. The comparison of opiates with non-opioid drugs is not a relevant comparison for this review
Ankumah 2016	IV morphine was compared with IV paracetamol. The comparison of opiates with non-opioid drugs is not a relevant comparison for this review
Balcioglu 2007	In this study group allocation was by order of hospital admission (alternate allocation). Not an RCT
Balki 2007	In this study both groups received the same drug (remifentanil) by PCA. The focus of the study was on variation in the bolus size versus variation in the background infusion rate. Studies that examine variation in mode of administration will be considered in a separate related Cochrane review
Balki 2012	In this study both groups had opioids (remifentanil administration in the form of either an infusion or PCA demand bolus (intravenous injection of a single dose over a short period of time)
Ballas 1976	There was no evidence that this study was an RCT. There were 3 study groups and all 3 received pethidine (1 after 1-hour delay). The aim of the study was to monitor uterine activity over 60 minutes
Bare 1962	This study examined the effects of hydroxine hydrochloride, an antihistamine. None of the study groups received an opioid analgesic drug
Bhatia 2013	IM tramadol was compared with IV paracetamol. The comparison of opiates with non-opioid drugs is not a relevant comparison for this review
Bredow 1992	This study was not an RCT. Alternate allocation to groups.

(*Continued*)

Brelje 1966	This was a quasi-randomised study with group allocation by month of birth. The aim of the study was to look at hydroxine as an adjunct to pethidine. both study groups had pethidine
Brookes 2013	This trial compares different routes of administration as well as different drugs
Busacca 1982	In this study, 1 group received pethidine with promethazine and 1 received no treatment. As the opioid group received a combination of drugs any differences between groups may have been due to the effect of the add-on drug
Cahal 1960	This study had 3 groups: SC pethidine, SC benzethidine and SC flurethidine. We are not aware that, apart from pethidine, these drugs are used any longer for pain relief in labour
Calderon 2006	In this study, 1 group received IV remifentanil and 1 group received IM pethidine with haloperidol. With 1 group receiving an add-on drug it would not be possible to compare the effects of the 2 opioids
Callaghan 1966	In this study pethidine was compared with the use of a sedative. It was not clear that this was an RCT
Camann 1992	This study compared IV sufentanil with epidural analgesia. Epidural analgesia in labour is covered in a related Cochrane review
Castro 2004	This study was for pain relief during second trimester labour for termination of pregnancy and so not for pain relief for labour of childbirth
Cavanagh 1966	This study had 4 groups: pethidine IM, anileridine IM, pethidine + perphenazine IM and anileridine + perphenazine IM. We are not aware that anileridine is used any longer in obstetric practice
Chandnani 2013	It was not clear whether or not this was a randomised trial. Women were divided into 2 equal-sized groups but there was no indication that allocation was random
Chang 1976	It was not clear that participants in this trial were all in labour. The aim of the study was to examine fetal acid balance, with maternal and fetal blood sampling 30 and 60 minutes after administering the drugs. No other outcomes were recorded
Cincadze 1978	Brief conference abstract. It was not clear that this was an RCT. We attempted to trace the authors for more information without success
Cullhed 1961	This was not an RCT. Groups were divided into groups according to date of hospital attendance
Dahiya 2015	IM tramadol was compared with IV paracetamol. The comparison of opiates with non-opioid drugs is not a relevant comparison for this review
Dan 1991	In this study 1 group received IV nalbuphine and the other pethidine with promethazine, as the pethidine group had an add-on drug it is not possible to compare the 2 opioids
De Kornfeld 1964	This study was excluded for methodological reasons; there was extremely high attrition for some outcomes (> 50%). SC pethidine and placebo were compared in this study; however, it appeared that the drugs were administered very late in labour. Of 224 women included in the analysis, it appeared that more than half had given birth within an hour of drug administration. There were data on pain relief for only approximately

(*Continued*)

	103 women at 1 hour. Results were very difficult to interpret
De Lamerens 1964	All study groups received pethidine. The aim of the study was to examine the effects of tranquillisers as adjuncts to analgesics
Eames 1964	This study had 2 groups: pethidine 100 mg IM and oxymorphone 1.5 mg IM. Oxymorphone is no longer used for pain relief in labour
Easton 2016	The trial registration refers to "crossover assignment" in the methods. Cross-over trials are not eligible for inclusion in this review
El Kinawy 2015b	This study compares pethidine with an NSAID; this is not a eligible comparison for this review
El-Kerdawy 2010	This study compared opioids with epidural analgesia. Epidural analgesia in labour is covered in a related Cochrane review
Elbohoty 2012	IV pethidine was compared with IV paracetamol. The comparison of opiates with non-opioid drugs is not a relevant comparison for this review
Elhalwagy 2017	This study examines ketamine which is not an opioid.
Eliot 1975	There was no evidence that there was random allocation in this study. There were 2 study groups and both received pethidine, the aim of the study was to compare drugs administered as an adjunct to the opioid analgesia (diazepam vs promazine)
Evron 2005	In this study 2 different drugs using different modes of administration were compared. IV pethidine (with dummy PCA) was compared with PCA remifentanil (with dummy background IV infusion). With both the drug and method being different in each arm of the trial results from this study are very difficult to interpret
Evron 2007	PCA IV pethidine was compared with epidural analgesia.
Evron 2008	In this study with 4 different treatment arms, 1 group received IV remifentanil, the remaining 3 received epidural analgesia. Epidurals are covered in a separate Cochrane review
Fernandez 2015	In this study pethidine was given with haloperidol compared with a birth ball. The addition of haloperidol means this comparison is not relevant for this review
Fleet 2015	In this study all the 3 groups received fentanyl but in different doses and by different routes of administration
Freeman 2012	PCA remifentanil was compared with epidural (this comparison is eligible for inclusion in a related review)
Gambling 1998	This study compared IV pethidine versus a combined spinal epidural
Ginosar 2003	Study examining IV versus epidural fentanyl.
Goodlin 1988	Entry in trials register. It is not clear that this study was completed. We attempted to contact the author and searched for any published results relating to this trial without success

(*Continued*)

Grandjean 1979	Study examining IV versus epidural analgesia.
Greer 1988	The study evaluated the effects of the interventions on platelet function in the newborn
Gupta 2016	This study is looking at IV paracetamol ad an adjunct to PCA epidural analgesia
Hashemiyan 2014	This study examine an opioid compared with paracetamol. This is not a relevant comparison for this review
Hodgkinson 1978	In this study both randomised groups received pethidine. One group also received naloxone. A third, non-randomised "matched" group received no narcotic drugs
Isenor 1993	In this study both groups received the same drug (pethidine). The focus of the study was on variation in route of administration; IM was compared with PCA (IV) pethidine. Studies that examine variation in mode of administration will be considered in a separate related Cochrane review
John 2013	Study examining cortisol levels in women receiving IV opioid vs epidural. This comparison is eligible for a related review
Jost 2015	This was a cross-over study which is not eligible for inclusion in this review. The study was examining different bolus doses of PCA remifentanil
Kalaskar 2007	No results were reported in this brief abstract. We attempted to contact the author without success
Kaltreider 1967	Only women in preterm labour were recruited to this study. This study was excluded for methodological reasons: there was no information about the number of women randomised and women who received any additional non-study medications were excluded post randomisation. Under these circumstances interpreting the findings of this study are very difficult
Karadjova 2016	IV PCA opioid vs epidural. This comparison is eligible for inclusion in a related review
Kaur 2015	IM opioid (tramadol) was compared with non opioid (IV paracetamol). This comparison is not eligible for inclusion in this review
Khooshideh 2015	Intervention and control were both IV remifentanil, comparing different regimens
Krins 1969	Study participants were not women in labour.
Lallar 2015	IM opioid (tramadol) was compared with non opioid (IV paracetamol). This comparison is not eligible for inclusion in this review
Li 1995	In this study, 2 opioid drugs were compared (tramadol and dihydroetorphine hydrochloride). However, the drugs were administered by different routes (sublingual versus oral) and results are therefore very difficult to interpret
Logtenberg 2017	This study compared PCA remifentanil with epidural; this comparison is not eligible for this review
MacVicar 1960	Not an RCT; consecutive allocation to groups. Study examining the sedative effects of drugs and their effects on memory

(*Continued*)

Malkasian 1967	In this study both groups received pethidine. The focus of the trial was on the use of promethazine versus hydroxyzine as add-on drugs
Marshalov 2012	This study compared and opiate (not clear what drug, route or dose) with epidural. This comparison is not eligible for this review
McDonald 1964	This study included 5 study arms and focused specifically on neonatal serum bilirubin, an outcome not relevant to this review
McGrath 1992	A study examining epidural versus IV analgesia.
McInnes 2004	In this study both groups received the same drug (diamorphine) either by PCA or IM. Studies that examine variation in mode of administration will be considered in a separate related Cochrane review
McQuitty 1967	This study focused on promethazine, promazine and propiomazine ad adjuncts to pethidine. All study groups received pethidine
Moore 1974	It was not clear that this was a randomised trial. Women were paired and then allocated in sequence to 4 study arms
Morgan 2004	This was a pilot study reported as an abstract only and there was too little information on methods and results to assess risk of bias and results did not include outcomes relevant to this review
Morris 1994	Study focusing on IV versus epidural fentanyl.
Nafisi 2006	Study comparing IV pethidine versus epidural.
Ng 2011	Although both the groups received different opioids, the mode of administration was not the same
Nikkola 2000	In this study, women in the 2 arms of the trials were given different drugs with different routes of administration. PCA IV fentanyl was compared with paracervical blockade; 10 mL 0.25% bupivacaine injected into 4 locations in the cervix
Overton 1992	This study comparing sublingual diamorphine with IM pethidine was reported in a brief abstract; no denominators for study groups were provided. We attempted to contact the study author for more information without success
Pandole 2003	In this study, women received either IM tramadol or IM pethidine. It was not clear that this was an RCT
Polley 2000	This study compared IV vs epidural fentanyl (epidural analgesia is the subject of separate Cochrane reviews)
Posner 1960	In this study both groups received pethidine; the focus of the study was on a narcotic antagonist (levallorphan) as an adjunct to pethidine
Powe 1962	All 3 groups in this study received pethidine. The aim of the study was to examine the effects of promethazine and propiomazine as adjuncts to pethidine
Rabie 2006	This study compared the use of IV PCA remifentanil versus epidural

(*Continued*)

Rahimi 2012	This was a cross-over study. This design is not eligible for inclusion in the review
Ransom 1966	This study had 2 groups: pethidine 125 mg IM and oxymorphone 1.25 mg IM
Rayburn 1989	In this study both groups received the same drug (pethidine) by PCA versus nurse administered (IV). Studies that examine variation in mode of administration will be considered in a separate related Cochrane review
Rayburn 1991	In this study both groups received the same drug (fentanyl) 1 group by PCA and 1 nurse administered (IV). Studies that examine variation in mode of administration will be considered in a separate related Cochrane review
Roberts 1957	In this study a mood-enhancing drug (methylpentonol) was compared with an analgesic (pethidine). The outcome was not pain relief but fetal expiratory volume. There was no comparison of analgesic drugs in labour. We are not aware that methylpentonol is any longer used during childbirth
Roberts 1960	In this study both groups received the same IM opioid analgesia (alphaprodine). The study examined the effects of a narcotic antagonist (levallorphan) as an adjunct to the opioid
Robinson 1980	This study compared different ways of administering pethidine (IM vs IV); the IM group received an anti-emetic the IV group did not. 386 women were randomised but there appears to have been serious attrition with complete data for only approximately a third of women randomised. Attrition was mainly due to protocol deviations. With these methodological problems findings from this study are very difficult to interpret
Ron 1984	Study examining the value of promethazine as an adjunct to pethidine. The study did include a placebo group but the only result reported was maternal blood pressure 10 minutes after injection of the drug/ placebo
Rowley 1963	This was a quasi-randomised study. The outcomes collected in this study were neonate bilirubin levels
Sabry 2011	In this study the comparison group received epidural. This comparison is examined in a related review
Samanta 2013	In this study the comparison group received epidural. This comparison is examined in a related review
Savage 1955	Quasi-randomised study with alternate allocation.
Sentnor 1966	This study had 4 groups: pethidine 50 mg, 75 mg or 100 mg IM, oxymorphone 0.75 mg, 1.125 mg or 1. 5 mg, pethidine + noroxymorphone IM and oxymorphone + noroxymorphone IM. Oxymorphone is no longer used in clinical practice
Shahriari 2007	In this study IV remifentanil was compared with IM pethidine. As both the drug and the route were different, we excluded this study as results are difficult to interpret
Singh 2001	Not an RCT.
Solek-Pastuszka 2009	This study compared opioids with epidural analgesia. Epidural analgesia in labour is covered in a related Cochrane review

(*Continued*)

Soontrapa 2002	This was a quasi-randomised study and allocation could be anticipated
Sosa 2004	This study focused on women with dystocia and the use of pethidine to promote progress in labour. Women requiring pain relief were excluded
Spellacy 1966	All study groups received pethidine; the aim of the study was to look at the effects of adjuncts
Stocki 2014	In this study the comparison group received epidural. This comparison is examined in a related review
Stourac 2014	In this study the comparison group received epidural. This comparison is examined in a related review
Suvonnakote 1986	In this study comparing IM pethidine and IM tramadol the report states that the sample was randomly selected, but there was no indication that there was random allocation to groups
Taskin 1993	In this study the focus was on the rate of cervical dilatation rather than pain relief. The study was reported in a brief abstract; we attempted to contact the authors for more information without success
Thurlow 2002	In this study 2 different drugs with different modes of administration were compared. IM pethidine (with an antiemetic) was compared with PCA remifentanil. In view of the different modes of administration we decided to exclude this study as results are very difficult to interpret
Tomlin 1965	It was not clear that the women included in this study were in labour; women were recruited in the third trimester admitted to hospital following complications or "awaiting caesarean section or the birth of multiple pregnancies"
Tournaire 1980	This study, otherwise eligible for the review, focused on the effect of pethidine on the frequency and intensity of uterine contractions and the rate of cervical dilatation; no other outcomes were reported
Treisser 1981	This study did not focus on pain relief in labour; rather, it examined the effects of different drugs on progress in labour for women with dystocia (oxytocin, chlorpromazine, ritodine and pethidine were compared)
Tripti 2006	Quasi-randomised study with alternate allocation.
Vavrinkova 2005	There was no evidence that this was an RCT.
Volmanen 2005	This study compares IV remifentanil with inhaled 50% nitrous oxide in a cross-over trial. Results were not reported separately for the first stage of this trial
Volmanen 2008	This study compared IV remifentanil versus epidural analgesia
Volmanen 2009	This study reported on different regimens of IVPCA remifentanil
Von Vorherr 1963	This study focused on speeding up progress in labour. In this group study groups received oxytocin as well as analgesics and women in the control arm received an higher dose of oxytocin
Walker 1992	In this study pethidine was compared with a NSAID ketorolac. Ketorolac is not used nowadays in obstetric analgesia

(*Continued*)

Wan 1965	Both study groups received pethidine; the aim of the study was to look at the effects of a sedative as an adjuvant therapy
Weissman 2006	The comparison group in this study received epidural; this is not a relevant comparison in this review
Wiener 1979	In this study epidural analgesia was compared with IM pethidine. It was not clear that this was an RCT
Williams 1962	Both groups in this study received pethidine. The aim of the study was to examine the effects of a narcotic antagonist (levallorphan) as an adjunct to pethidine
Wilson 2016	In this study different opioids were compared but the route of administration was also different
Wong 2005	This study is reported in a series of papers and conference abstracts. The study examined the use of an intrathecal opioid as part of a combined spinal epidural compared to a systemic opioid. Epidural analgesia is covered in a separate related Cochrane review

IM: intramuscular
IV: intravenous
NSAID: non-steroidal anti-inflammatory drug
PCA: patient controlled analgesia
RCT: randomised controlled trial
SC: subcutaneous

Characteristics of studies awaiting assessment *[ordered by study ID]*

Mohan 2015

Methods	Unclear
Participants	Unclear
Interventions	Unclear
Outcomes	Unclear
Notes	This report is awaiting classification pending further investigation

Sereshti 2013

Methods	RCT with individual randomisation
Participants	120 women randomised.

Sereshti 2013 (*Continued*)

Interventions	Group 1: massage Group 2: intramuscular pethidine Group 3: standard care
Outcomes	Pain intensity Duration of labour only
Notes	Setting: Valiasr hospital in Broojen, Iran Abstract only, full-text awaiting translation.

RCT: randomised controlled trial

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

Kokki 2015

Trial name or title	The effect of oxycodone to placental and fetal circulation during the phase I of labour and the efficacy, safety and neonatal effects of oxycodone
Methods	Clinical trial (methods not clear)
Participants	Women at the onset of labour
Interventions	IV oxycodone versus placebo
Outcomes	Fetal circulation and condition of the newborn.
Starting date	Not clear
Contact information	Dr Kokki at Kuopio University Hospital, Finland. Merja.Kokki@kuh.fi Author contacted 26th June 2017.
Notes	

Raheja 2016

Trial name or title	Tramadol for labour analgesia in low-risk women: a placebo controlled randomised trial
Methods	Placebo controlled RCT with parallel assignment
Participants	86 women in labour
Interventions	50 mg IM tramadol vs placebo (IV water)

Raheja 2016 (*Continued*)

Outcomes	Pain (VAS), satisfaction (1-5 Likert), fetal distress, mode of birth, duration of labour
Starting date	December 2018 (completion planned for May 2018
Contact information	aastha_raheja2000@yahoo.com Dr Aastha Raheja, Maulana Azad Medical College
Notes	

Reyes 2013

Trial name or title	Tramadol for labour analgesia in low-risk primiparous women
Methods	Double-blind randomised trial
Participants	Primiparous women with singleton pregnancy in labour with intact membranes
Interventions	Subcutaneous 100 mg tramadol vs placebo
Outcomes	Pain in labour, duration of labour, neonatal outcomes, side effects, oxytocin
Starting date	October 2012. (Reported to be completed by June 2013)
Contact information	Osvaldo A. Reyes T., Saint Thomas Hospital, Panama
Notes	No email address and unable to contact author.

Sahin 2012

Trial name or title	Study of the effectiveness of administration of meperidine on the length of active phase of labour in women
Methods	Clinical trial
Participants	Not clear
Interventions	Not clear
Outcomes	Not clear
Starting date	The recruitment status of this study is unknown. The completion date has passed and the status has not been verified in more than 2 years
Contact information	This study was due for completion in 2012. There is no email address.Orhan SAHIN, M.D., Kanuni Sultan Suleyman Training and Research
Notes	

Shen 2008

Trial name or title	Intravenous Remifentanil for Labour Analgesia (IRELAN)
Methods	Reported to be parallel RCT.
Participants	Planned enrolment 1000 nulliparous women in spontaneous labour requesting analgesia
Interventions	IV PCA remifentanil versus IV intermittent hydromorphone 1 mg (on request)
Outcomes	Pain (VAS) during labour, mode of birth, maternal satisfaction with analgesia, use of other analgesia, use of oxytocin, breastfeeding at 6 weeks, neonatal outcomes
Starting date	July 2008, planned completion September 2009. There is no evidence that this study was completed. No email address. The record has not been updated since 2009
Contact information	XiaoFeng Shen, Nanjing Medical University
Notes	*ClinicalTrials.gov: NCT00710086*

IV: intravenous
RCT: randomised controlled trial:
PCA: patient-controlled analgesia
VAS: visual analogue scale

DATA AND ANALYSES

Comparison 1. IM pethidine 50 mg/100 mg versus placebo

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Maternal satisfaction with analgesia measured during labour (number of women satisfied or very satisfied after 30 minutes)	1	50	Risk Ratio (M-H, Fixed, 95% CI)	7.0 [0.38, 128.87]
2 Maternal pain score or pain measured in labour (described as good or fair after 1 hour)	1	116	Risk Ratio (M-H, Fixed, 95% CI)	1.75 [1.24, 2.47]
3 Maternal pain score or pain measured in labour (reduction in VAS of at least 40 mm after 30 minutes)	1	50	Risk Ratio (M-H, Fixed, 95% CI)	25.0 [1.56, 400.54]
4 Additional analgesia required	1	50	Risk Ratio (M-H, Fixed, 95% CI)	0.71 [0.54, 0.94]
5 Epidural	1	50	Risk Ratio (M-H, Fixed, 95% CI)	0.5 [0.14, 1.78]
6 Nausea and vomiting	2	166	Risk Ratio (M-H, Fixed, 95% CI)	1.47 [0.65, 3.31]
7 Maternal sleepiness	2	166	Risk Ratio (M-H, Fixed, 95% CI)	4.67 [2.43, 8.95]
8 Assisted vaginal delivery	1	50	Risk Ratio (M-H, Fixed, 95% CI)	0.86 [0.34, 2.19]
9 Caesarean section	2	140	Risk Ratio (M-H, Fixed, 95% CI)	0.71 [0.36, 1.37]
10 Neonatal resuscitation	1	50	Risk Ratio (M-H, Fixed, 95% CI)	1.67 [0.45, 6.24]
11 Low Apgar score (≤ 7) at 1 and 5 minutes	3		Risk Ratio (M-H, Random, 95% CI)	Subtotals only
11.1 Low scores at 1 minute	2	166	Risk Ratio (M-H, Random, 95% CI)	1.64 [0.52, 5.18]
11.2 Low scores at 5 minutes	2	200	Risk Ratio (M-H, Random, 95% CI)	0.0 [0.0, 0.0]
12 Admission to NICU	1	50	Risk Ratio (M-H, Fixed, 95% CI)	1.0 [0.07, 15.12]

Comparison 2. IM pentazocine versus placebo

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Maternal pain score measured during labour	1	89	Mean Difference (IV, Fixed, 95% CI)	-3.60 [-9.91, 2.71]
2 Nausea and vomiting	1	89	Risk Ratio (M-H, Fixed, 95% CI)	0.0 [0.0, 0.0]
3 Caesarean section	1	89	Risk Ratio (M-H, Fixed, 95% CI)	0.89 [0.24, 3.35]
4 Assisted vaginal birth	1	89	Risk Ratio (M-H, Fixed, 95% CI)	0.60 [0.10, 3.39]

Comparison 3. IM tramadol versus no treatment

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Maternal satisfaction with analgesia (Analgesic effect described as satisfactory (not clear when measured))	1	60	Risk Ratio (M-H, Fixed, 95% CI)	11.0 [0.64, 190.53]

Comparison 4. IM meptazinol versus pethidine

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Maternal pain score or pain measured in labour (Maternal pain relief poor or none (3-5 PN))	1	801	Risk Ratio (M-H, Fixed, 95% CI)	1.01 [0.91, 1.12]
2 Maternal pain score or pain measured in labour (Pain intensity 4 or 5 on 5-point scale (1 hour))	2	239	Risk Ratio (M-H, Random, 95% CI)	1.11 [0.69, 1.80]
3 Additional analgesia required	2	233	Risk Ratio (M-H, Fixed, 95% CI)	1.03 [0.88, 1.20]
4 Epidural	4	788	Risk Ratio (M-H, Fixed, 95% CI)	0.96 [0.71, 1.29]
5 Maternal sleepiness	3	1590	Risk Ratio (M-H, Random, 95% CI)	0.55 [0.28, 1.07]
6 Nausea and vomiting	3		Risk Ratio (M-H, Fixed, 95% CI)	Subtotals only
6.1 Nausea	3	1590	Risk Ratio (M-H, Fixed, 95% CI)	1.11 [0.95, 1.28]
6.2 Vomiting	3	1589	Risk Ratio (M-H, Fixed, 95% CI)	1.25 [1.06, 1.47]
7 Caesarean section	3	1266	Risk Ratio (M-H, Random, 95% CI)	0.56 [0.16, 2.00]
8 Assisted vaginal birth	3	1266	Risk Ratio (M-H, Fixed, 95% CI)	1.00 [0.81, 1.22]
9 Breastfeeding at discharge (problems)	1	197	Risk Ratio (M-H, Fixed, 95% CI)	0.76 [0.17, 3.30]
10 Fetal heart rate changes (decelerations)	1	34	Risk Ratio (M-H, Fixed, 95% CI)	1.23 [0.92, 1.64]
11 Naloxone administration	1	998	Risk Ratio (M-H, Fixed, 95% CI)	0.89 [0.77, 1.02]
11.1 < 36 weeks' gestation	1	23	Risk Ratio (M-H, Fixed, 95% CI)	0.96 [0.49, 1.89]
11.2 ≥ 36 weeks' gestation	1	975	Risk Ratio (M-H, Fixed, 95% CI)	0.89 [0.77, 1.02]
12 Neonatal resuscitation (by gestation)	2	1356	Risk Ratio (M-H, Fixed, 95% CI)	1.00 [0.95, 1.05]
12.1 < 36 weeks' gestation	1	23	Risk Ratio (M-H, Fixed, 95% CI)	0.89 [0.69, 1.16]
12.2 ≥ 36 weeks' gestation	2	1333	Risk Ratio (M-H, Fixed, 95% CI)	1.00 [0.95, 1.05]
13 Neonatal resuscitation	1	100	Risk Ratio (M-H, Fixed, 95% CI)	1.5 [0.26, 8.60]
14 Apgar score ≤ 7 at 1 minute	6	791	Risk Ratio (M-H, Fixed, 95% CI)	0.79 [0.56, 1.11]
15 Apgar score ≤ 7 at 5 minutes	3	616	Risk Ratio (M-H, Fixed, 95% CI)	0.50 [0.05, 5.37]
16 Admission to NICU	1	199	Risk Ratio (M-H, Fixed, 95% CI)	0.88 [0.48, 1.63]

Comparison 5. IM diamorphine + prochlorperazine versus pethidine + prochlorperazine

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Maternal satisfaction with analgesia in labour measured during the postnatal period (Global assessment of pain relief at 24 hours)	1	133	Risk Ratio (M-H, Fixed, 95% CI)	0.88 [0.67, 1.16]
2 Maternal pain score or pain measured in labour (Pain intensity at 1 hour (moderate or severe))	1	133	Risk Ratio (M-H, Fixed, 95% CI)	0.85 [0.72, 1.01]
3 Additonal analgesia required	1	133	Risk Ratio (M-H, Fixed, 95% CI)	1.35 [0.53, 3.40]
4 Epidural	1	133	Risk Ratio (M-H, Fixed, 95% CI)	1.22 [0.72, 2.07]
5 Maternal sleepiness during labour	1	133	Risk Ratio (M-H, Fixed, 95% CI)	0.93 [0.52, 1.66]
6 Vomiting in labour	1	133	Risk Ratio (M-H, Fixed, 95% CI)	0.39 [0.17, 0.86]
7 Caesarean section	1	133	Risk Ratio (M-H, Fixed, 95% CI)	0.52 [0.10, 2.76]
8 Assisted vaginal birth	1	133	Risk Ratio (M-H, Fixed, 95% CI)	0.96 [0.46, 2.02]
9 Neonatal resuscitation	1	133	Risk Ratio (M-H, Fixed, 95% CI)	1.21 [0.73, 2.02]
10 Apgar < 7 at 1 minute	1	133	Risk Ratio (M-H, Fixed, 95% CI)	0.41 [0.18, 0.91]
11 Apgar < 7 at 5 minutes	1	133	Risk Ratio (M-H, Fixed, 95% CI)	0.35 [0.04, 3.27]
12 Admission to NICU	1	133	Risk Ratio (M-H, Fixed, 95% CI)	0.58 [0.21, 1.64]

Comparison 6. IM tramadol versus pethidine

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Maternal pain score or pain measured in labour (Pain intensity: women with poor pain relief)	4	243	Risk Ratio (M-H, Fixed, 95% CI)	1.56 [1.10, 2.21]
2 Additional analgesia required	3	295	Risk Ratio (M-H, Random, 95% CI)	1.07 [0.60, 1.91]
3 Maternal sleepiness in labour	5	409	Risk Ratio (M-H, Random, 95% CI)	0.57 [0.33, 0.97]
4 Nausea and vomiting in labour	6	454	Risk Ratio (M-H, Random, 95% CI)	0.97 [0.34, 2.76]
5 Caesarean section	3	260	Risk Ratio (M-H, Fixed, 95% CI)	0.71 [0.23, 2.18]
6 Assisted vaginal birth	3	260	Risk Ratio (M-H, Fixed, 95% CI)	0.56 [0.12, 2.56]
7 Neonatal resuscitation	1	90	Risk Ratio (M-H, Fixed, 95% CI)	0.0 [0.0, 0.0]
8 Apgar scores ≤ 7 at 1 and 5 minutes	2		Risk Ratio (M-H, Fixed, 95% CI)	Subtotals only
8.1 Less than 7 at 1 minute	2	250	Risk Ratio (M-H, Fixed, 95% CI)	0.0 [0.0, 0.0]
8.2 Less than 7 at 5 minutes	1	160	Risk Ratio (M-H, Fixed, 95% CI)	0.0 [0.0, 0.0]
9 Neonatal respiratory distress	1	59	Risk Ratio (M-H, Fixed, 95% CI)	2.26 [0.64, 7.89]
10 Admission to NICU	1	59	Risk Ratio (M-H, Fixed, 95% CI)	2.26 [0.64, 7.89]

Comparison 7. IM tramadol + triflupromazine versus pethidine + triflupromazine

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Maternal sleepiness in labour	1	40	Risk Ratio (M-H, Fixed, 95% CI)	2.86 [0.68, 12.12]
2 Nausea and vomiting in labour	1		Risk Ratio (M-H, Fixed, 95% CI)	Subtotals only
2.1 Nausea	1	40	Risk Ratio (M-H, Fixed, 95% CI)	0.82 [0.13, 5.25]
2.2 Vomiting	1	40	Risk Ratio (M-H, Fixed, 95% CI)	0.40 [0.02, 9.35]

Comparison 8. IM dihydrocodeine 50 mg versus pethidine 100 mg

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Maternal pain score or pain measured in labour (Maternal pain relief poor at 1 hour)	1	138	Risk Ratio (M-H, Fixed, 95% CI)	1.09 [0.64, 1.86]
2 Maternal sleepiness in labour	1	138	Risk Ratio (M-H, Fixed, 95% CI)	0.67 [0.43, 1.04]
3 Nausea and vomiting in labour	1	138	Risk Ratio (M-H, Fixed, 95% CI)	0.87 [0.40, 1.88]
4 Apgar ≤ 7 at 1 minute	1	138	Risk Ratio (M-H, Fixed, 95% CI)	0.57 [0.39, 0.84]

Comparison 9. IM pentazocine versus pethidine

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Maternal satisfaction with analgesia measured during labour (Pain relief (good or very good) at delivery)	2	253	Risk Ratio (M-H, Fixed, 95% CI)	1.08 [0.92, 1.27]
2 Maternal pain score or pain measured in labour (Pain relief poor (partial, none or worse))	4		Risk Ratio (M-H, Random, 95% CI)	Subtotals only
2.1 No add-on drugs	3	365	Risk Ratio (M-H, Random, 95% CI)	1.23 [0.74, 2.05]
2.2 With promazine	1	85	Risk Ratio (M-H, Random, 95% CI)	1.53 [0.66, 3.58]
3 Additional analgesia required	2		Risk Ratio (M-H, Fixed, 95% CI)	Subtotals only
3.1 Pentazocine	1	94	Risk Ratio (M-H, Fixed, 95% CI)	0.91 [0.50, 1.65]
3.2 Pentazocine + promazine	1	85	Risk Ratio (M-H, Fixed, 95% CI)	1.67 [0.73, 3.84]
4 Maternal sleepiness in labour	3	391	Risk Ratio (M-H, Fixed, 95% CI)	1.00 [0.89, 1.12]
5 Nausea and vomiting in labour	3		Risk Ratio (M-H, Fixed, 95% CI)	Subtotals only
5.1 Nausea	3	391	Risk Ratio (M-H, Fixed, 95% CI)	0.46 [0.24, 0.90]
5.2 Vomiting	1	73	Risk Ratio (M-H, Fixed, 95% CI)	0.92 [0.27, 3.14]
6 Assisted vaginal birth	2		Risk Ratio (M-H, Fixed, 95% CI)	Subtotals only
6.1 No add-on drugs	1	94	Risk Ratio (M-H, Fixed, 95% CI)	5.22 [0.63, 42.97]
6.2 With promazine	1	85	Risk Ratio (M-H, Fixed, 95% CI)	0.78 [0.23, 2.71]

7 Naloxone administration	1	85	Risk Ratio (M-H, Fixed, 95% CI)	0.49 [0.09, 2.53]
7.1 With promazine	1	85	Risk Ratio (M-H, Fixed, 95% CI)	0.49 [0.09, 2.53]
8 Apgar score ≤ 7 at 1 minute	3		Risk Ratio (M-H, Random, 95% CI)	Subtotals only
8.1 No add-on drugs	2	242	Risk Ratio (M-H, Random, 95% CI)	1.39 [0.06, 32.97]
8.2 With promazine	1	66	Risk Ratio (M-H, Random, 95% CI)	1.13 [0.07, 17.30]
9 Apgar score ≤ 7 at 5 minutes	2		Risk Ratio (M-H, Fixed, 95% CI)	Subtotals only
9.1 No add-on drugs	1	62	Risk Ratio (M-H, Fixed, 95% CI)	0.23 [0.01, 4.54]
9.2 With promazine	1	66	Risk Ratio (M-H, Fixed, 95% CI)	0.38 [0.02, 8.88]

Comparison 10. IM nalbuphine versus pethidine

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Maternal satisfaction with analgesia measured during the postnatal period (numbers dissatisfied)	1	72	Risk Ratio (M-H, Fixed, 95% CI)	0.73 [0.55, 0.96]
2 Maternal satisfaction with analgesia measured during labour (Pain free)	1	40	Risk Ratio (M-H, Fixed, 95% CI)	6.0 [0.79, 45.42]
3 Maternal pain score or pain measured in labour (Pain intensity at 30 minutes: women with severe pain)	1	295	Risk Ratio (M-H, Fixed, 95% CI)	0.86 [0.59, 1.26]
4 Maternal pain score or pain measured in labour (VAS at 60 minutes (at peak of contraction))	1	72	Mean Difference (IV, Fixed, 95% CI)	-8.0 [-18.55, 2.55]
5 Additional analgesia required	1	72	Risk Ratio (M-H, Fixed, 95% CI)	1.26 [0.49, 3.27]
6 Epidural	1	307	Risk Ratio (M-H, Fixed, 95% CI)	1.65 [0.55, 4.94]
7 Maternal sleepiness in labour	1	72	Risk Ratio (M-H, Fixed, 95% CI)	3.78 [0.86, 16.60]
8 Nausea and vomiting in labour	2		Risk Ratio (M-H, Fixed, 95% CI)	Subtotals only
8.1 Nausea	1	301	Risk Ratio (M-H, Fixed, 95% CI)	0.62 [0.42, 0.91]
8.2 Vomiting	1	301	Risk Ratio (M-H, Fixed, 95% CI)	0.41 [0.22, 0.76]
8.3 Nausea and vomiting	1	72	Risk Ratio (M-H, Fixed, 95% CI)	0.41 [0.18, 0.94]
9 Caesarean section	1	310	Risk Ratio (M-H, Fixed, 95% CI)	0.45 [0.12, 1.69]
10 Assisted vaginal birth	2	382	Risk Ratio (M-H, Random, 95% CI)	0.98 [0.25, 3.85]
11 Naloxone administration	1	72	Risk Ratio (M-H, Fixed, 95% CI)	6.63 [0.35, 123.93]
12 Apgar score ≤ 7 at 1 and 5 minutes	2		Risk Ratio (M-H, Random, 95% CI)	Subtotals only
12.1 Low score at 1 minute	2	382	Risk Ratio (M-H, Random, 95% CI)	1.18 [0.72, 1.95]
12.2 Low score at 5 minutes	1	72	Risk Ratio (M-H, Random, 95% CI)	0.47 [0.04, 4.99]
13 Admission to NICU	1	299	Risk Ratio (M-H, Fixed, 95% CI)	1.07 [0.61, 1.89]
14 Neonatal neurobehavioural (Scanlon) 2-4 hours PN	1	72	Mean Difference (IV, Fixed, 95% CI)	-3.70 [-6.14, -1.26]

Comparison 11. IM phenazocine versus pethidine

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Epidural	1	212	Risk Ratio (M-H, Fixed, 95% CI)	1.31 [0.58, 2.97]
2 Vomiting	1	212	Risk Ratio (M-H, Fixed, 95% CI)	0.39 [0.20, 0.78]

Comparison 12. IM diamorphine/morphine versus pethidine

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Maternal satisfaction with analgesia (number of women satisfied or very satisfied)	1	484	Risk Ratio (M-H, Fixed, 95% CI)	1.13 [1.02, 1.26]
2 Maternal satisfaction with analgesia measured during labour or during the postnatal period (Pain relief described as poor)	1	90	Risk Ratio (M-H, Fixed, 95% CI)	1.22 [0.56, 2.66]
3 Maternal pain score or pain measured in labour (pain relief at 30 mins)	1	484	Mean Difference (IV, Fixed, 95% CI)	-0.80 [-1.24, -0.36]
4 Maternal pain score or pain measured in labour (pain relief at 60 mins)	1	484	Mean Difference (IV, Fixed, 95% CI)	-0.80 [-1.26, -0.34]
5 Additional analgesia required	2	574	Risk Ratio (M-H, Fixed, 95% CI)	1.00 [0.92, 1.10]
6 Maternal sleepiness	1	90	Risk Ratio (M-H, Fixed, 95% CI)	0.6 [0.29, 1.23]
7 Nausea and vomiting	1	90	Risk Ratio (M-H, Fixed, 95% CI)	1.0 [0.21, 4.69]
8 Caesarean section	1	484	Risk Ratio (M-H, Fixed, 95% CI)	0.94 [0.66, 1.35]
9 Assisted vaginal birth	1	484	Risk Ratio (M-H, Fixed, 95% CI)	1.28 [0.91, 1.80]
10 Naloxone administration	1	484	Risk Ratio (M-H, Fixed, 95% CI)	0.98 [0.20, 4.83]
11 Neonatal resuscitation	2	574	Risk Ratio (M-H, Fixed, 95% CI)	0.96 [0.66, 1.41]
12 Apgar < 7 at 1 minute	2	574	Risk Ratio (M-H, Fixed, 95% CI)	1.15 [0.76, 1.73]
13 Admission to NICU	1	484	Risk Ratio (M-H, Fixed, 95% CI)	0.87 [0.34, 2.23]

Comparison 13. IM butorphanol versus pethidine

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Additional analgesia required	1	80	Risk Ratio (M-H, Fixed, 95% CI)	0.89 [0.55, 1.45]
2 Nausea	1	80	Risk Ratio (M-H, Fixed, 95% CI)	0.2 [0.01, 4.04]
3 Vomiting	1	80	Risk Ratio (M-H, Fixed, 95% CI)	0.5 [0.05, 5.30]
4 Neonatal resuscitation	1	80	Risk Ratio (M-H, Fixed, 95% CI)	0.33 [0.01, 7.95]
5 Naloxone administration (neonatal)	1	80	Risk Ratio (M-H, Fixed, 95% CI)	0.33 [0.01, 7.95]

Comparison 14. IM Avacan® versus IM pentazocine

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Additional analgesia required - Entonox	1	160	Risk Ratio (M-H, Fixed, 95% CI)	0.92 [0.53, 1.63]
2 Additional analgesia required - pudendal-paracervical block	1	160	Risk Ratio (M-H, Fixed, 95% CI)	2.02 [1.16, 3.53]
3 Caesarean section	1	184	Risk Ratio (M-H, Fixed, 95% CI)	0.63 [0.21, 1.84]
4 Low Apgar score (< 7) "at birth"	1	160	Risk Ratio (M-H, Fixed, 95% CI)	0.59 [0.27, 1.26]

Comparison 15. IM pentazocine versus IM Pethilorfan®

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Maternal pain score measured during labour (Pain relief (women NOT obtaining pain relief) at 1 hour)	1	69	Risk Ratio (M-H, Fixed, 95% CI)	1.22 [0.77, 1.95]
2 Additional analgesia required	1	98	Risk Ratio (M-H, Fixed, 95% CI)	0.52 [0.10, 2.71]
3 Assisted vaginal birth	1	98	Risk Ratio (M-H, Fixed, 95% CI)	1.04 [0.07, 16.19]
4 Apgar < 8 at 1 minute (non pre-specified)	1	82	Risk Ratio (M-H, Fixed, 95% CI)	5.71 [0.72, 45.39]
5 Apgar < 8 at 5 minutes (non pre-specified)	1	82	Risk Ratio (M-H, Fixed, 95% CI)	0.0 [0.0, 0.0]

Comparison 16. IM pentazocine versus complementary and alternate medicine (CAM)

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Maternal pain score measured during labour	1	89	Mean Difference (IV, Fixed, 95% CI)	-0.40 [-7.61, 6.81]
2 Nausea and vomiting	1	89	Risk Ratio (M-H, Fixed, 95% CI)	0.30 [0.01, 7.14]
3 Caesarean section	1	89	Risk Ratio (M-H, Fixed, 95% CI)	0.89 [0.24, 3.35]
4 Assisted vaginal delivery	1	89	Risk Ratio (M-H, Fixed, 95% CI)	0.89 [0.13, 6.07]

Comparison 17. IM pentazocine versus IM tramadol

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Maternal satisfaction with analgesia measured during labour (pain relief after 30 mins)	1	100	Risk Ratio (M-H, Fixed, 95% CI)	2.4 [1.28, 4.48]
2 Maternal satisfaction with analgesia measured during labour (pain after 60 mins)	1	100	Risk Ratio (M-H, Fixed, 95% CI)	1.62 [0.91, 2.86]
3 Maternal pain score or pain measured in labour (moderate or severe at 30 mins)	1	100	Risk Ratio (M-H, Fixed, 95% CI)	0.75 [0.55, 1.02]
4 Maternal pain score or pain measured in labour (moderate or severe at 60 mins)	1	100	Risk Ratio (M-H, Fixed, 95% CI)	0.81 [0.60, 1.08]
5 Maternal sleepiness during labour	1	100	Risk Ratio (M-H, Fixed, 95% CI)	1.67 [0.66, 4.24]
6 Nausea and vomiting	1	100	Risk Ratio (M-H, Fixed, 95% CI)	1.0 [0.06, 15.55]
7 Caesarean section	1	100	Risk Ratio (M-H, Fixed, 95% CI)	1.5 [0.45, 4.99]
8 Assisted vaginal delivery	1	100	Risk Ratio (M-H, Fixed, 95% CI)	2.0 [0.19, 21.36]
9 Apgar score < 7 at 1 minute	1	100	Risk Ratio (M-H, Fixed, 95% CI)	1.67 [0.42, 6.60]
10 Apgar score < 7 at 5 minutes	1	100	Risk Ratio (M-H, Fixed, 95% CI)	3.0 [0.13, 71.92]
11 Admission to NICU	1	86	Risk Ratio (M-H, Fixed, 95% CI)	2.87 [0.12, 68.47]

Comparison 18. IM pethidine versus Entonox

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Maternal pain score or pain measured in labour (after 30 mins)	1	100	Mean Difference (IV, Fixed, 95% CI)	1.66 [1.17, 2.15]
2 Maternal pain score or pain measured in labour (after 60 mins)	1	100	Mean Difference (IV, Fixed, 95% CI)	-0.36 [-0.85, 0.13]

Comparison 19. IV pethidine versus placebo

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Maternal pain score or pain measured in labour (Pain score 30 mins post analgesia)	1	240	Mean Difference (IV, Fixed, 95% CI)	-4.1 [-4.56, -3.64]
2 Nausea and vomiting	1	240	Risk Ratio (M-H, Fixed, 95% CI)	2.43 [1.05, 5.64]
3 Caesarean section	1	240	Risk Ratio (M-H, Fixed, 95% CI)	0.88 [0.46, 1.68]
4 Assisted vaginal birth	1	240	Risk Ratio (M-H, Fixed, 95% CI)	0.75 [0.33, 1.71]
5 Admission to NICU	1	240	Risk Ratio (M-H, Fixed, 95% CI)	0.67 [0.11, 3.92]

Comparison 20. IV fentanyl versus no treatment

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Maternal pain score or pain measured in labour (Pain score 1 hour post-analgesia)	1	70	Mean Difference (IV, Fixed, 95% CI)	-5.0 [-5.47, -4.53]
2 Maternal pain score or pain measured in labour (Pain intensity (Severe) after 1 hour)	1	70	Risk Ratio (M-H, Fixed, 95% CI)	0.02 [0.00, 0.25]
3 Caesarean section	1	70	Risk Ratio (M-H, Fixed, 95% CI)	1.5 [0.27, 8.43]

Comparison 21. IV fentanyl versus IV pethidine

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Maternal pain score or pain measured in labour (Pain score 1 hour after drug administration)	1	105	Mean Difference (IV, Fixed, 95% CI)	-0.20 [-1.18, 0.78]
2 Mean doses of analgesia (non pre-specified)	1	105	Mean Difference (IV, Fixed, 95% CI)	0.40 [0.14, 0.66]
3 Maternal sleepiness in labour (sedation)	1	105	Risk Ratio (M-H, Fixed, 95% CI)	0.05 [0.00, 0.82]
4 Nausea and/or vomiting	1	105	Risk Ratio (M-H, Fixed, 95% CI)	0.51 [0.17, 1.55]
5 Anti-emetic required (non pre-specified)	1	105	Risk Ratio (M-H, Fixed, 95% CI)	0.09 [0.01, 1.52]
6 Caesarean section	1	105	Risk Ratio (M-H, Fixed, 95% CI)	1.14 [0.24, 5.40]
7 Naloxone administered	1	105	Risk Ratio (M-H, Fixed, 95% CI)	0.16 [0.02, 1.28]
8 Babies requiring resuscitation/ventilatory support	1	105	Risk Ratio (M-H, Fixed, 95% CI)	1.03 [0.46, 2.32]
9 Apgar score < 7 at 1 minute	1		Risk Ratio (M-H, Fixed, 95% CI)	Subtotals only
10 Apgar score < 7 at 5 minutes	1		Risk Ratio (M-H, Fixed, 95% CI)	Subtotals only
11 Neurobehavioural score (1 - 2 hours after delivery)	1	105	Mean Difference (IV, Fixed, 95% CI)	1.30 [0.15, 2.45]
12 Neurobehavioural score (2 hours - 24 hours)	1	105	Mean Difference (IV, Fixed, 95% CI)	0.90 [-0.42, 2.22]

Comparison 22. IV nalbuphine versus IV pethidine

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Caesarean section	1	28	Risk Ratio (M-H, Fixed, 95% CI)	5.0 [0.26, 95.61]
2 Apgar score < 7 at 1 minute	1		Risk Ratio (M-H, Fixed, 95% CI)	Subtotals only
3 Apgar score < 7 at 5 minutes	1		Risk Ratio (M-H, Fixed, 95% CI)	Subtotals only

Comparison 23. IV phenazocine versus IV pethidine

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Maternal satisfaction with analgesia measured during labour (women with fair or poor relief)	1	194	Risk Ratio (M-H, Fixed, 95% CI)	0.72 [0.48, 1.10]
2 Nausea with vomiting	1	194	Risk Ratio (M-H, Fixed, 95% CI)	0.4 [0.08, 2.01]
3 Perinatal death	1	194	Risk Ratio (M-H, Fixed, 95% CI)	0.0 [0.0, 0.0]
4 Apgar score < 7 at 1 minute	1	194	Risk Ratio (M-H, Fixed, 95% CI)	0.0 [0.0, 0.0]

Comparison 24. IV butorphanol versus IV pethidine

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Maternal pain score or pain measured in labour (Pain relief score)	1	80	Mean Difference (IV, Fixed, 95% CI)	0.67 [0.25, 1.09]
2 Maternal pain score or pain measured in labour (Pain score (1 hour after drug administration))	1	80	Mean Difference (IV, Fixed, 95% CI)	-0.60 [-1.02, -0.18]
3 Additional analgesia required	1	100	Risk Ratio (M-H, Fixed, 95% CI)	0.96 [0.63, 1.45]
4 Epidural	1	200	Risk Ratio (M-H, Fixed, 95% CI)	1.0 [0.30, 3.35]
5 Nausea and/or vomiting	1	200	Risk Ratio (M-H, Fixed, 95% CI)	0.04 [0.00, 0.67]
6 Caesarean section	1	200	Risk Ratio (M-H, Fixed, 95% CI)	0.8 [0.22, 2.89]
7 Assisted vaginal birth	1	200	Risk Ratio (M-H, Fixed, 95% CI)	1.3 [0.60, 2.83]
8 Apgar score < 7 at 1 minute	2		Risk Ratio (M-H, Fixed, 95% CI)	Subtotals only
9 Apgar score < 7 at 5 minutes	2		Risk Ratio (M-H, Fixed, 95% CI)	Subtotals only

Comparison 25. IV morphine versus IV pethidine

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Maternal satisfaction with analgesia (assessed 3 days postpartum)	1	141	Risk Ratio (M-H, Fixed, 95% CI)	0.87 [0.78, 0.98]
2 Additional analgesia required	1	143	Risk Ratio (M-H, Fixed, 95% CI)	3.41 [1.90, 6.12]
3 Nausea and vomiting	1		Risk Ratio (M-H, Fixed, 95% CI)	Subtotals only
3.1 Nausea	1	20	Risk Ratio (M-H, Fixed, 95% CI)	0.17 [0.02, 1.14]
3.2 Vomiting	1	20	Risk Ratio (M-H, Fixed, 95% CI)	0.25 [0.03, 1.86]
4 Caesarean section	1	20	Risk Ratio (M-H, Fixed, 95% CI)	0.0 [0.0, 0.0]

Comparison 26. IV Nisentil versus IV pethidine

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Nausea and vomiting	1		Risk Ratio (M-H, Fixed, 95% CI)	Subtotals only
1.1 Nausea	1	395	Risk Ratio (M-H, Fixed, 95% CI)	0.71 [0.33, 1.52]
1.2 Vomiting	1	395	Risk Ratio (M-H, Fixed, 95% CI)	0.38 [0.22, 0.66]
2 Neonatal resuscitation/ventilatory support	1	395	Risk Ratio (M-H, Fixed, 95% CI)	1.99 [0.85, 4.63]

Comparison 27. IV fentanyl versus IV butorphanol

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Additional analgesia required	1	100	Risk Ratio (M-H, Fixed, 95% CI)	1.39 [1.05, 1.85]
2 Epidural	1	100	Risk Ratio (M-H, Fixed, 95% CI)	2.0 [1.00, 4.02]
3 Matenal sleepiness (required tactile rousing)	1	100	Risk Ratio (M-H, Fixed, 95% CI)	3.0 [0.64, 14.16]
4 Caesarean section	1	100	Risk Ratio (M-H, Fixed, 95% CI)	0.8 [0.23, 2.81]
5 Naloxone required	1	100	Risk Ratio (M-H, Fixed, 95% CI)	1.75 [0.81, 3.80]
6 Neonatal resuscitation (Babies requiring ventilatory support)	1	100	Risk Ratio (M-H, Fixed, 95% CI)	11.0 [0.62, 193.80]
7 Apgar score < 7 at 5 minutes	1	100	Risk Ratio (M-H, Fixed, 95% CI)	1.2 [0.39, 3.68]
8 Newborn neurobehavioural score at 2-4 hours	1	100	Mean Difference (IV, Fixed, 95% CI)	0.0 [-1.61, 1.61]
9 Newborn neurobehavioural score at 24-36 hours	1	100	Mean Difference (IV, Fixed, 95% CI)	-0.50 [-1.62, 0.62]

Comparison 28. PCA pentazocine versus PCA pethidine

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Maternal pan score or pain measured in labour	1	23	Mean Difference (IV, Fixed, 95% CI)	-1.45 [-2.96, 0.06]
2 Maternal pan score or pain measured in labour (rated as good one day after birth)	1	28	Risk Ratio (M-H, Fixed, 95% CI)	0.82 [0.51, 1.32]
3 Epidural	1	28	Risk Ratio (M-H, Fixed, 95% CI)	1.5 [0.29, 7.65]
4 Nausea and vomiting	1	29	Risk Ratio (M-H, Fixed, 95% CI)	0.10 [0.01, 1.61]
5 Maternal sleepiness during labour (Sedation)	1	29	Risk Ratio (M-H, Fixed, 95% CI)	0.21 [0.01, 4.09]
6 Caesarean section	1	29	Risk Ratio (M-H, Fixed, 95% CI)	0.36 [0.02, 8.07]

7 Breastfeeding at discharge	1	23	Risk Ratio (M-H, Fixed, 95% CI)	1.0 [0.85, 1.17]
8 Apgar score < 7 at 5 minutes	1	29	Risk Ratio (M-H, Fixed, 95% CI)	0.0 [0.0, 0.0]

Comparison 29. PCA remifentanil versus PCA pethidine

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Maternal pain score in labour	2	122	Mean Difference (IV, Random, 95% CI)	-8.59 [-27.61, 10.44]
2 Additional analgesia required	2	56	Risk Ratio (M-H, Fixed, 95% CI)	0.86 [0.69, 1.08]
3 Epidural	2	122	Risk Ratio (M-H, Fixed, 95% CI)	0.42 [0.20, 0.89]
4 Maternal sleepiness during labour	1	105	Mean Difference (IV, Fixed, 95% CI)	0.40 [0.14, 0.66]
5 Nausea and vomiting	2	119	Risk Ratio (M-H, Fixed, 95% CI)	0.95 [0.61, 1.49]
6 Caesarean section	2	97	Risk Ratio (M-H, Fixed, 95% CI)	1.81 [0.60, 5.46]
7 Assisted vaginal birth	2	97	Risk Ratio (M-H, Fixed, 95% CI)	0.96 [0.46, 2.00]
8 Satisfaction with childbirth experience	1	68	Mean Difference (IV, Fixed, 95% CI)	1.10 [0.46, 1.74]
9 Naloxone administered	2	56	Risk Ratio (M-H, Fixed, 95% CI)	0.3 [0.01, 6.47]
10 Apgar score < 7 at 5 minutes	1	17	Risk Ratio (M-H, Fixed, 95% CI)	0.13 [0.01, 2.16]
11 Admission to NICU	1	17	Risk Ratio (M-H, Fixed, 95% CI)	0.3 [0.01, 6.47]
12 Newborn neurobehavioural score (15 minutes post delivery)	1	56	Mean Difference (IV, Fixed, 95% CI)	0.20 [-0.93, 1.33]
13 Newborn neurobehavioural score (2 hours post delivery)	1	56	Mean Difference (IV, Fixed, 95% CI)	0.60 [-0.66, 1.86]

Comparison 30. PCA nalbuphine versus PCA pethidine

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Maternal satisfaction with analgesia in labour measured during the postnatal period (rated good or excellent)	1	60	Risk Ratio (M-H, Fixed, 95% CI)	1.29 [0.88, 1.89]
2 Maternal satisfaction with analgesia in labour measured during the postnatal period (Would use the same pain relief again)	1	59	Risk Ratio (M-H, Fixed, 95% CI)	1.06 [0.79, 1.43]
3 Maternal pain score or pain measured in labour	1	60	Mean Difference (IV, Fixed, 95% CI)	-0.40 [-0.79, -0.01]
4 Additional analgesia required	1	59	Risk Ratio (M-H, Fixed, 95% CI)	0.83 [0.46, 1.48]
5 Nausea and vomiting	1	59	Risk Ratio (M-H, Fixed, 95% CI)	0.68 [0.30, 1.54]
6 Apgar score < 7 at 5 minutes	1	41	Risk Ratio (M-H, Fixed, 95% CI)	0.42 [0.02, 9.76]

Comparison 31. PCA fentanyl versus PCA alfentanil

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Maternal satisfaction with analgesia in labour measured during the postnatal period (described as adequate)	1	23	Risk Ratio (M-H, Fixed, 95% CI)	1.56 [0.93, 2.60]
2 Maternal pain score or pain measured in labour (Pain score at 4-6 cm cervical dilatation)	1	21	Mean Difference (IV, Fixed, 95% CI)	-12.80 [-32.12, 6.52]
3 Nausea	1	23	Risk Ratio (M-H, Fixed, 95% CI)	2.73 [0.66, 11.30]
4 Caesarean section	1	23	Risk Ratio (M-H, Fixed, 95% CI)	1.64 [0.33, 8.03]
5 Naloxone required	1	24	Risk Ratio (M-H, Fixed, 95% CI)	2.36 [0.53, 10.55]

Comparison 32. PCA fentanyl versus PCA pethidine

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Maternla pain score measured in labour	1	107	Mean Difference (IV, Fixed, 95% CI)	-0.65 [-1.56, 0.26]
2 Epidural	1	107	Risk Ratio (M-H, Fixed, 95% CI)	0.44 [0.21, 0.92]
3 Maternal sleepiness during labour	1	107	Mean Difference (IV, Fixed, 95% CI)	-0.06 [-0.25, 0.13]
4 Nausea and vomiting	1	102	Risk Ratio (M-H, Fixed, 95% CI)	0.87 [0.55, 1.37]
5 Caesarean section	1	81	Risk Ratio (M-H, Fixed, 95% CI)	0.25 [0.03, 2.34]
6 Assisted vaginal birth	1	81	Risk Ratio (M-H, Fixed, 95% CI)	0.57 [0.22, 1.49]
7 Newborn neurobehavioural score (15 minutes post delivery)	1	63	Mean Difference (IV, Fixed, 95% CI)	-0.90 [-2.31, 0.51]
8 Newborn neurobehavioural score (2 hours post delivery)	1	64	Mean Difference (IV, Fixed, 95% CI)	-0.5 [-1.95, 0.95]

Comparison 33. PCA (IM) meptazinol versus PCA (IM) pethidine

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Maternal pain score or pain measured in labour (measured 1 day after delivery)	1	10	Mean Difference (IV, Fixed, 95% CI)	-17.60 [-49.93, 14.73]
2 Satisfied with mode of administration (PCA IM) (non pre-specified)	1	10	Risk Ratio (M-H, Fixed, 95% CI)	1.0 [0.71, 1.41]
3 Epidural	1	10	Risk Ratio (M-H, Fixed, 95% CI)	3.0 [0.15, 59.89]

4 Maternal sleepiness in labour (Drowsiness score in labour rated 1 day after delivery)	1	10	Mean Difference (IV, Fixed, 95% CI)	5.60 [-28.19, 39.39]
5 Nausea (score in labour rated 1 day after delivery)	1	10	Mean Difference (IV, Fixed, 95% CI)	-8.0 [-48.70, 32.70]
6 Naloxone administered	1	10	Risk Ratio (M-H, Fixed, 95% CI)	1.0 [0.08, 11.93]

Comparison 34. Opioids versus TENS

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Maternal satisfaction with analgesia measured post delivery (rated as good)	2	104	Risk Ratio (M-H, Fixed, 95% CI)	1.23 [0.79, 1.92]
2 Maternal pain score measured during labour	2	290	Risk Ratio (M-H, Random, 95% CI)	1.15 [0.81, 1.61]
3 Maternal pain score in labour	1		Mean Difference (IV, Fixed, 95% CI)	Subtotals only
3.1 Pain score (after 30 minutes)	1	60	Mean Difference (IV, Fixed, 95% CI)	-20.0 [-26.09, -13.91]
3.2 Pain score (after 60 minutes)	1	60	Mean Difference (IV, Fixed, 95% CI)	-20.0 [-25.16, -14.84]
4 Maternal sleepiness during labour (Drowsiness)	2	290	Risk Ratio (M-H, Fixed, 95% CI)	8.96 [1.13, 71.07]
5 Nausea and vomiting	3	350	Risk Ratio (M-H, Fixed, 95% CI)	13.73 [2.72, 69.24]
6 Caesarean section	2	260	Risk Ratio (M-H, Fixed, 95% CI)	2.0 [0.19, 20.90]
7 Assisted vaginal birth	2	260	Risk Ratio (M-H, Fixed, 95% CI)	1.8 [0.40, 8.18]
8 Fetal heart rate changes in labour (Fetal distress)	1	200	Risk Ratio (M-H, Fixed, 95% CI)	5.0 [0.24, 102.85]

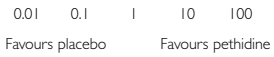
Analysis 1.1. Comparison 1 IM pethidine 50 mg/100 mg versus placebo, Outcome 1 Maternal satisfaction with analgesia measured during labour (number of women satisfied or very satisfied after 30 minutes).

Review: Parenteral opioids for maternal pain management in labour

Comparison: 1 IM pethidine 50 mg/100 mg versus placebo

Outcome: 1 Maternal satisfaction with analgesia measured during labour (number of women satisfied or very satisfied after 30 minutes)

Study or subgroup	Pethidine IM n/N	Placebo n/N	Risk Ratio M-H,Fixed,95% CI	Weight	Risk Ratio M-H,Fixed,95% CI
Tsui 2004 (1)	3/25	0/25		100.0 %	7.00 [0.38, 128.87]
Total (95% CI)	**25**	**25**		**100.0 %**	**7.00 [0.38, 128.87]**
Total events: 3 (Pethidine IM), 0 (Placebo)					
Heterogeneity: not applicable					
Test for overall effect: Z = 1.31 (P = 0.19)					
Test for subgroup differences: Not applicable					



(1) Maternal satisfaction rated as 4 or 5 on rating scale 0-5 where 0 = very disatisfied to 5= very satisfied

Analysis 1.2. Comparison 1 IM pethidine 50 mg/100 mg versus placebo, Outcome 2 Maternal pain score or pain measured in labour (described as good or fair after 1 hour).

Review: Parenteral opioids for maternal pain management in labour

Comparison: 1 IM pethidine 50 mg/100 mg versus placebo

Outcome: 2 Maternal pain score or pain measured in labour (described as good or fair after 1 hour)

Study or subgroup	Pethidine IM n/N	Placebo n/N	Risk Ratio M-H,Fixed,95% CI	Weight	Risk Ratio M-H,Fixed,95% CI
Sliom 1970	42/58	24/58		100.0 %	1.75 [1.24, 2.47]
Total (95% CI)	**58**	**58**		**100.0 %**	**1.75 [1.24, 2.47]**
Total events: 42 (Pethidine IM), 24 (Placebo)					
Heterogeneity: not applicable					
Test for overall effect: Z = 3.18 (P = 0.0015)					
Test for subgroup differences: Not applicable					

Analysis 1.3. Comparison 1 IM pethidine 50 mg/100 mg versus placebo, Outcome 3 Maternal pain score or pain measured in labour (reduction in VAS of at least 40 mm after 30 minutes).

Review: Parenteral opioids for maternal pain management in labour

Comparison: 1 IM pethidine 50 mg/100 mg versus placebo

Outcome: 3 Maternal pain score or pain measured in labour (reduction in VAS of at least 40 mm after 30 minutes)

Study or subgroup	Pethidine IM n/N	Placebo n/N	Risk Ratio M-H,Fixed,95% CI	Weight	Risk Ratio M-H,Fixed,95% CI
Tsui 2004	12/25	0/25		100.0 %	25.00 [1.56, 400.54]
Total (95% CI)	**25**	**25**		**100.0 %**	**25.00 [1.56, 400.54]**
Total events: 12 (Pethidine IM), 0 (Placebo)					
Heterogeneity: not applicable					
Test for overall effect: Z = 2.27 (P = 0.023)					
Test for subgroup differences: Not applicable					

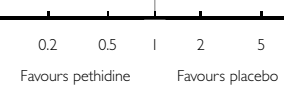
Analysis 1.4. Comparison 1 IM pethidine 50 mg/100 mg versus placebo, Outcome 4 Additional analgesia required.

Review: Parenteral opioids for maternal pain management in labour

Comparison: 1 IM pethidine 50 mg/100 mg versus placebo

Outcome: 4 Additional analgesia required

Study or subgroup	Pethidine IM n/N	Placebo n/N	Risk Ratio M-H,Fixed,95% CI	Weight	Risk Ratio M-H,Fixed,95% CI
Tsui 2004 (1)	17/25	24/25		100.0 %	0.71 [0.54, 0.94]
Total (95% CI)	**25**	**25**		**100.0 %**	**0.71 [0.54, 0.94]**
Total events: 17 (Pethidine IM), 24 (Placebo)					
Heterogeneity: not applicable					
Test for overall effect: Z = 2.41 (P = 0.016)					
Test for subgroup differences: Not applicable					



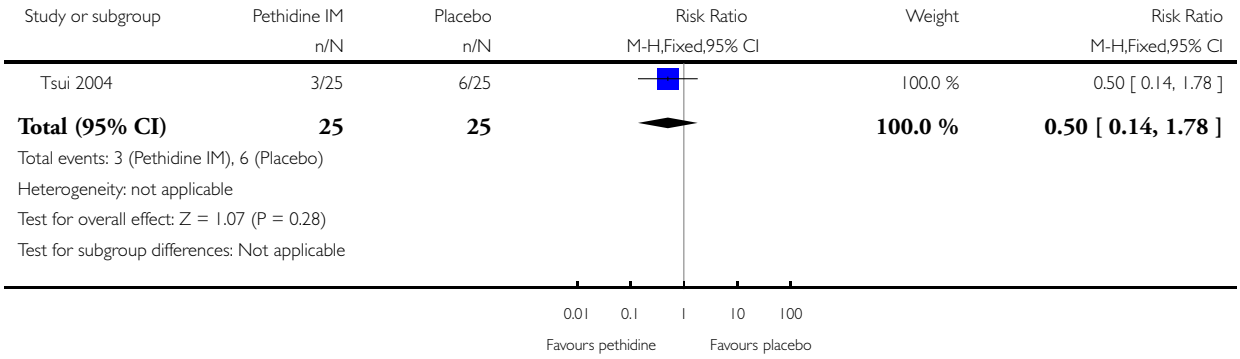
(1) Epidural, pethidine, and Entonox

Analysis 1.5. Comparison 1 IM pethidine 50 mg/100 mg versus placebo, Outcome 5 Epidural.

Review: Parenteral opioids for maternal pain management in labour

Comparison: 1 IM pethidine 50 mg/100 mg versus placebo

Outcome: 5 Epidural

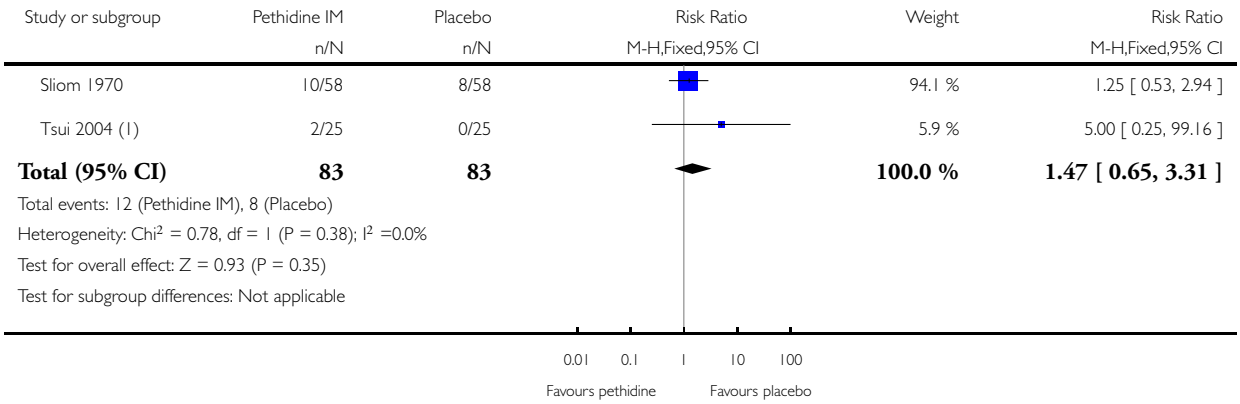


Analysis 1.6. Comparison 1 IM pethidine 50 mg/100 mg versus placebo, Outcome 6 Nausea and vomiting.

Review: Parenteral opioids for maternal pain management in labour

Comparison: 1 IM pethidine 50 mg/100 mg versus placebo

Outcome: 6 Nausea and vomiting



(1) Figures for vomiting only

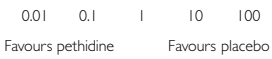
Analysis 1.7. Comparison 1 IM pethidine 50 mg/100 mg versus placebo, Outcome 7 Maternal sleepiness.

Review: Parenteral opioids for maternal pain management in labour

Comparison: 1 IM pethidine 50 mg/100 mg versus placebo

Outcome: 7 Maternal sleepiness

Study or subgroup	Pethidine IM n/N	Placebo n/N	Risk Ratio M-H,Fixed,95% CI	Weight	Risk Ratio M-H,Fixed,95% CI
Sliom 1970	26/58	6/58		66.7 %	4.33 [1.93, 9.74]
Tsui 2004	16/25	3/25		33.3 %	5.33 [1.77, 16.05]
Total (95% CI)	**83**	**83**		**100.0 %**	**4.67 [2.43, 8.95]**
Total events: 42 (Pethidine IM), 9 (Placebo)					
Heterogeneity: Chi^2 = 0.09, df = 1 (P = 0.77); I^2 =0.0%					
Test for overall effect: Z = 4.63 (P < 0.00001)					
Test for subgroup differences: Not applicable					



Analysis 1.8. Comparison 1 IM pethidine 50 mg/100 mg versus placebo, Outcome 8 Assisted vaginal delivery.

Review: Parenteral opioids for maternal pain management in labour

Comparison: 1 IM pethidine 50 mg/100 mg versus placebo

Outcome: 8 Assisted vaginal delivery

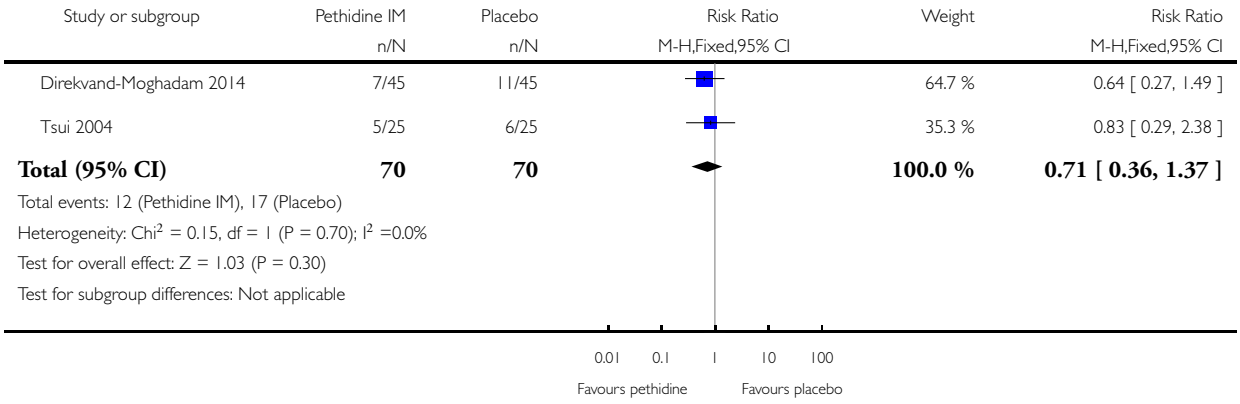
Study or subgroup	Pethidine IM n/N	Placebo n/N	Risk Ratio M-H,Fixed,95% CI	Weight	Risk Ratio M-H,Fixed,95% CI
Tsui 2004	6/25	7/25		100.0 %	0.86 [0.34, 2.19]
Total (95% CI)	**25**	**25**		**100.0 %**	**0.86 [0.34, 2.19]**
Total events: 6 (Pethidine IM), 7 (Placebo)					
Heterogeneity: not applicable					
Test for overall effect: Z = 0.32 (P = 0.75)					
Test for subgroup differences: Not applicable					

Analysis 1.9. Comparison 1 IM pethidine 50 mg/100 mg versus placebo, Outcome 9 Caesarean section.

Review: Parenteral opioids for maternal pain management in labour

Comparison: 1 IM pethidine 50 mg/100 mg versus placebo

Outcome: 9 Caesarean section

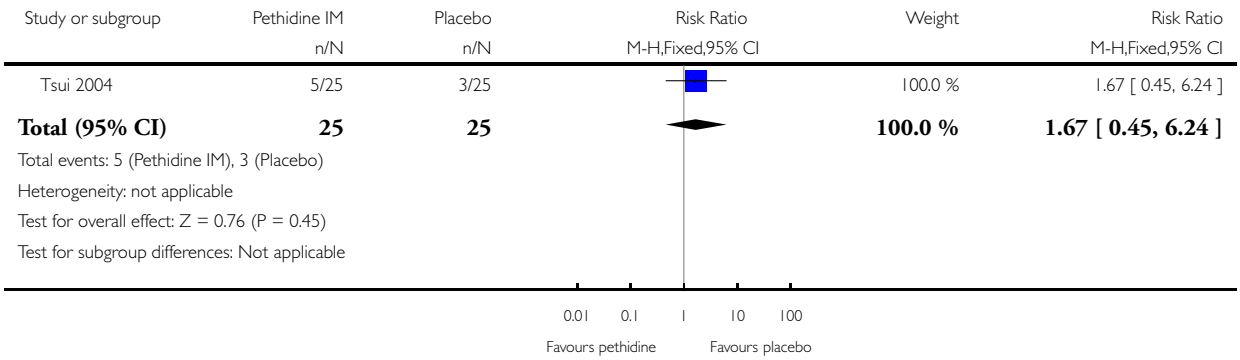


Analysis 1.10. Comparison 1 IM pethidine 50 mg/100 mg versus placebo, Outcome 10 Neonatal resuscitation.

Review: Parenteral opioids for maternal pain management in labour

Comparison: 1 IM pethidine 50 mg/100 mg versus placebo

Outcome: 10 Neonatal resuscitation

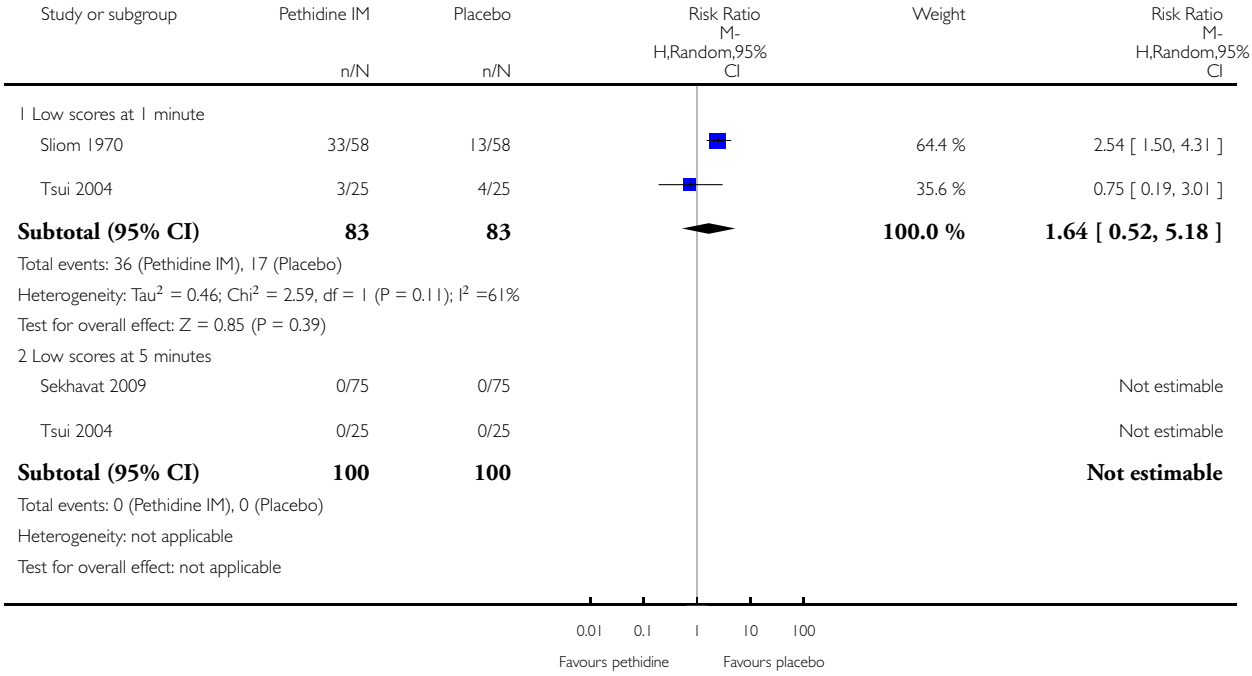


Analysis 1.11. Comparison 1 IM pethidine 50 mg/100 mg versus placebo, Outcome 11 Low Apgar score (≤ 7) at 1 and 5 minutes.

Review: Parenteral opioids for maternal pain management in labour

Comparison: 1 IM pethidine 50 mg/100 mg versus placebo

Outcome: 11 Low Apgar score (≤ 7) at 1 and 5 minutes

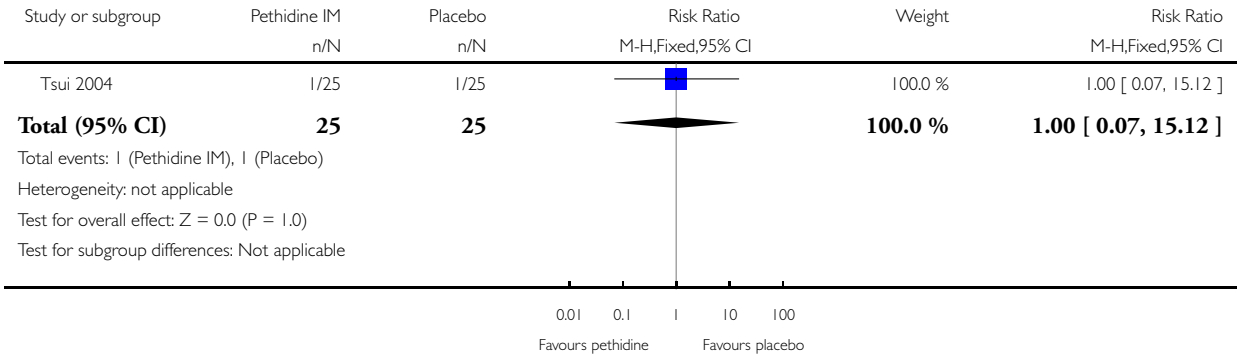


Analysis 1.12. Comparison 1 IM pethidine 50 mg/100 mg versus placebo, Outcome 12 Admission to NICU.

Review: Parenteral opioids for maternal pain management in labour

Comparison: 1 IM pethidine 50 mg/100 mg versus placebo

Outcome: 12 Admission to NICU

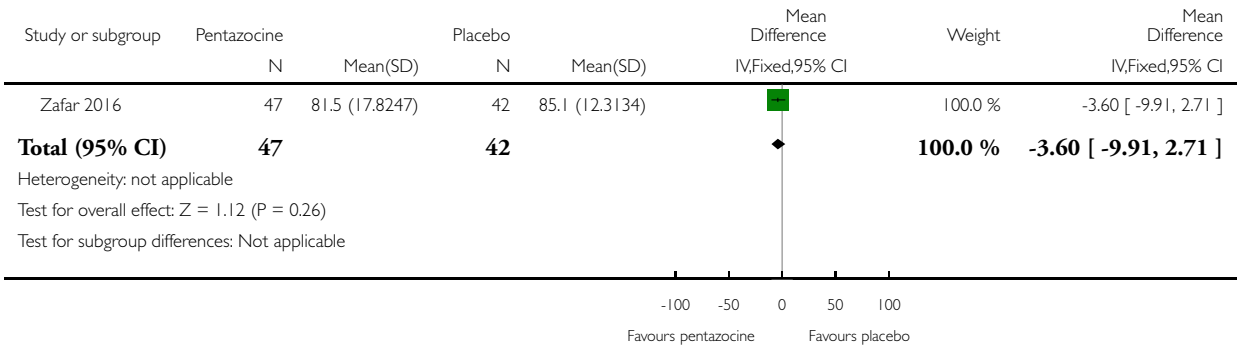


Analysis 2.1. Comparison 2 IM pentazocine versus placebo, Outcome 1 Maternal pain score measured during labour.

Review: Parenteral opioids for maternal pain management in labour

Comparison: 2 IM pentazocine versus placebo

Outcome: 1 Maternal pain score measured during labour

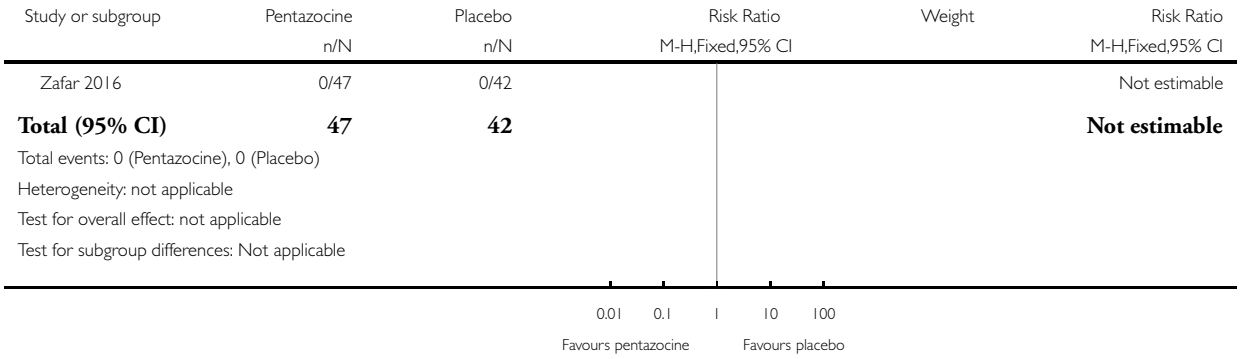


Analysis 2.2. Comparison 2 IM pentazocine versus placebo, Outcome 2 Nausea and vomiting.

Review: Parenteral opioids for maternal pain management in labour

Comparison: 2 IM pentazocine versus placebo

Outcome: 2 Nausea and vomiting

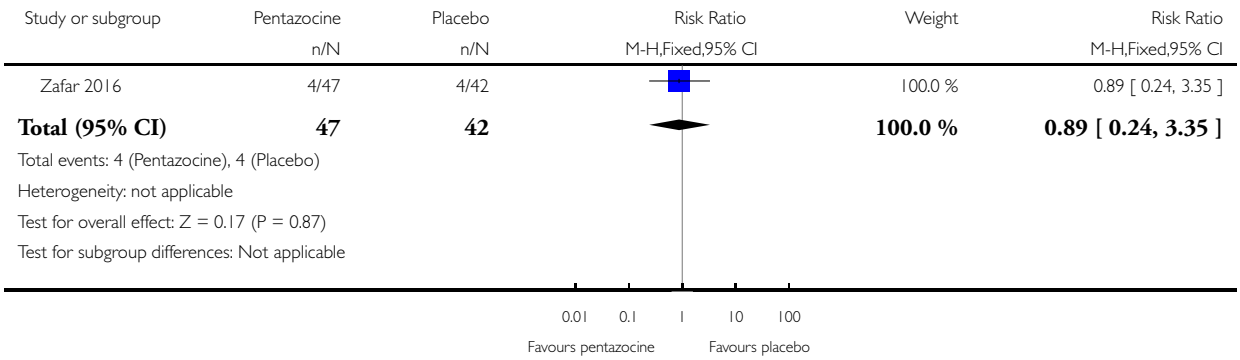


Analysis 2.3. Comparison 2 IM pentazocine versus placebo, Outcome 3 Caesarean section.

Review: Parenteral opioids for maternal pain management in labour

Comparison: 2 IM pentazocine versus placebo

Outcome: 3 Caesarean section

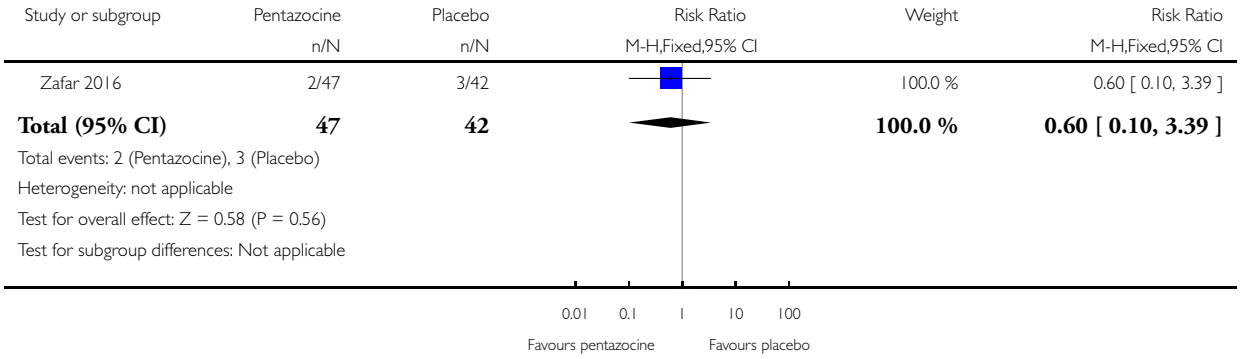


Analysis 2.4. Comparison 2 IM pentazocine versus placebo, Outcome 4 Assisted vaginal birth.

Review: Parenteral opioids for maternal pain management in labour

Comparison: 2 IM pentazocine versus placebo

Outcome: 4 Assisted vaginal birth

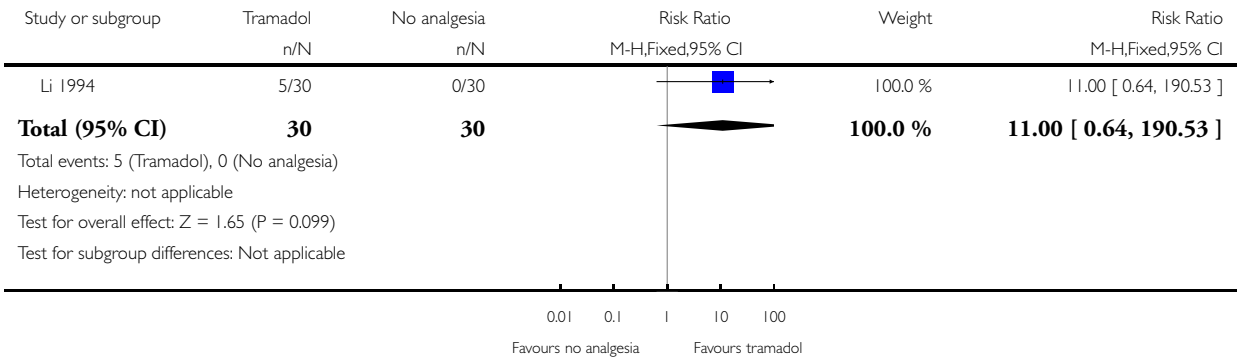


Analysis 3.1. Comparison 3 IM tramadol versus no treatment, Outcome 1 Maternal satisfaction with analgesia (Analgesic effect described as satisfactory (not clear when measured)).

Review: Parenteral opioids for maternal pain management in labour

Comparison: 3 IM tramadol versus no treatment

Outcome: 1 Maternal satisfaction with analgesia (Analgesic effect described as satisfactory (not clear when measured))



Analysis 4.1. Comparison 4 IM meptazinol versus pethidine, Outcome 1 Maternal pain score or pain measured in labour (Maternal pain relief poor or none (3-5 PN)).

Review: Parenteral opioids for maternal pain management in labour

Comparison: 4 IM meptazinol versus pethidine

Outcome: 1 Maternal pain score or pain measured in labour (Maternal pain relief poor or none (3-5 PN))

Study or subgroup	Meptazinol n/N	Pethidine n/N	Risk Ratio M-H,Fixed,95% CI	Weight	Risk Ratio M-H,Fixed,95% CI
Morrison 1987 (1)	255/394	260/407		100.0 %	1.01 [0.91, 1.12]
Total (95% CI)	**394**	**407**		**100.0 %**	**1.01 [0.91, 1.12]**
Total events: 255 (Meptazinol), 260 (Pethidine)					
Heterogeneity: not applicable					
Test for overall effect: Z = 0.25 (P = 0.80)					
Test for subgroup differences: Not applicable					

(1) Post partum assessment of analgesia 3-5 postpartum

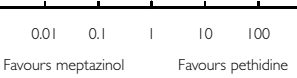
Analysis 4.2. Comparison 4 IM meptazinol versus pethidine, Outcome 2 Maternal pain score or pain measured in labour (Pain intensity 4 or 5 on 5-point scale (1 hour)).

Review: Parenteral opioids for maternal pain management in labour

Comparison: 4 IM meptazinol versus pethidine

Outcome: 2 Maternal pain score or pain measured in labour (Pain intensity 4 or 5 on 5-point scale (1 hour))

Study or subgroup	Meptazinol n/N	Pethidine n/N	Risk Ratio M-H,Random,95% CI	Weight	Risk Ratio M-H,Random,95% CI
Nel 1981	11/34	6/30		22.5 %	1.62 [0.68, 3.84]
Sheikh 1986	78/87	79/88		77.5 %	1.00 [0.90, 1.10]
Total (95% CI)	**121**	**118**		**100.0 %**	**1.11 [0.69, 1.80]**
Total events: 89 (Meptazinol), 85 (Pethidine)					
Heterogeneity: Tau^2 = 0.08; Chi^2 = 1.77, df = 1 (P = 0.18); I^2 =43%					
Test for overall effect: Z = 0.43 (P = 0.66)					
Test for subgroup differences: Not applicable					



Analysis 4.3. Comparison 4 IM meptazinol versus pethidine, Outcome 3 Additional analgesia required.

Review: Parenteral opioids for maternal pain management in labour

Comparison: 4 IM meptazinol versus pethidine

Outcome: 3 Additional analgesia required

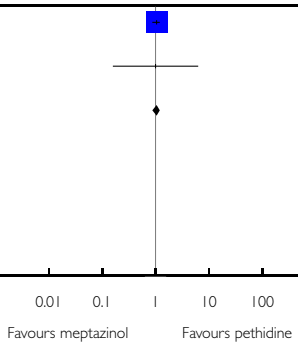
Study or subgroup	Meptazinol n/N	Pethidine n/N	Risk Ratio M-H,Fixed,95% CI	Weight	Risk Ratio M-H,Fixed,95% CI
Osler 1987 (1)	79/100	76/99		97.4 %	1.03 [0.89, 1.19]
Wheble 1988	2/17	2/17		2.6 %	1.00 [0.16, 6.30]
Total (95% CI)	**117**	**116**		**100.0 %**	**1.03 [0.88, 1.20]**

Total events: 81 (Meptazinol), 78 (Pethidine)

Heterogeneity: $Chi^2 = 0.00$, df = 1 (P = 0.98); $I^2 = 0.0\%$

Test for overall effect: Z = 0.36 (P = 0.72)

Test for subgroup differences: Not applicable



(1) For Osler 1987 additional analgesia relates to a pudendal, whereas for Wheble it relates to a second dose of study drug.

Analysis 4.4. Comparison 4 IM meptazinol versus pethidine, Outcome 4 Epidural.

Review: Parenteral opioids for maternal pain management in labour

Comparison: 4 IM meptazinol versus pethidine

Outcome: 4 Epidural

Study or subgroup	Meptazinol n/N	Pethidine n/N	Risk Ratio M-H,Fixed,95% CI	Weight	Risk Ratio M-H,Fixed,95% CI
Nicholas 1982	36/186	37/172		53.9 %	0.90 [0.60, 1.35]
Osler 1987	11/100	9/99		12.7 %	1.21 [0.52, 2.79]
Sheikh 1986	17/98	20/99		27.9 %	0.86 [0.48, 1.54]
Wheble 1988	6/17	4/17		5.6 %	1.50 [0.51, 4.38]
Total (95% CI)	**401**	**387**		**100.0 %**	**0.96 [0.71, 1.29]**

Total events: 70 (Meptazinol), 70 (Pethidine)

Heterogeneity: Chi^2 = 1.20, df = 3 (P = 0.75); I^2 =0.0%

Test for overall effect: Z = 0.26 (P = 0.79)

Test for subgroup differences: Not applicable

Analysis 4.5. Comparison 4 IM meptazinol versus pethidine, Outcome 5 Maternal sleepiness.

Review: Parenteral opioids for maternal pain management in labour

Comparison: 4 IM meptazinol versus pethidine

Outcome: 5 Maternal sleepiness

Study or subgroup	Meptazinol n/N	Pethidine n/N	Risk Ratio M-H,Random,95% CI	Weight	Risk Ratio M-H,Random,95% CI
Morrison 1987	147/513	202/522		63.3 %	0.74 [0.62, 0.88]
Nicholas 1982	4/186	14/172		23.9 %	0.26 [0.09, 0.79]
Sheikh 1986	2/98	4/99		12.8 %	0.51 [0.09, 2.69]
Total (95% CI)	**797**	**793**		**100.0 %**	**0.55 [0.28, 1.07]**

Total events: 153 (Meptazinol), 220 (Pethidine)

Heterogeneity: $Tau^2 = 0.18$; $Chi^2 = 3.57$, df = 2 (P = 0.17); $I^2 = 44\%$

Test for overall effect: Z = 1.75 (P = 0.080)

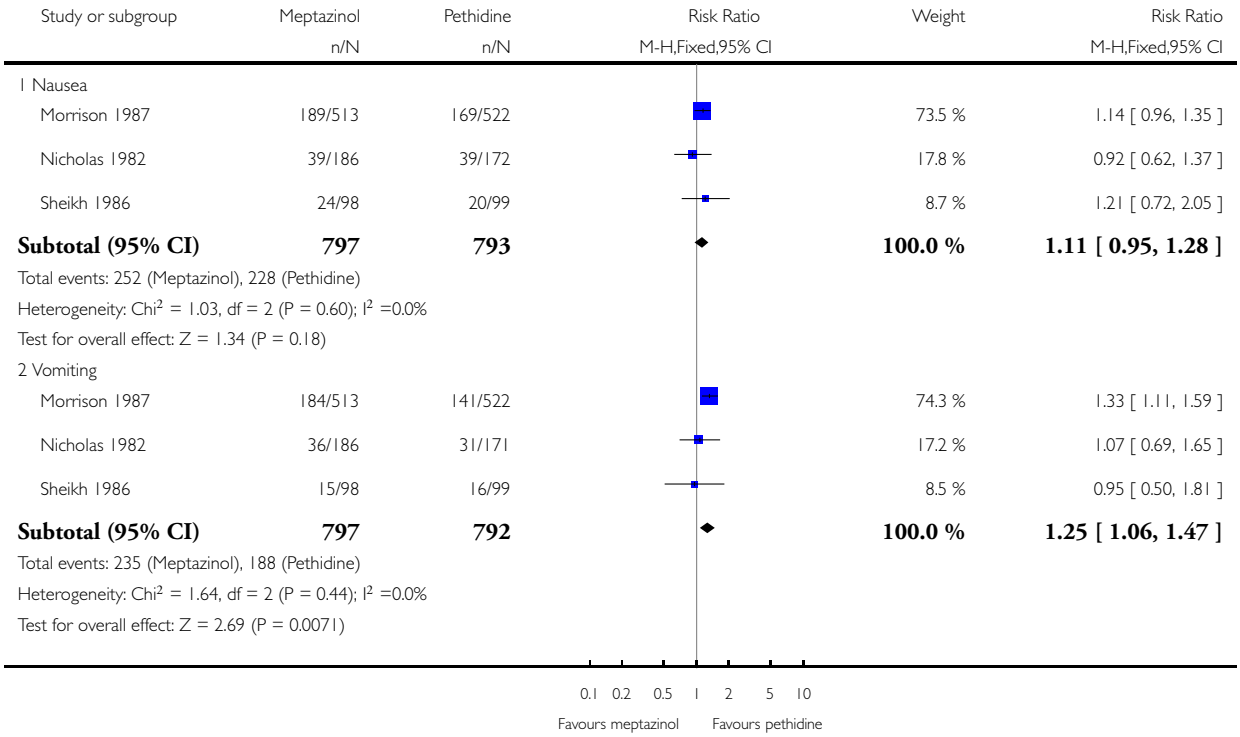
Test for subgroup differences: Not applicable

Analysis 4.6. Comparison 4 IM meptazinol versus pethidine, Outcome 6 Nausea and vomiting.

Review: Parenteral opioids for maternal pain management in labour

Comparison: 4 IM meptazinol versus pethidine

Outcome: 6 Nausea and vomiting



Analysis 4.7. Comparison 4 IM meptazinol versus pethidine, Outcome 7 Caesarean section.

Review: Parenteral opioids for maternal pain management in labour

Comparison: 4 IM meptazinol versus pethidine

Outcome: 7 Caesarean section

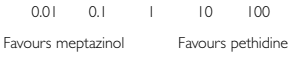
Study or subgroup	Meptazinol n/N	Pethidine n/N	Risk Ratio M-H,Random,95% CI	Weight	Risk Ratio M-H,Random,95% CI
Morrison 1987	33/512	25/521		46.8 %	1.34 [0.81, 2.23]
Osler 1987	5/100	13/99		38.7 %	0.38 [0.14, 1.03]
Wheble 1988	0/17	5/17		14.6 %	0.09 [0.01, 1.53]
Total (95% CI)	**629**	**637**		**100.0 %**	**0.56 [0.16, 2.00]**

Total events: 38 (Meptazinol), 43 (Pethidine)

Heterogeneity: $Tau^2 = 0.84$; $Chi^2 = 7.85$, df = 2 (P = 0.02); $I^2 = 75\%$

Test for overall effect: Z = 0.90 (P = 0.37)

Test for subgroup differences: Not applicable



Analysis 4.8. Comparison 4 IM meptazinol versus pethidine, Outcome 8 Assisted vaginal birth.

Review: Parenteral opioids for maternal pain management in labour

Comparison: 4 IM meptazinol versus pethidine

Outcome: 8 Assisted vaginal birth

Study or subgroup	Meptazinol n/N	Pethidine n/N	Risk Ratio M-H,Fixed,95% CI	Weight	Risk Ratio M-H,Fixed,95% CI
Morrison 1987	97/512	107/521		75.7 %	0.92 [0.72, 1.18]
Osler 1987	36/100	28/99		20.1 %	1.27 [0.85, 1.91]
Wheble 1988	6/17	6/17		4.3 %	1.00 [0.40, 2.48]
Total (95% CI)	**629**	**637**		**100.0 %**	**1.00 [0.81, 1.22]**

Total events: 139 (Meptazinol), 141 (Pethidine)

Heterogeneity: $Chi^2 = 1.76$, df = 2 (P = 0.42); $I^2 = 0.0\%$

Test for overall effect: Z = 0.04 (P = 0.97)

Test for subgroup differences: Not applicable

Analysis 4.9. Comparison 4 IM meptazinol versus pethidine, Outcome 9 Breastfeeding at discharge (problems).

Review: Parenteral opioids for maternal pain management in labour

Comparison: 4 IM meptazinol versus pethidine

Outcome: 9 Breastfeeding at discharge (problems)

Study or subgroup	Meptazinol n/N	Pethidine n/N	Risk Ratio M-H,Fixed,95% CI	Weight	Risk Ratio M-H,Fixed,95% CI
Sheikh 1986	3/98	4/99		100.0 %	0.76 [0.17, 3.30]
Total (95% CI)	**98**	**99**		**100.0 %**	**0.76 [0.17, 3.30]**

Total events: 3 (Meptazinol), 4 (Pethidine)

Heterogeneity: not applicable

Test for overall effect: Z = 0.37 (P = 0.71)

Test for subgroup differences: Not applicable

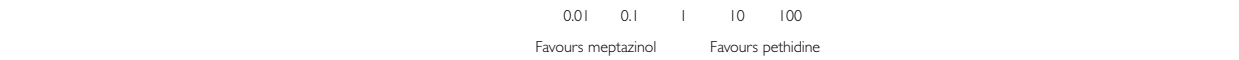
Analysis 4.10. Comparison 4 IM meptazinol versus pethidine, Outcome 10 Fetal heart rate changes (decelerations).

Review: Parenteral opioids for maternal pain management in labour

Comparison: 4 IM meptazinol versus pethidine

Outcome: 10 Fetal heart rate changes (decelerations)

Study or subgroup	Meptazinol n/N	Pethidine n/N	Risk Ratio M-H,Fixed,95% CI	Weight	Risk Ratio M-H,Fixed,95% CI
De Boer 1987	16/17	13/17		100.0 %	1.23 [0.92, 1.64]
Total (95% CI)	**17**	**17**		**100.0 %**	**1.23 [0.92, 1.64]**
Total events: 16 (Meptazinol), 13 (Pethidine)					
Heterogeneity: not applicable					
Test for overall effect: Z = 1.41 (P = 0.16)					
Test for subgroup differences: Not applicable					

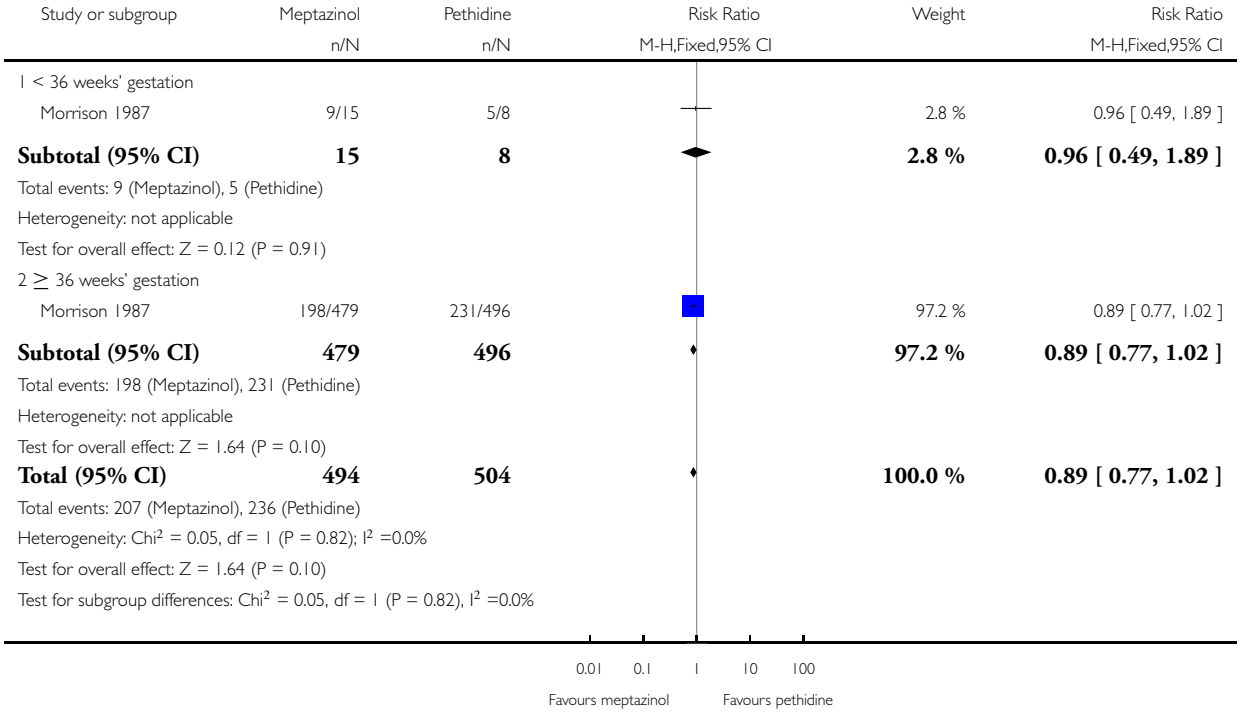


Analysis 4.11. Comparison 4 IM meptazinol versus pethidine, Outcome 11 Naloxone administration.

Review: Parenteral opioids for maternal pain management in labour

Comparison: 4 IM meptazinol versus pethidine

Outcome: 11 Naloxone administration

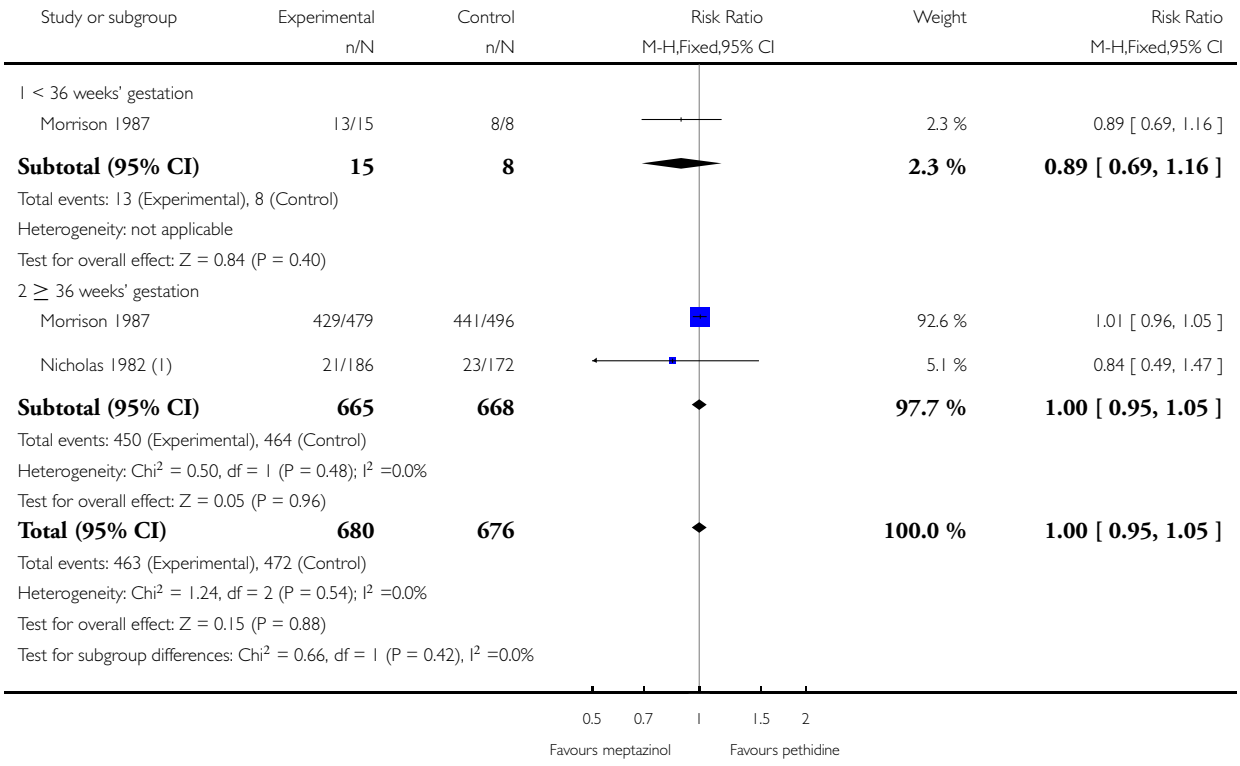


Analysis 4.12. Comparison 4 IM meptazinol versus pethidine, Outcome 12 Neonatal resuscitation (by gestation).

Review: Parenteral opioids for maternal pain management in labour

Comparison: 4 IM meptazinol versus pethidine

Outcome: 12 Neonatal resuscitation (by gestation)



(1) Nicholas = apnoea interpreted as requirement for resuscitation

Analysis 4.13. Comparison 4 IM meptazinol versus pethidine, Outcome 13 Neonatal resuscitation.

Review: Parenteral opioids for maternal pain management in labour

Comparison: 4 IM meptazinol versus pethidine

Outcome: 13 Neonatal resuscitation

Study or subgroup	Meptazinol n/N	Pethidine n/N	Risk Ratio M-H,Fixed,95% CI	Weight	Risk Ratio M-H,Fixed,95% CI
Jackson 1983	3/50	2/50		100.0 %	1.50 [0.26, 8.60]
Total (95% CI)	**50**	**50**		**100.0 %**	**1.50 [0.26, 8.60]**

Total events: 3 (Meptazinol), 2 (Pethidine)
Heterogeneity: not applicable
Test for overall effect: Z = 0.46 (P = 0.65)
Test for subgroup differences: Not applicable

Analysis 4.14. Comparison 4 IM meptazinol versus pethidine, Outcome 14 Apgar score ≤ 7 at 1 minute.

Review: Parenteral opioids for maternal pain management in labour

Comparison: 4 IM meptazinol versus pethidine

Outcome: 14 Apgar score ≤ 7 at 1 minute

Study or subgroup	Meptazinol n/N	Pethidine n/N	Risk Ratio M-H,Fixed,95% CI	Weight	Risk Ratio M-H,Fixed,95% CI
De Boer 1987	3/17	4/17		6.4 %	0.75 [0.20, 2.86]
Jackson 1983	11/47	12/48		19.0 %	0.94 [0.46, 1.91]
Nel 1981 (1)	3/35	3/36		4.7 %	1.03 [0.22, 4.76]
Nicholas 1982 (2)	15/186	18/172		29.9 %	0.77 [0.40, 1.48]
Osler 1987 (3)	15/100	20/99		32.1 %	0.74 [0.40, 1.37]
Wheble 1988 (4)	3/17	5/17		8.0 %	0.60 [0.17, 2.12]
Total (95% CI)	**402**	**389**		**100.0 %**	**0.79 [0.56, 1.11]**

Total events: 50 (Meptazinol), 62 (Pethidine)
Heterogeneity: Chi^2 = 0.57, df = 5 (P = 0.99); I^2 =0.0%
Test for overall effect: Z = 1.35 (P = 0.18)
Test for subgroup differences: Not applicable

(1) Nel = Apgar < 7

(2) Nicholas = Apgar < 7

(3) Osler <= 7

(4) Wheble Apgar < 7

Analysis 4.15. Comparison 4 IM meptazinol versus pethidine, Outcome 15 Apgar score ≤ 7 at 5 minutes.

Review: Parenteral opioids for maternal pain management in labour

Comparison: 4 IM meptazinol versus pethidine

Outcome: 15 Apgar score ≤ 7 at 5 minutes

Study or subgroup	Meptazinol n/N	Pethidine n/N	Risk Ratio M-H,Fixed,95% CI	Weight	Risk Ratio M-H,Fixed,95% CI
Nel 1981	0/35	0/35			Not estimable
Nicholas 1982	0/181	0/166			Not estimable
Osler 1987 (1)	1/100	2/99		100.0 %	0.50 [0.05, 5.37]
Total (95% CI)	**316**	**300**		**100.0 %**	**0.50 [0.05, 5.37]**
Total events: 1 (Meptazinol), 2 (Pethidine)					
Heterogeneity: not applicable					
Test for overall effect: Z = 0.58 (P = 0.56)					
Test for subgroup differences: Not applicable					

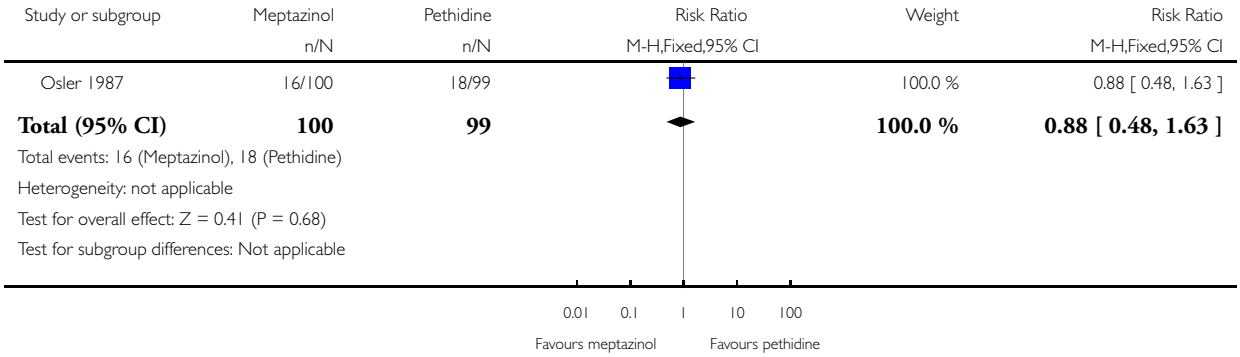
(1) Osler Apgar =< 7

Analysis 4.16. Comparison 4 IM meptazinol versus pethidine, Outcome 16 Admission to NICU.

Review: Parenteral opioids for maternal pain management in labour

Comparison: 4 IM meptazinol versus pethidine

Outcome: 16 Admission to NICU

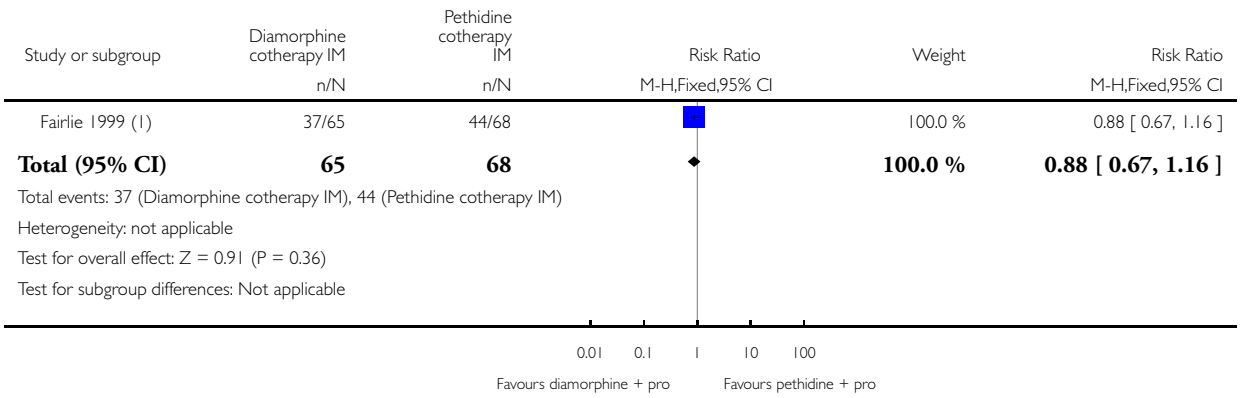


Analysis 5.1. Comparison 5 IM diamorphine + prochlorperazine versus pethidine + prochlorperazine, Outcome 1 Maternal satisfaction with analgesia in labour measured during the postnatal period (Global assessment of pain relief at 24 hours).

Review: Parenteral opioids for maternal pain management in labour

Comparison: 5 IM diamorphine + prochlorperazine versus pethidine + prochlorperazine

Outcome: 1 Maternal satisfaction with analgesia in labour measured during the postnatal period (Global assessment of pain relief at 24 hours)



(1) Pain relief as rated as poor or fair

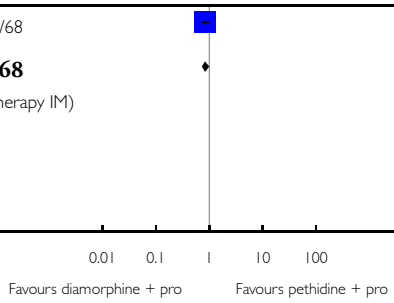
Analysis 5.2. Comparison 5 IM diamorphine + prochlorperazine versus pethidine + prochlorperazine, Outcome 2 Maternal pain score or pain measured in labour (Pain intensity at 1 hour (moderate or severe)).

Review: Parenteral opioids for maternal pain management in labour

Comparison: 5 IM diamorphine + prochlorperazine versus pethidine + prochlorperazine

Outcome: 2 Maternal pain score or pain measured in labour (Pain intensity at 1 hour (moderate or severe))

Study or subgroup	Diamorphine cotherapy IM n/N	Pethidine cotherapy IM n/N	Risk Ratio M-H,Fixed,95% CI	Weight	Risk Ratio M-H,Fixed,95% CI
Fairlie 1999	48/65	59/68		100.0 %	0.85 [0.72, 1.01]
Total (95% CI)	**65**	**68**		**100.0 %**	**0.85 [0.72, 1.01]**
Total events: 48 (Diamorphine cotherapy IM), 59 (Pethidine cotherapy IM)					
Heterogeneity: not applicable					
Test for overall effect: Z = 1.84 (P = 0.066)					
Test for subgroup differences: Not applicable					



Analysis 5.3. Comparison 5 IM diamorphine + prochlorperazine versus pethidine + prochlorperazine, Outcome 3 Additonal analgesia required.

Review: Parenteral opioids for maternal pain management in labour

Comparison: 5 IM diamorphine + prochlorperazine versus pethidine + prochlorperazine

Outcome: 3 Additonal analgesia required

Study or subgroup	Diamorphine cotherapy IM n/N	Pethidine cotherapy IM n/N	Risk Ratio M-H,Fixed,95% CI	Weight	Risk Ratio M-H,Fixed,95% CI
Fairlie 1999 (1)	9/65	7/68		100.0 %	1.35 [0.53, 3.40]
Total (95% CI)	**65**	**68**		**100.0 %**	**1.35 [0.53, 3.40]**

Total events: 9 (Diamorphine cotherapy IM), 7 (Pethidine cotherapy IM)

Heterogeneity: not applicable

Test for overall effect: Z = 0.63 (P = 0.53)

Test for subgroup differences: Not applicable

(1) Second dose of study drug

Analysis 5.4. Comparison 5 IM diamorphine + prochlorperazine versus pethidine + prochlorperazine, Outcome 4 Epidural.

Review: Parenteral opioids for maternal pain management in labour

Comparison: 5 IM diamorphine + prochlorperazine versus pethidine + prochlorperazine

Outcome: 4 Epidural

Study or subgroup	Diamorphine cotherapy IM n/N	Pethidine cotherapy IM n/N	Risk Ratio M-H,Fixed,95% CI	Weight	Risk Ratio M-H,Fixed,95% CI
Fairlie 1999 (1)	21/65	18/68		100.0 %	1.22 [0.72, 2.07]
Total (95% CI)	**65**	**68**		**100.0 %**	**1.22 [0.72, 2.07]**

Total events: 21 (Diamorphine cotherapy IM), 18 (Pethidine cotherapy IM)

Heterogeneity: not applicable

Test for overall effect: Z = 0.74 (P = 0.46)

Test for subgroup differences: Not applicable

(1) 2nd dose of study drug

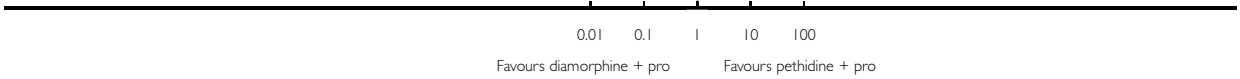
Analysis 5.5. Comparison 5 IM diamorphine + prochlorperazine versus pethidine + prochlorperazine, Outcome 5 Maternal sleepiness during labour.

Review: Parenteral opioids for maternal pain management in labour

Comparison: 5 IM diamorphine + prochlorperazine versus pethidine + prochlorperazine

Outcome: 5 Maternal sleepiness during labour

Study or subgroup	Diamorphine cotherapy IM n/N	Pethidine cotherapy IM n/N	Risk Ratio M-H,Fixed,95% CI	Weight	Risk Ratio M-H,Fixed,95% CI
Fairlie 1999 (1)	16/65	18/68		100.0 %	0.93 [0.52, 1.66]
Total (95% CI)	**65**	**68**		**100.0 %**	**0.93 [0.52, 1.66]**
Total events: 16 (Diamorphine cotherapy IM), 18 (Pethidine cotherapy IM)					
Heterogeneity: not applicable					
Test for overall effect: Z = 0.24 (P = 0.81)					
Test for subgroup differences: Not applicable					



(1) Moderately drowsy or asleep at 60 minutes post-injection

Analysis 5.6. Comparison 5 IM diamorphine + prochlorperazine versus pethidine + prochlorperazine, Outcome 6 Vomiting in labour.

Review: Parenteral opioids for maternal pain management in labour

Comparison: 5 IM diamorphine + prochlorperazine versus pethidine + prochlorperazine

Outcome: 6 Vomiting in labour

Study or subgroup	Diamorphine cotherapy IM n/N	Pethidine cotherapy IM n/N	Risk Ratio M-H,Fixed,95% CI	Weight	Risk Ratio M-H,Fixed,95% CI
Fairlie 1999 (1)	7/65	19/68		100.0 %	0.39 [0.17, 0.86]
Total (95% CI)	**65**	**68**		**100.0 %**	**0.39 [0.17, 0.86]**
Total events: 7 (Diamorphine cotherapy IM), 19 (Pethidine cotherapy IM)					
Heterogeneity: not applicable					
Test for overall effect: Z = 2.34 (P = 0.019)					
Test for subgroup differences: Not applicable					

(1) 1 hour post-adminstration

Analysis 5.7. Comparison 5 IM diamorphine + prochlorperazine versus pethidine + prochlorperazine, Outcome 7 Caesarean section.

Review: Parenteral opioids for maternal pain management in labour

Comparison: 5 IM diamorphine + prochlorperazine versus pethidine + prochlorperazine

Outcome: 7 Caesarean section

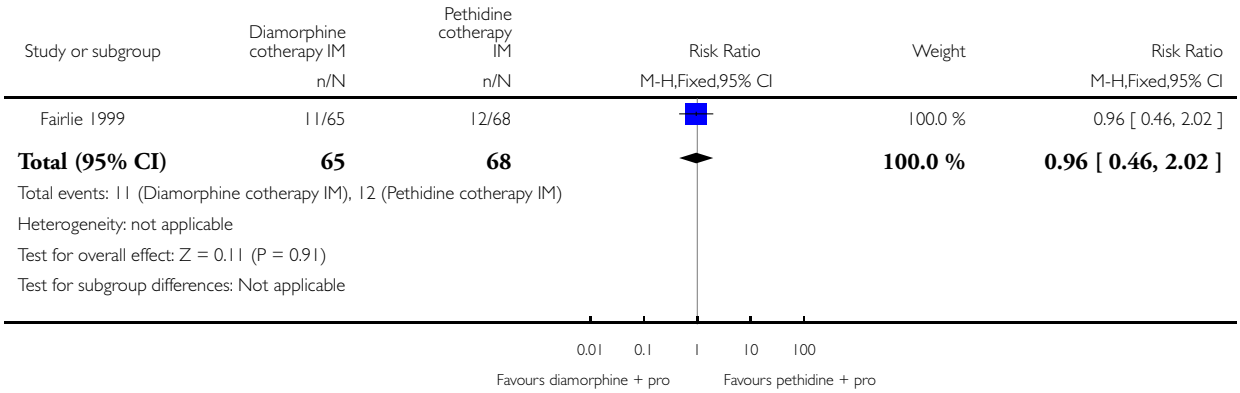
Study or subgroup	Diamorphine cotherapy IM n/N	Pethidine cotherapy IM n/N	Risk Ratio M-H,Fixed,95% CI	Weight	Risk Ratio M-H,Fixed,95% CI
Fairlie 1999	2/65	4/68		100.0 %	0.52 [0.10, 2.76]
Total (95% CI)	**65**	**68**		**100.0 %**	**0.52 [0.10, 2.76]**
Total events: 2 (Diamorphine cotherapy IM), 4 (Pethidine cotherapy IM)					
Heterogeneity: not applicable					
Test for overall effect: Z = 0.76 (P = 0.45)					
Test for subgroup differences: Not applicable					

Analysis 5.8. Comparison 5 IM diamorphine + prochlorperazine versus pethidine + prochlorperazine, Outcome 8 Assisted vaginal birth.

Review: Parenteral opioids for maternal pain management in labour

Comparison: 5 IM diamorphine + prochlorperazine versus pethidine + prochlorperazine

Outcome: 8 Assisted vaginal birth

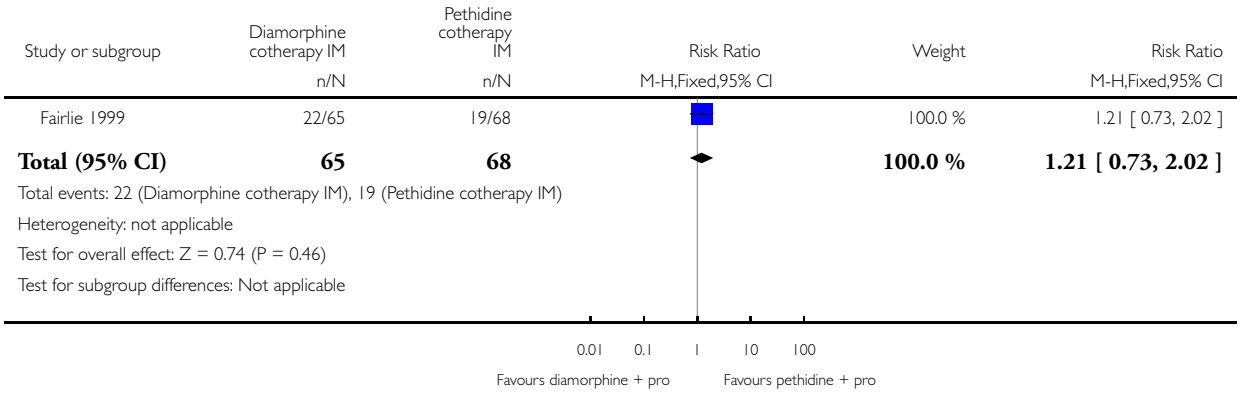


Analysis 5.9. Comparison 5 IM diamorphine + prochlorperazine versus pethidine + prochlorperazine, Outcome 9 Neonatal resuscitation.

Review: Parenteral opioids for maternal pain management in labour

Comparison: 5 IM diamorphine + prochlorperazine versus pethidine + prochlorperazine

Outcome: 9 Neonatal resuscitation

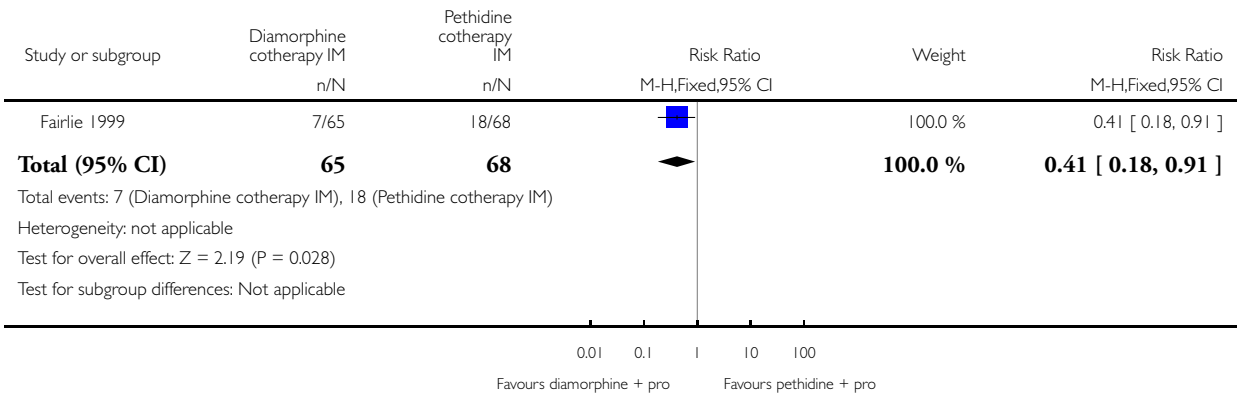


Analysis 5.10. Comparison 5 IM diamorphine + prochlorperazine versus pethidine + prochlorperazine, Outcome 10 Apgar < 7 at 1 minute.

Review: Parenteral opioids for maternal pain management in labour

Comparison: 5 IM diamorphine + prochlorperazine versus pethidine + prochlorperazine

Outcome: 10 Apgar < 7 at 1 minute



Analysis 5.11. Comparison 5 IM diamorphine + prochlorperazine versus pethidine + prochlorperazine, Outcome 11 Apgar < 7 at 5 minutes.

Review: Parenteral opioids for maternal pain management in labour

Comparison: 5 IM diamorphine + prochlorperazine versus pethidine + prochlorperazine

Outcome: 11 Apgar < 7 at 5 minutes

Study or subgroup	Diamorphine cotherapy IM n/N	Pethidine cotherapy IM n/N	Risk Ratio M-H,Fixed,95% CI	Weight	Risk Ratio M-H,Fixed,95% CI
Fairlie 1999	1/65	3/68		100.0 %	0.35 [0.04, 3.27]
Total (95% CI)	**65**	**68**		**100.0 %**	**0.35 [0.04, 3.27]**

Total events: 1 (Diamorphine cotherapy IM), 3 (Pethidine cotherapy IM)

Heterogeneity: not applicable

Test for overall effect: Z = 0.92 (P = 0.36)

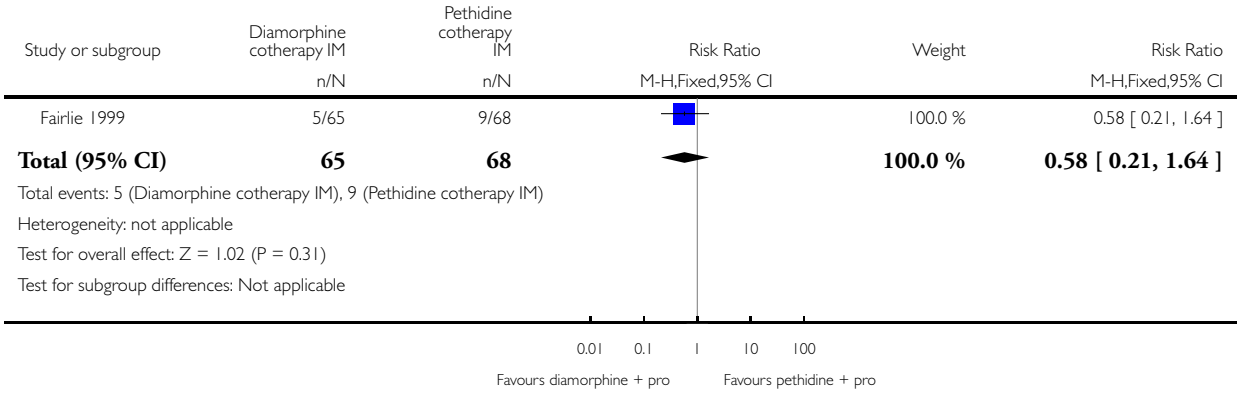
Test for subgroup differences: Not applicable

Analysis 5.12. Comparison 5 IM diamorphine + prochlorperazine versus pethidine + prochlorperazine, Outcome 12 Admission to NICU.

Review: Parenteral opioids for maternal pain management in labour

Comparison: 5 IM diamorphine + prochlorperazine versus pethidine + prochlorperazine

Outcome: 12 Admission to NICU

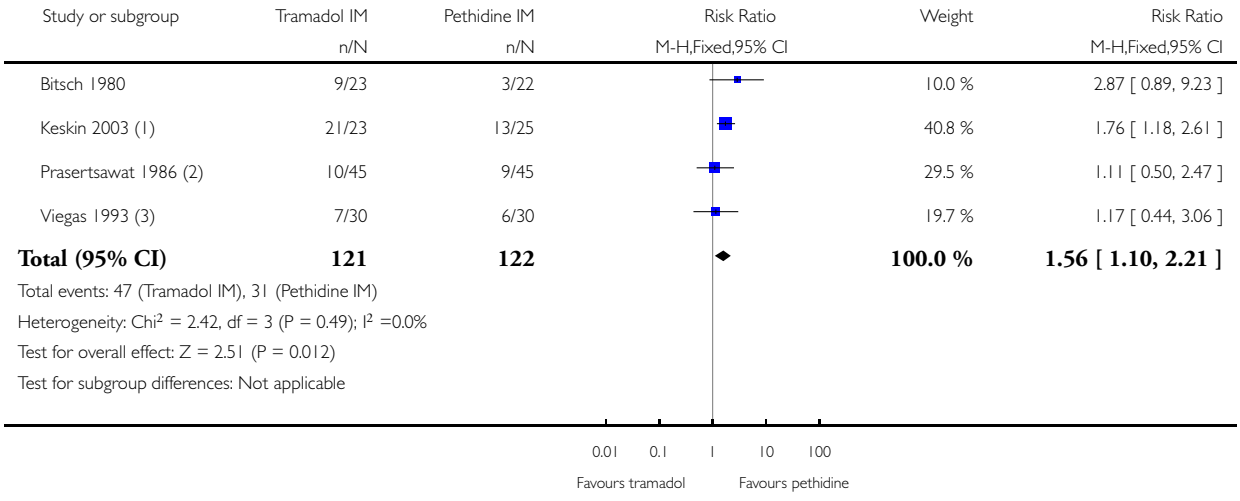


Analysis 6.1. Comparison 6 IM tramadol versus pethidine, Outcome 1 Maternal pain score or pain measured in labour (Pain intensity: women with poor pain relief).

Review: Parenteral opioids for maternal pain management in labour

Comparison: 6 IM tramadol versus pethidine

Outcome: 1 Maternal pain score or pain measured in labour (Pain intensity: women with poor pain relief)



(1) Keskin 4 or 5 at 60 mins; Bitsch 5-10 mins post-admin

(2) Prasertsawat Poor response after 1st dose.

(3) Viegas none or insufficient relief

Analysis 6.2. Comparison 6 IM tramadol versus pethidine, Outcome 2 Additional analgesia required.

Review: Parenteral opioids for maternal pain management in labour

Comparison: 6 IM tramadol versus pethidine

Outcome: 2 Additional analgesia required

Study or subgroup	Tramadol IM n/N	Pethidine IM n/N	Risk Ratio M-H,Random,95% CI	Weight	Risk Ratio M-H,Random,95% CI
Bitsch 1980 (1)	16/23	17/22		69.0 %	0.90 [0.63, 1.28]
Khooshideh 2009 (2)	0/80	0/80			Not estimable
Prasertsawat 1986 (3)	11/45	7/45		31.0 %	1.57 [0.67, 3.69]
Total (95% CI)	**148**	**147**		**100.0 %**	**1.07 [0.60, 1.91]**
Total events: 27 (Tramadol IM), 24 (Pethidine IM)					
Heterogeneity: $Tau^2 = 0.10$; $Chi^2 = 1.86$, df = 1 (P = 0.17); $I^2 = 46\%$					
Test for overall effect: Z = 0.23 (P = 0.82)					
Test for subgroup differences: Not applicable					

(1) Second and third doses of study drug

(2) Second dose

(3) Second dose of study drug, half dose

Analysis 6.3. Comparison 6 IM tramadol versus pethidine, Outcome 3 Maternal sleepiness in labour.

Review: Parenteral opioids for maternal pain management in labour

Comparison: 6 IM tramadol versus pethidine

Outcome: 3 Maternal sleepiness in labour

Study or subgroup	Tramadol IM n/N	Pethidine IM n/N	Risk Ratio M-H,Random,95% CI	Weight	Risk Ratio M-H,Random,95% CI
Husslein 1987	6/20	10/20		17.9 %	0.60 [0.27, 1.34]
Keskin 2003 (1)	16/30	14/29		23.7 %	1.10 [0.67, 1.83]
Khooshideh 2009	23/80	64/80		26.4 %	0.36 [0.25, 0.52]
Prasertsawat 1986	10/45	15/45		20.0 %	0.67 [0.34, 1.32]
Viegas 1993	3/30	10/30		12.0 %	0.30 [0.09, 0.98]
Total (95% CI)	**205**	**204**		**100.0 %**	**0.57 [0.33, 0.97]**

Total events: 58 (Tramadol IM), 113 (Pethidine IM)

Heterogeneity: $Tau^2 = 0.24$; $Chi^2 = 14.15$, df = 4 (P = 0.01); $I^2 = 72\%$

Test for overall effect: Z = 2.08 (P = 0.037)

Test for subgroup differences: Not applicable

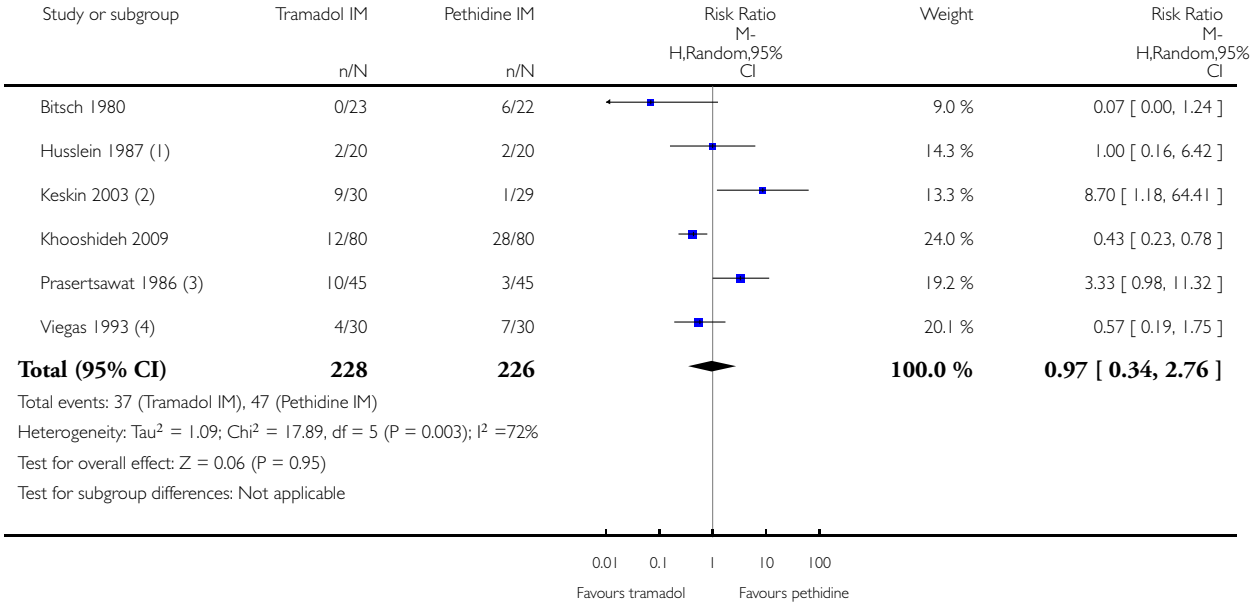
(1) Keskin - assessed at 60 mins.

Analysis 6.4. Comparison 6 IM tramadol versus pethidine, Outcome 4 Nausea and vomiting in labour.

Review: Parenteral opioids for maternal pain management in labour

Comparison: 6 IM tramadol versus pethidine

Outcome: 4 Nausea and vomiting in labour



(1) Husslein is nausea only or vomiting only as the data are identical

(2) Keskin: nausea at 60 mins - vomiting 1 case in pathidine group.

(3) nausea - vomiting in 2/45 tramadol and 2/45 pethidine.

(4) Viegas vomiting 3/30 Tramadol 100 mg and 7/30 Pethidine. Nausea in FP.

Analysis 6.5. Comparison 6 IM tramadol versus pethidine, Outcome 5 Caesarean section.

Review: Parenteral opioids for maternal pain management in labour

Comparison: 6 IM tramadol versus pethidine

Outcome: 5 Caesarean section

Study or subgroup	Tramadol IM n/N	Pethidine IM n/N	Risk Ratio M-H,Fixed,95% CI	Weight	Risk Ratio M-H,Fixed,95% CI
Husslein 1987	0/20	0/20			Not estimable
Khooshideh 2009	4/80	5/80		71.4 %	0.80 [0.22, 2.87]
Viegas 1993	1/30	2/30		28.6 %	0.50 [0.05, 5.22]
Total (95% CI)	**130**	**130**		**100.0 %**	**0.71 [0.23, 2.18]**

Total events: 5 (Tramadol IM), 7 (Pethidine IM)

Heterogeneity: $Chi^2 = 0.12$, df = 1 (P = 0.73); $I^2 = 0.0\%$

Test for overall effect: Z = 0.59 (P = 0.55)

Test for subgroup differences: Not applicable

Analysis 6.6. Comparison 6 IM tramadol versus pethidine, Outcome 6 Assisted vaginal birth.

Review: Parenteral opioids for maternal pain management in labour

Comparison: 6 IM tramadol versus pethidine

Outcome: 6 Assisted vaginal birth

Study or subgroup	Tramadol IM n/N	Pethidine IM n/N	Risk Ratio M-H,Fixed,95% CI	Weight	Risk Ratio M-H,Fixed,95% CI
Husslein 1987	0/20	1/20		33.3 %	0.33 [0.01, 7.72]
Khooshideh 2009	0/80	2/80		55.6 %	0.20 [0.01, 4.10]
Viegas 1993	1/30	0/30		11.1 %	3.00 [0.13, 70.83]
Total (95% CI)	**130**	**130**		**100.0 %**	**0.56 [0.12, 2.56]**

Total events: 1 (Tramadol IM), 3 (Pethidine IM)

Heterogeneity: $Chi^2 = 1.63$, df = 2 (P = 0.44); $I^2 = 0.0\%$

Test for overall effect: Z = 0.75 (P = 0.45)

Test for subgroup differences: Not applicable

Analysis 6.7. Comparison 6 IM tramadol versus pethidine, Outcome 7 Neonatal resuscitation.

Review: Parenteral opioids for maternal pain management in labour

Comparison: 6 IM tramadol versus pethidine

Outcome: 7 Neonatal resuscitation

Study or subgroup	Tramadol IM n/N	Pethidine IM n/N	Risk Ratio M-H,Fixed,95% CI	Weight	Risk Ratio M-H,Fixed,95% CI
Prasertsawat 1986	0/45	0/45			Not estimable
Total (95% CI)	**45**	**45**			**Not estimable**
Total events: 0 (Tramadol IM), 0 (Pethidine IM)					
Heterogeneity: not applicable					
Test for overall effect: not applicable					
Test for subgroup differences: Not applicable					

Analysis 6.8. Comparison 6 IM tramadol versus pethidine, Outcome 8 Apgar scores ≤ 7 at 1 and 5 minutes.

Review: Parenteral opioids for maternal pain management in labour

Comparison: 6 IM tramadol versus pethidine

Outcome: 8 Apgar scores ≤ 7 at 1 and 5 minutes

Study or subgroup	Tramadol IM n/N	Pethidine IM n/N	Risk Ratio M-H,Fixed,95% CI	Weight	Risk Ratio M-H,Fixed,95% CI
1 Less than 7 at 1 minute					
Khooshideh 2009	0/80	0/80			Not estimable
Prasertsawat 1986	0/45	0/45			Not estimable
Subtotal (95% CI)	**125**	**125**			**Not estimable**
Total events: 0 (Tramadol IM), 0 (Pethidine IM)					
Heterogeneity: not applicable					
Test for overall effect: not applicable					
2 Less than 7 at 5 minutes					
Khooshideh 2009	0/80	0/80			Not estimable
Subtotal (95% CI)	**80**	**80**			**Not estimable**
Total events: 0 (Tramadol IM), 0 (Pethidine IM)					
Heterogeneity: not applicable					
Test for overall effect: not applicable					

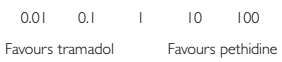
Analysis 6.9. Comparison 6 IM tramadol versus pethidine, Outcome 9 Neonatal respiratory distress.

Review: Parenteral opioids for maternal pain management in labour

Comparison: 6 IM tramadol versus pethidine

Outcome: 9 Neonatal respiratory distress

Study or subgroup	Tramadol IM n/N	Pethidine IM n/N	Risk Ratio M-H,Fixed,95% CI	Weight	Risk Ratio M-H,Fixed,95% CI
Keskin 2003	7/30	3/29		100.0 %	2.26 [0.64, 7.89]
Total (95% CI)	**30**	**29**		**100.0 %**	**2.26 [0.64, 7.89]**
Total events: 7 (Tramadol IM), 3 (Pethidine IM)					
Heterogeneity: not applicable					
Test for overall effect: Z = 1.27 (P = 0.20)					
Test for subgroup differences: Not applicable					



Analysis 6.10. Comparison 6 IM tramadol versus pethidine, Outcome 10 Admission to NICU.

Review: Parenteral opioids for maternal pain management in labour

Comparison: 6 IM tramadol versus pethidine

Outcome: 10 Admission to NICU

Study or subgroup	Tramadol IM n/N	Pethidine IM n/N	Risk Ratio M-H,Fixed,95% CI	Weight	Risk Ratio M-H,Fixed,95% CI
Keskin 2003	7/30	3/29		100.0 %	2.26 [0.64, 7.89]
Total (95% CI)	**30**	**29**		**100.0 %**	**2.26 [0.64, 7.89]**
Total events: 7 (Tramadol IM), 3 (Pethidine IM)					
Heterogeneity: not applicable					
Test for overall effect: Z = 1.27 (P = 0.20)					
Test for subgroup differences: Not applicable					

Analysis 7.1. Comparison 7 IM tramadol + triflupromazine versus pethidine + triflupromazine, Outcome 1 Maternal sleepiness in labour.

Review: Parenteral opioids for maternal pain management in labour

Comparison: 7 IM tramadol + triflupromazine versus pethidine + triflupromazine

Outcome: 1 Maternal sleepiness in labour

Study or subgroup	Tramadol IM+tri n/N	Pethidine IM+tri n/N	Risk Ratio M-H,Fixed,95% CI	Weight	Risk Ratio M-H,Fixed,95% CI
Kainz 1992	7/22	2/18		100.0 %	2.86 [0.68, 12.12]
Total (95% CI)	**22**	**18**		**100.0 %**	**2.86 [0.68, 12.12]**

Total events: 7 (Tramadol IM+tri), 2 (Pethidine IM+tri)

Heterogeneity: not applicable

Test for overall effect: Z = 1.43 (P = 0.15)

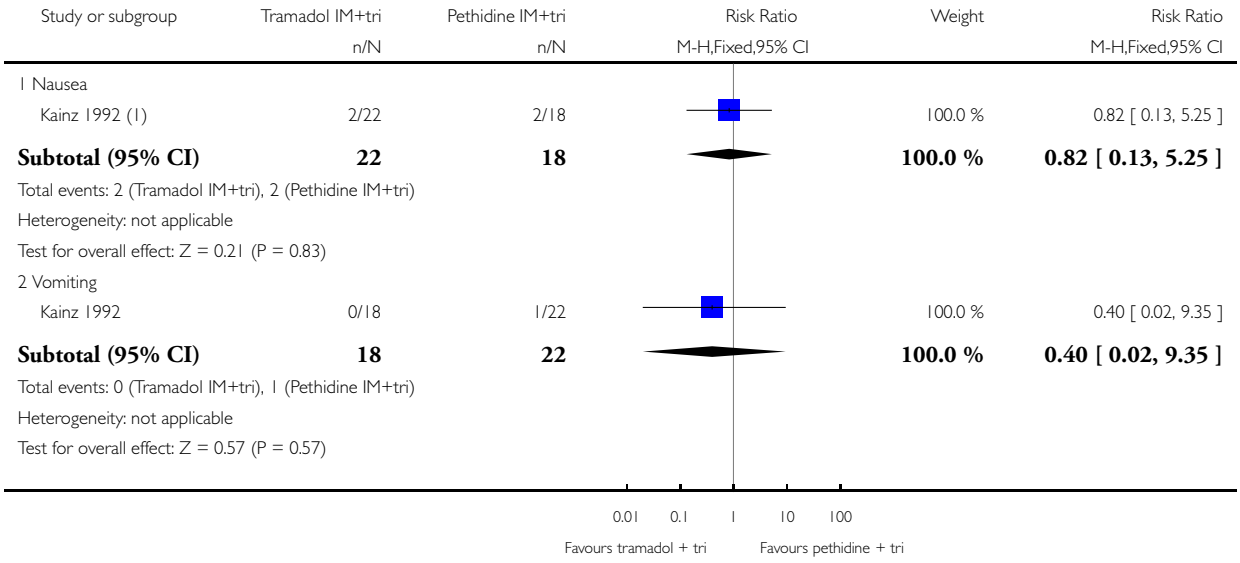
Test for subgroup differences: Not applicable

Analysis 7.2. Comparison 7 IM tramadol + triflupromazine versus pethidine + triflupromazine, Outcome 2 Nausea and vomiting in labour.

Review: Parenteral opioids for maternal pain management in labour

Comparison: 7 IM tramadol + triflupromazine versus pethidine + triflupromazine

Outcome: 2 Nausea and vomiting in labour



(1) assessment at 60 minutes

Analysis 8.1. Comparison 8 IM dihydrocodeine 50 mg versus pethidine 100 mg, Outcome 1 Maternal pain score or pain measured in labour (Maternal pain relief poor at 1 hour).

Review: Parenteral opioids for maternal pain management in labour

Comparison: 8 IM dihydrocodeine 50 mg versus pethidine 100 mg

Outcome: 1 Maternal pain score or pain measured in labour (Maternal pain relief poor at 1 hour)

Study or subgroup	Dihydrocodeine IM n/N	Pethidine IM n/N	Risk Ratio M-H,Fixed,95% CI	Weight	Risk Ratio M-H,Fixed,95% CI
Sliom 1970	24/80	16/58		100.0 %	1.09 [0.64, 1.86]
Total (95% CI)	**80**	**58**		**100.0 %**	**1.09 [0.64, 1.86]**
Total events: 24 (Dihydrocodeine IM), 16 (Pethidine IM)					
Heterogeneity: not applicable					
Test for overall effect: Z = 0.31 (P = 0.76)					
Test for subgroup differences: Not applicable					

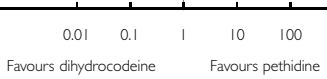
Analysis 8.2. Comparison 8 IM dihydrocodeine 50 mg versus pethidine 100 mg, Outcome 2 Maternal sleepiness in labour.

Review: Parenteral opioids for maternal pain management in labour

Comparison: 8 IM dihydrocodeine 50 mg versus pethidine 100 mg

Outcome: 2 Maternal sleepiness in labour

Study or subgroup	Dihydrocodeine IM n/N	Pethidine IM n/N	Risk Ratio M-H,Fixed,95% CI	Weight	Risk Ratio M-H,Fixed,95% CI
Sliom 1970	24/80	26/58		100.0 %	0.67 [0.43, 1.04]
Total (95% CI)	**80**	**58**		**100.0 %**	**0.67 [0.43, 1.04]**
Total events: 24 (Dihydrocodeine IM), 26 (Pethidine IM)					
Heterogeneity: not applicable					
Test for overall effect: Z = 1.79 (P = 0.074)					
Test for subgroup differences: Not applicable					



Analysis 8.3. Comparison 8 IM dihydrocodeine 50 mg versus pethidine 100 mg, Outcome 3 Nausea and vomiting in labour.

Review: Parenteral opioids for maternal pain management in labour

Comparison: 8 IM dihydrocodeine 50 mg versus pethidine 100 mg

Outcome: 3 Nausea and vomiting in labour

Study or subgroup	Dihydrocodeine IM n/N	Pethidine IM n/N	Risk Ratio M-H,Fixed,95% CI	Weight	Risk Ratio M-H,Fixed,95% CI
Sliom 1970	12/80	10/58		100.0 %	0.87 [0.40, 1.88]
Total (95% CI)	**80**	**58**		**100.0 %**	**0.87 [0.40, 1.88]**
Total events: 12 (Dihydrocodeine IM), 10 (Pethidine IM)					
Heterogeneity: not applicable					
Test for overall effect: Z = 0.36 (P = 0.72)					
Test for subgroup differences: Not applicable					

Analysis 8.4. Comparison 8 IM dihydrocodeine 50 mg versus pethidine 100 mg, Outcome 4 Apgar ≤ 7 at 1 minute.

Review: Parenteral opioids for maternal pain management in labour

Comparison: 8 IM dihydrocodeine 50 mg versus pethidine 100 mg

Outcome: 4 Apgar ≤ 7 at 1 minute

Study or subgroup	Dihydrocodeine IM n/N	Pethidine IM n/N	Risk Ratio M-H,Fixed,95% CI	Weight	Risk Ratio M-H,Fixed,95% CI
Sliom 1970	26/80	33/58		100.0 %	0.57 [0.39, 0.84]
Total (95% CI)	**80**	**58**		**100.0 %**	**0.57 [0.39, 0.84]**
Total events: 26 (Dihydrocodeine IM), 33 (Pethidine IM)					
Heterogeneity: not applicable					
Test for overall effect: Z = 2.83 (P = 0.0046)					
Test for subgroup differences: Not applicable					

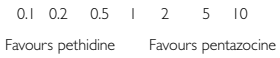
Analysis 9.1. Comparison 9 IM pentazocine versus pethidine, Outcome 1 Maternal satisfaction with analgesia measured during labour (Pain relief (good or very good) at delivery).

Review: Parenteral opioids for maternal pain management in labour

Comparison: 9 IM pentazocine versus pethidine

Outcome: 1 Maternal satisfaction with analgesia measured during labour (Pain relief (good or very good) at delivery)

Study or subgroup	Pentazocine IM n/N	Pethidine IM n/N	Risk Ratio M-H,Fixed,95% CI	Weight	Risk Ratio M-H,Fixed,95% CI
Borglin 1971	74/91	65/89		81.5 %	1.11 [0.95, 1.31]
Mowat 1970 (1)	13/34	16/39		18.5 %	0.93 [0.53, 1.65]
Total (95% CI)	**125**	**128**		**100.0 %**	**1.08 [0.92, 1.27]**
Total events: 87 (Pentazocine IM), 81 (Pethidine IM)					
Heterogeneity: Chi^2 = 0.40, df = 1 (P = 0.53); I^2 =0.0%					
Test for overall effect: Z = 0.91 (P = 0.36)					
Test for subgroup differences: Not applicable					



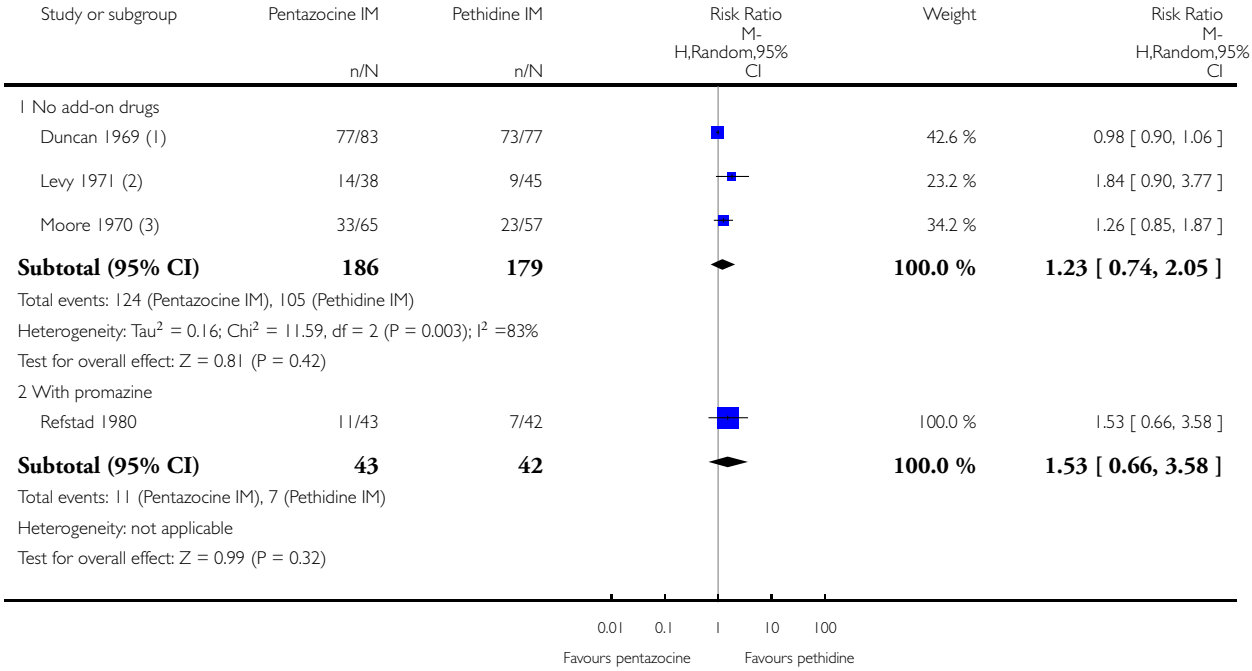
(1) Obtained relief after 1st injection.

Analysis 9.2. Comparison 9 IM pentazocine versus pethidine, Outcome 2 Maternal pain score or pain measured in labour (Pain relief poor (partial, none or worse)).

Review: Parenteral opioids for maternal pain management in labour

Comparison: 9 IM pentazocine versus pethidine

Outcome: 2 Maternal pain score or pain measured in labour (Pain relief poor (partial, none or worse))



(1) After 1st injection only.

(2) Unclear when pain assessed but following first dose.

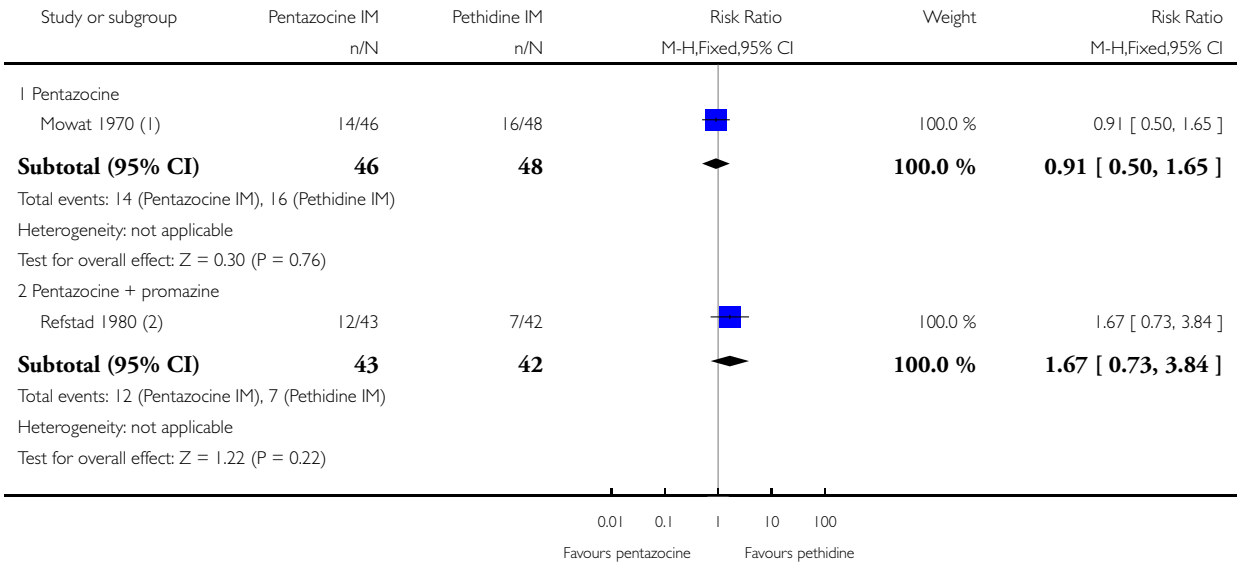
(3) Severe pain at 60 minutes.

Analysis 9.3. Comparison 9 IM pentazocine versus pethidine, Outcome 3 Additional analgesia required.

Review: Parenteral opioids for maternal pain management in labour

Comparison: 9 IM pentazocine versus pethidine

Outcome: 3 Additional analgesia required



(1) Additional doses of study drug.

(2) 2nd dose of study drug

Analysis 9.4. Comparison 9 IM pentazocine versus pethidine, Outcome 4 Maternal sleepiness in labour.

Review: Parenteral opioids for maternal pain management in labour

Comparison: 9 IM pentazocine versus pethidine

Outcome: 4 Maternal sleepiness in labour

Study or subgroup	Pentazocine IM n/N	Pethidine IM n/N	Risk Ratio M-H,Fixed,95% CI	Weight	Risk Ratio M-H,Fixed,95% CI
Borglin 1971 (1)	82/91	80/89		62.7 %	1.00 [0.91, 1.11]
Moore 1970	21/73	19/65		15.6 %	0.98 [0.58, 1.66]
Mowat 1970 (2)	26/34	30/39		21.7 %	0.99 [0.77, 1.28]
Total (95% CI)	**198**	**193**		**100.0 %**	**1.00 [0.89, 1.12]**

Total events: 129 (Pentazocine IM), 129 (Pethidine IM)

Heterogeneity: $Chi^2 = 0.01$, df = 2 (P = 0.99); $I^2 = 0.0\%$

Test for overall effect: Z = 0.04 (P = 0.97)

Test for subgroup differences: Not applicable

(1) Borglin 1971 - Sedating and relaxing effects

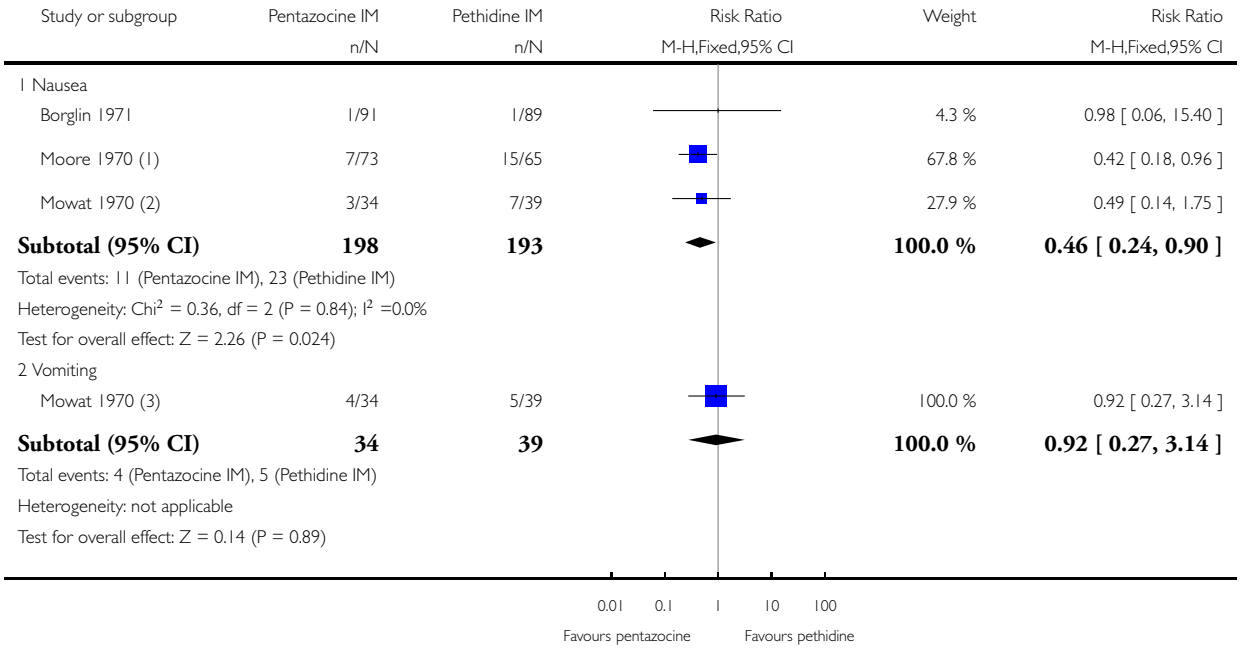
(2) After 1st injection

Analysis 9.5. Comparison 9 IM pentazocine versus pethidine, Outcome 5 Nausea and vomiting in labour.

Review: Parenteral opioids for maternal pain management in labour

Comparison: 9 IM pentazocine versus pethidine

Outcome: 5 Nausea and vomiting in labour



(1) Nausea or vomiting

(2) After 1st injection.

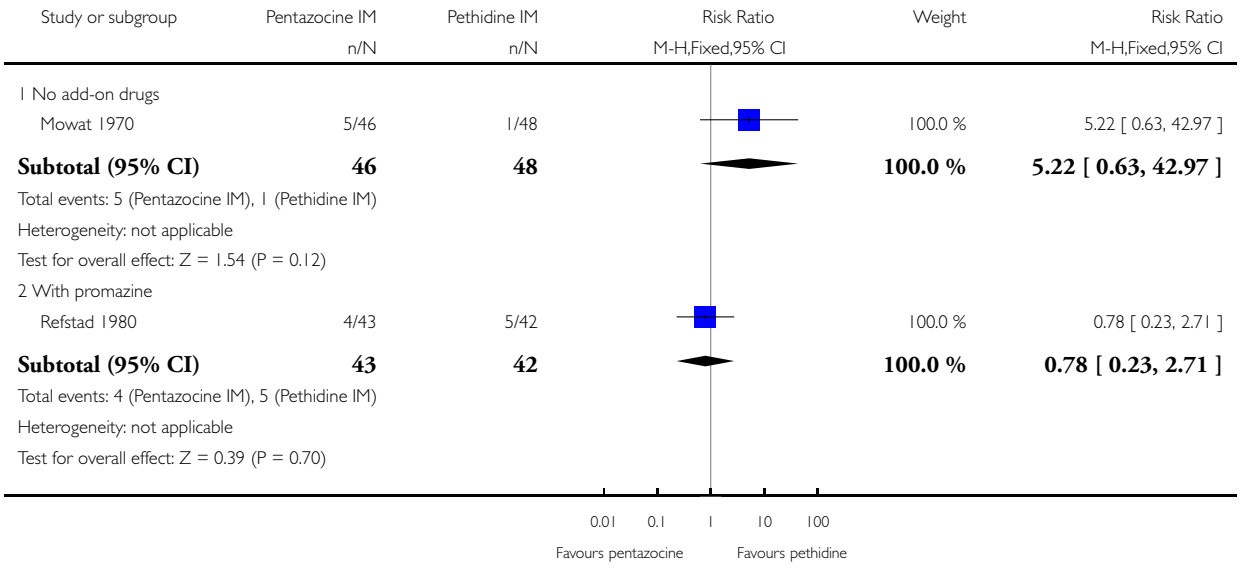
(3) After 1st injection.

Analysis 9.6. Comparison 9 IM pentazocine versus pethidine, Outcome 6 Assisted vaginal birth.

Review: Parenteral opioids for maternal pain management in labour

Comparison: 9 IM pentazocine versus pethidine

Outcome: 6 Assisted vaginal birth



Analysis 9.7. Comparison 9 IM pentazocine versus pethidine, Outcome 7 Naloxone administration.

Review: Parenteral opioids for maternal pain management in labour

Comparison: 9 IM pentazocine versus pethidine

Outcome: 7 Naloxone administration

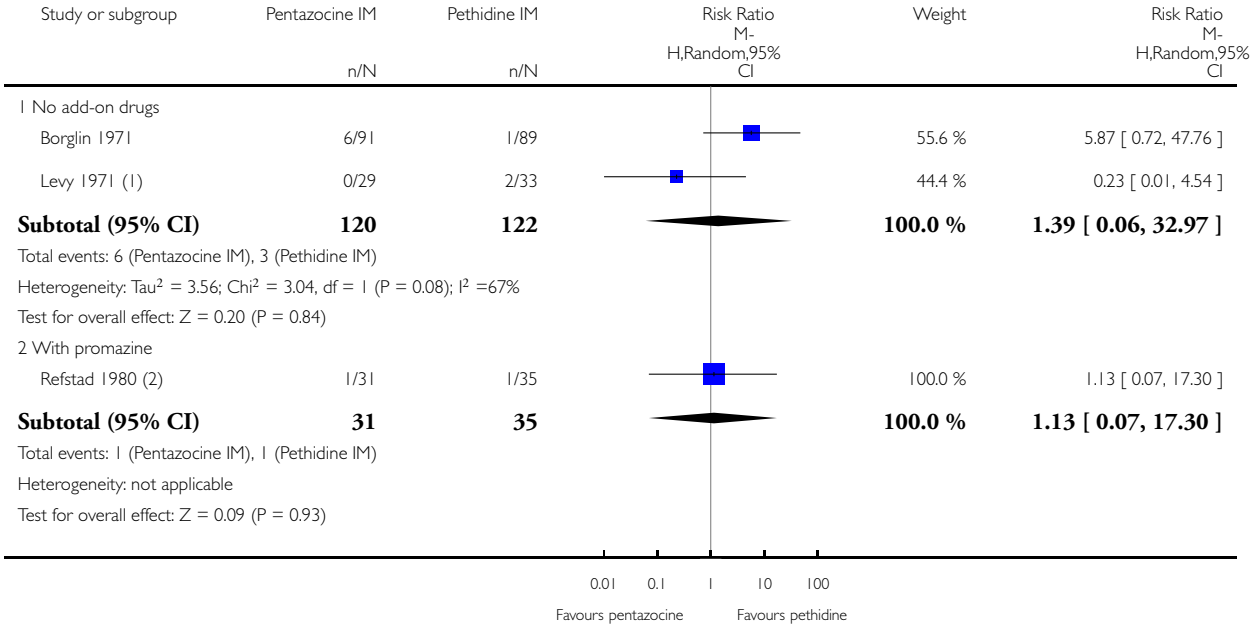
Study or subgroup	Pentazocine IM n/N	Pethidine IM n/N	Risk Ratio M-H,Fixed,95% CI	Weight	Risk Ratio M-H,Fixed,95% CI
1 With promazine					
Refstad 1980	2/43	4/42		100.0 %	0.49 [0.09, 2.53]
Total (95% CI)	**43**	**42**		**100.0 %**	**0.49 [0.09, 2.53]**
Total events: 2 (Pentazocine IM), 4 (Pethidine IM)					
Heterogeneity: not applicable					
Test for overall effect: Z = 0.85 (P = 0.39)					
Test for subgroup differences: Not applicable					

Analysis 9.8. Comparison 9 IM pentazocine versus pethidine, Outcome 8 Apgar score ≤ 7 at 1 minute.

Review: Parenteral opioids for maternal pain management in labour

Comparison: 9 IM pentazocine versus pethidine

Outcome: 8 Apgar score ≤ 7 at 1 minute



(1) Apgar is for babies that had 1 dose only and does not include data for 1st dose of women who had 2 doses

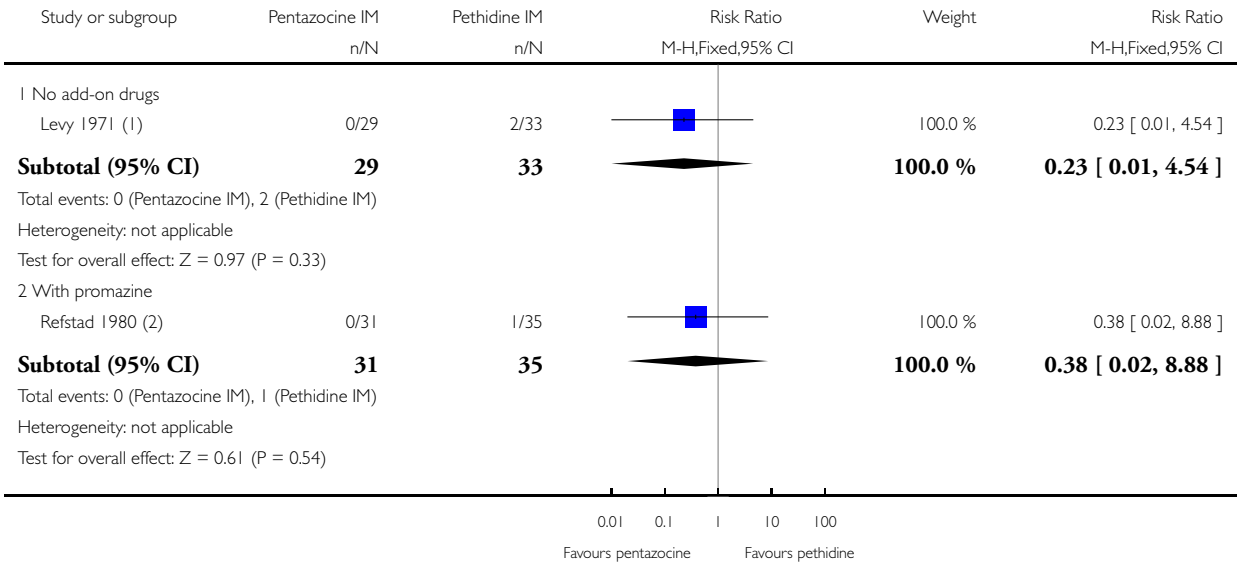
(2) After 1 dose only

Analysis 9.9. Comparison 9 IM pentazocine versus pethidine, Outcome 9 Apgar score ≤ 7 at 5 minutes.

Review: Parenteral opioids for maternal pain management in labour

Comparison: 9 IM pentazocine versus pethidine

Outcome: 9 Apgar score ≤ 7 at 5 minutes



(1) Apgar is for babies that had 1 dose only and does not include data for 1st dose of women who had 2 doses

(2) After 1st dose only

Analysis 10.1. Comparison 10 IM nalbuphine versus pethidine, Outcome 1 Maternal satisfaction with analgesia measured during the postnatal period (numbers dissatisfied).

Review: Parenteral opioids for maternal pain management in labour

Comparison: 10 IM nalbuphine versus pethidine

Outcome: 1 Maternal satisfaction with analgesia measured during the postnatal period (numbers dissatisfied)

Study or subgroup	Nalbuphine IM n/N	Pethidine IM n/N	Risk Ratio M-H,Fixed,95% CI	Weight	Risk Ratio M-H,Fixed,95% CI
Wilson 1986 (1)	23/37	30/35		100.0 %	0.73 [0.55, 0.96]
Total (95% CI)	**37**	**35**		**100.0 %**	**0.73 [0.55, 0.96]**
Total events: 23 (Nalbuphine IM), 30 (Pethidine IM)					
Heterogeneity: not applicable					
Test for overall effect: Z = 2.21 (P = 0.027)					
Test for subgroup differences: Not applicable					

(1) Rated as minimally effective.

Analysis 10.2. Comparison 10 IM nalbuphine versus pethidine, Outcome 2 Maternal satisfaction with analgesia measured during labour (Pain free).

Review: Parenteral opioids for maternal pain management in labour

Comparison: 10 IM nalbuphine versus pethidine

Outcome: 2 Maternal satisfaction with analgesia measured during labour (Pain free)

Study or subgroup	Nalbuphine IM n/N	Pethidine IM n/N	Risk Ratio M-H,Fixed,95% CI	Weight	Risk Ratio M-H,Fixed,95% CI
Mitterschiffthaler 1991 (1)	6/20	1/20		100.0 %	6.00 [0.79, 45.42]
Total (95% CI)	**20**	**20**		**100.0 %**	**6.00 [0.79, 45.42]**
Total events: 6 (Nalbuphine IM), 1 (Pethidine IM)					
Heterogeneity: not applicable					
Test for overall effect: Z = 1.73 (P = 0.083)					
Test for subgroup differences: Not applicable					

(1) Unclear when pain assessed

Analysis 10.3. Comparison 10 IM nalbuphine versus pethidine, Outcome 3 Maternal pain score or pain measured in labour (Pain intensity at 30 minutes: women with severe pain).

Review: Parenteral opioids for maternal pain management in labour

Comparison: 10 IM nalbuphine versus pethidine

Outcome: 3 Maternal pain score or pain measured in labour (Pain intensity at 30 minutes: women with severe pain)

Study or subgroup	Nalbuphine IM n/N	Pethidine IM n/N	Risk Ratio M-H,Fixed,95% CI	Weight	Risk Ratio M-H,Fixed,95% CI
Lardizabal 1999	37/149	42/146		100.0 %	0.86 [0.59, 1.26]
Total (95% CI)	**149**	**146**		**100.0 %**	**0.86 [0.59, 1.26]**
Total events: 37 (Nalbuphine IM), 42 (Pethidine IM)					
Heterogeneity: not applicable					
Test for overall effect: Z = 0.76 (P = 0.45)					
Test for subgroup differences: Not applicable					

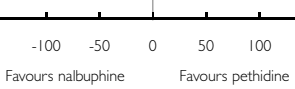
Analysis 10.4. Comparison 10 IM nalbuphine versus pethidine, Outcome 4 Maternal pain score or pain measured in labour (VAS at 60 minutes (at peak of contraction)).

Review: Parenteral opioids for maternal pain management in labour

Comparison: 10 IM nalbuphine versus pethidine

Outcome: 4 Maternal pain score or pain measured in labour (VAS at 60 minutes (at peak of contraction))

Study or subgroup	Nalbuphine IM N	Mean(SD)	Pethidine IM N	Mean(SD)	Mean Difference IV,Fixed,95% CI	Weight	Mean Difference IV,Fixed,95% CI
Wilson 1986	37	66 (24.9)	35	74 (20.7)		100.0 %	-8.00 [-18.55, 2.55]
Total (95% CI)	**37**		**35**			**100.0 %**	**-8.00 [-18.55, 2.55]**
Heterogeneity: not applicable							
Test for overall effect: Z = 1.49 (P = 0.14)							
Test for subgroup differences: Not applicable							

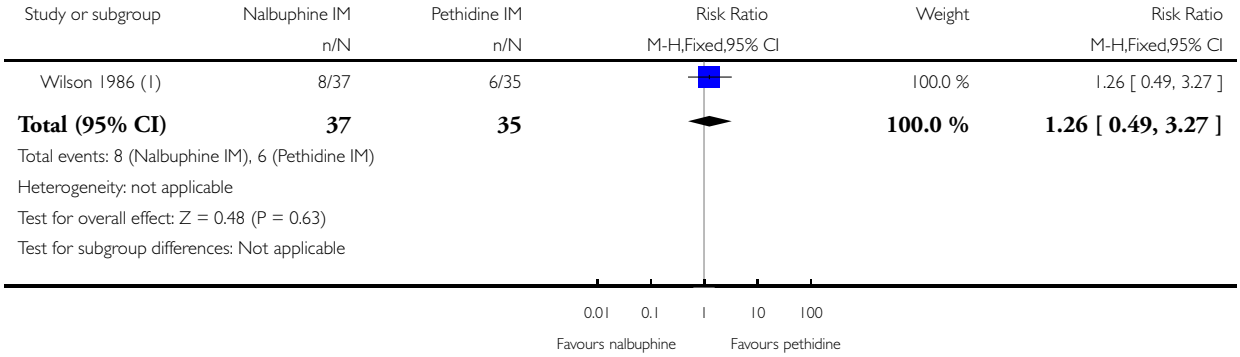


Analysis 10.5. Comparison 10 IM nalbuphine versus pethidine, Outcome 5 Additional analgesia required.

Review: Parenteral opioids for maternal pain management in labour

Comparison: 10 IM nalbuphine versus pethidine

Outcome: 5 Additional analgesia required



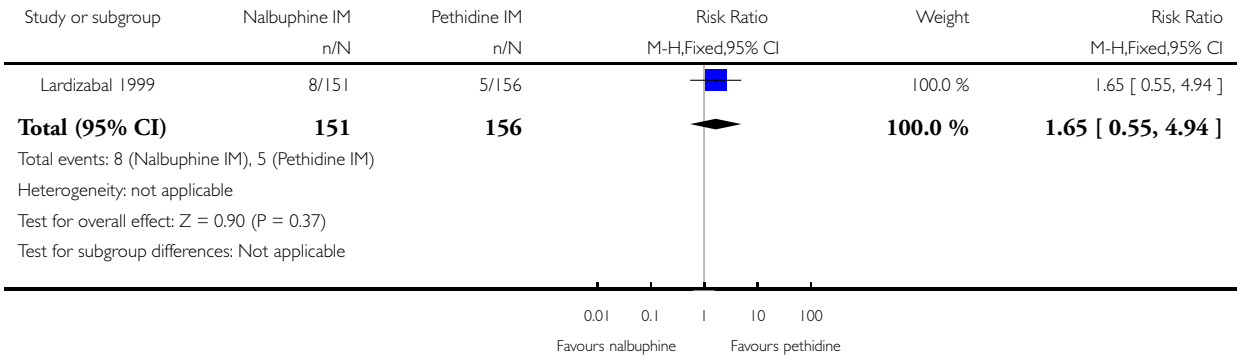
(1) 2nd dose of study drug

Analysis 10.6. Comparison 10 IM nalbuphine versus pethidine, Outcome 6 Epidural.

Review: Parenteral opioids for maternal pain management in labour

Comparison: 10 IM nalbuphine versus pethidine

Outcome: 6 Epidural

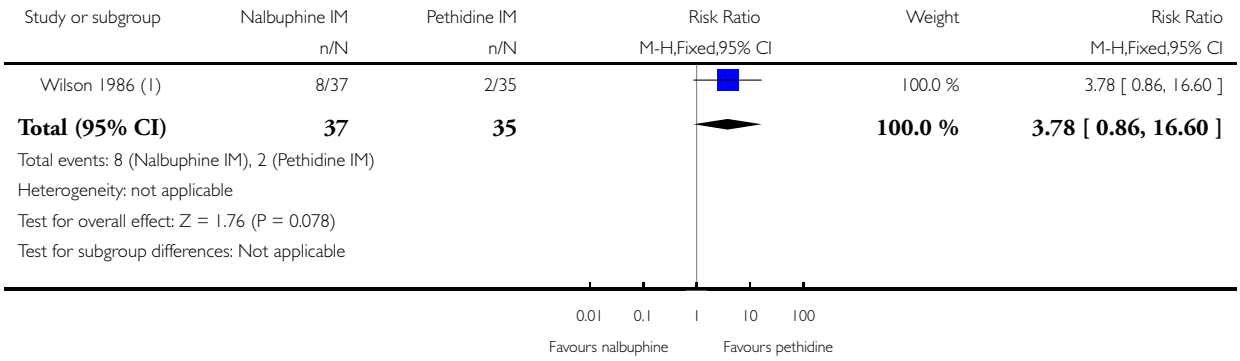


Analysis 10.7. Comparison 10 IM nalbuphine versus pethidine, Outcome 7 Maternal sleepiness in labour.

Review: Parenteral opioids for maternal pain management in labour

Comparison: 10 IM nalbuphine versus pethidine

Outcome: 7 Maternal sleepiness in labour



(1) Excessive sedation

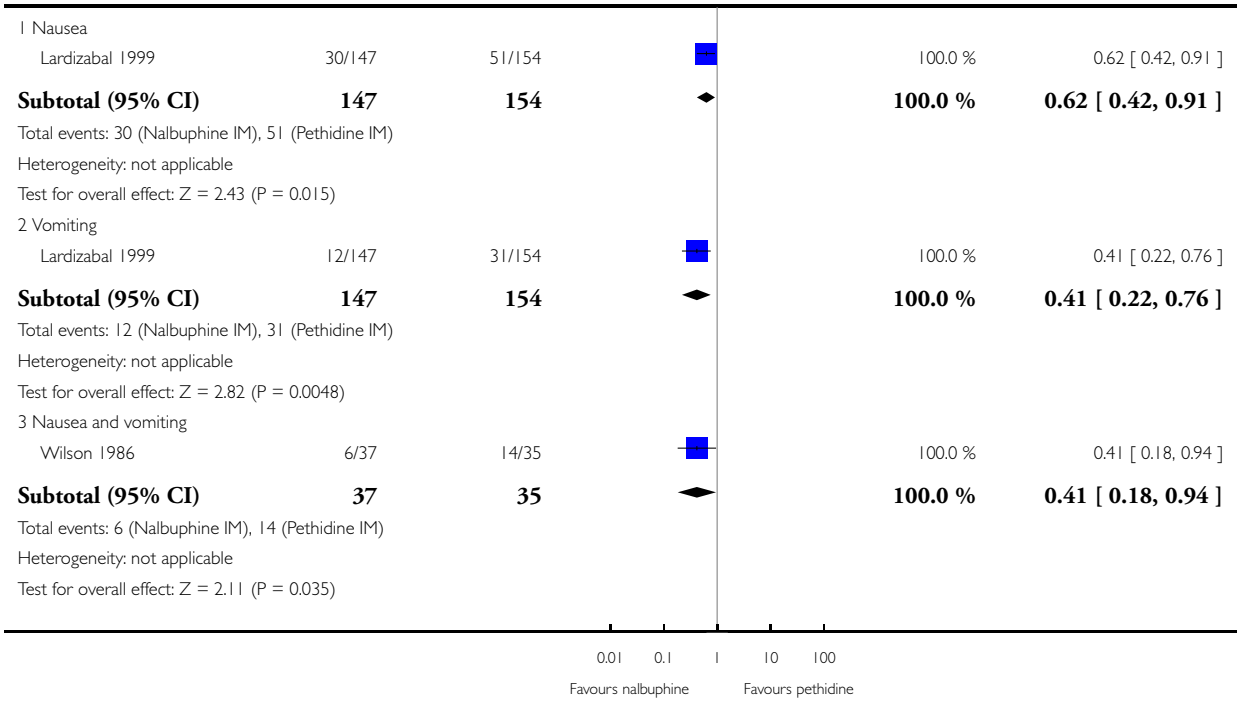
Analysis 10.8. Comparison 10 IM nalbuphine versus pethidine, Outcome 8 Nausea and vomiting in labour.

Review: Parenteral opioids for maternal pain management in labour

Comparison: 10 IM nalbuphine versus pethidine

Outcome: 8 Nausea and vomiting in labour

Study or subgroup	Nalbuphine IM n/N	Pethidine IM n/N	Risk Ratio M-H,Fixed,95% CI	Weight	Risk Ratio M-H,Fixed,95% CI
1 Nausea					
Lardizabal 1999	30/147	51/154		100.0 %	0.62 [0.42, 0.91]
Subtotal (95% CI)	**147**	**154**		**100.0 %**	**0.62 [0.42, 0.91]**
Total events: 30 (Nalbuphine IM), 51 (Pethidine IM)					
Heterogeneity: not applicable					
Test for overall effect: Z = 2.43 (P = 0.015)					
2 Vomiting					
Lardizabal 1999	12/147	31/154		100.0 %	0.41 [0.22, 0.76]
Subtotal (95% CI)	**147**	**154**		**100.0 %**	**0.41 [0.22, 0.76]**
Total events: 12 (Nalbuphine IM), 31 (Pethidine IM)					
Heterogeneity: not applicable					
Test for overall effect: Z = 2.82 (P = 0.0048)					
3 Nausea and vomiting					
Wilson 1986	6/37	14/35		100.0 %	0.41 [0.18, 0.94]
Subtotal (95% CI)	**37**	**35**		**100.0 %**	**0.41 [0.18, 0.94]**
Total events: 6 (Nalbuphine IM), 14 (Pethidine IM)					
Heterogeneity: not applicable					
Test for overall effect: Z = 2.11 (P = 0.035)					

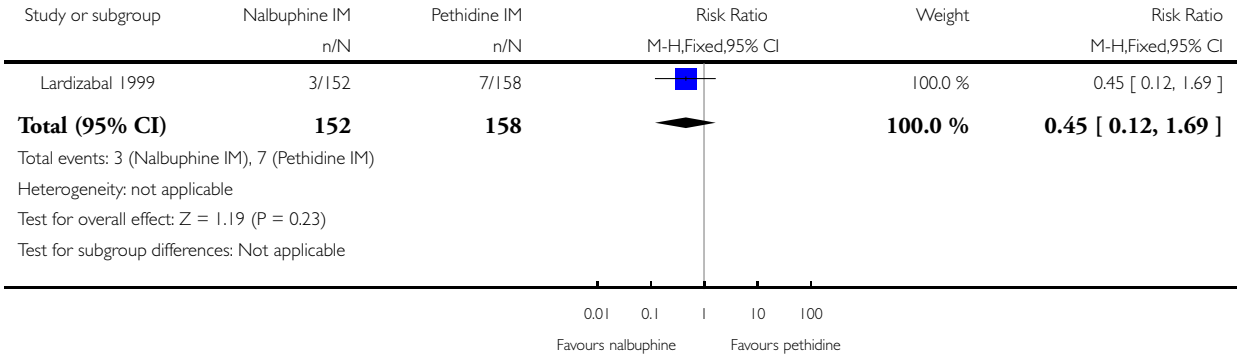


Analysis 10.9. Comparison 10 IM nalbuphine versus pethidine, Outcome 9 Caesarean section.

Review: Parenteral opioids for maternal pain management in labour

Comparison: 10 IM nalbuphine versus pethidine

Outcome: 9 Caesarean section

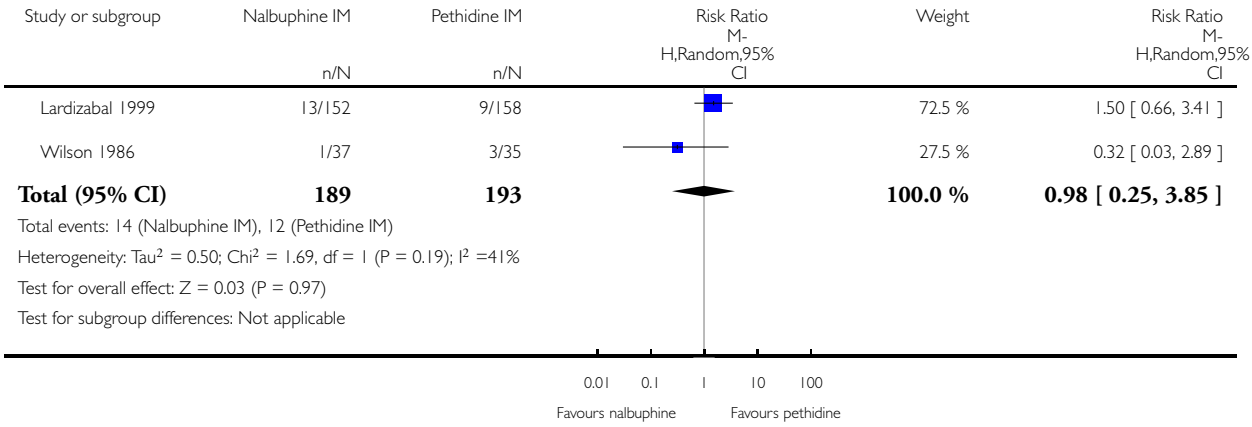


Analysis 10.10. Comparison 10 IM nalbuphine versus pethidine, Outcome 10 Assisted vaginal birth.

Review: Parenteral opioids for maternal pain management in labour

Comparison: 10 IM nalbuphine versus pethidine

Outcome: 10 Assisted vaginal birth

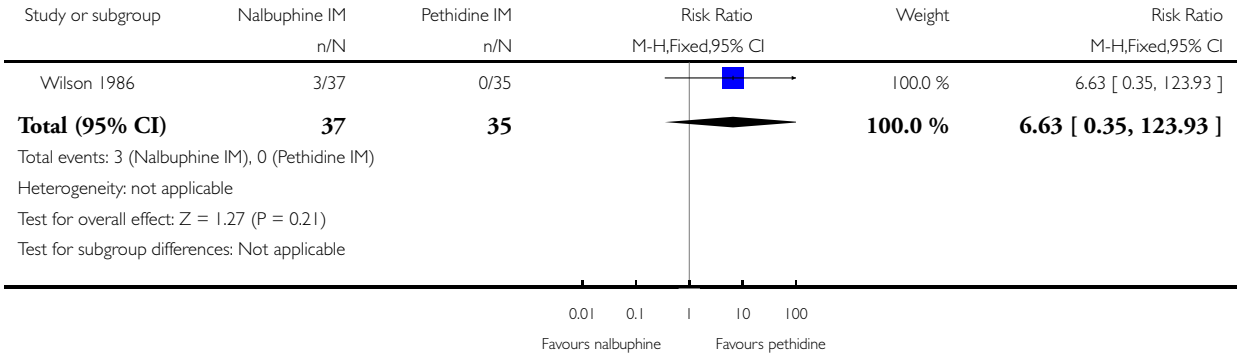


Analysis 10.11. Comparison 10 IM nalbuphine versus pethidine, Outcome 11 Naloxone administration.

Review: Parenteral opioids for maternal pain management in labour

Comparison: 10 IM nalbuphine versus pethidine

Outcome: 11 Naloxone administration

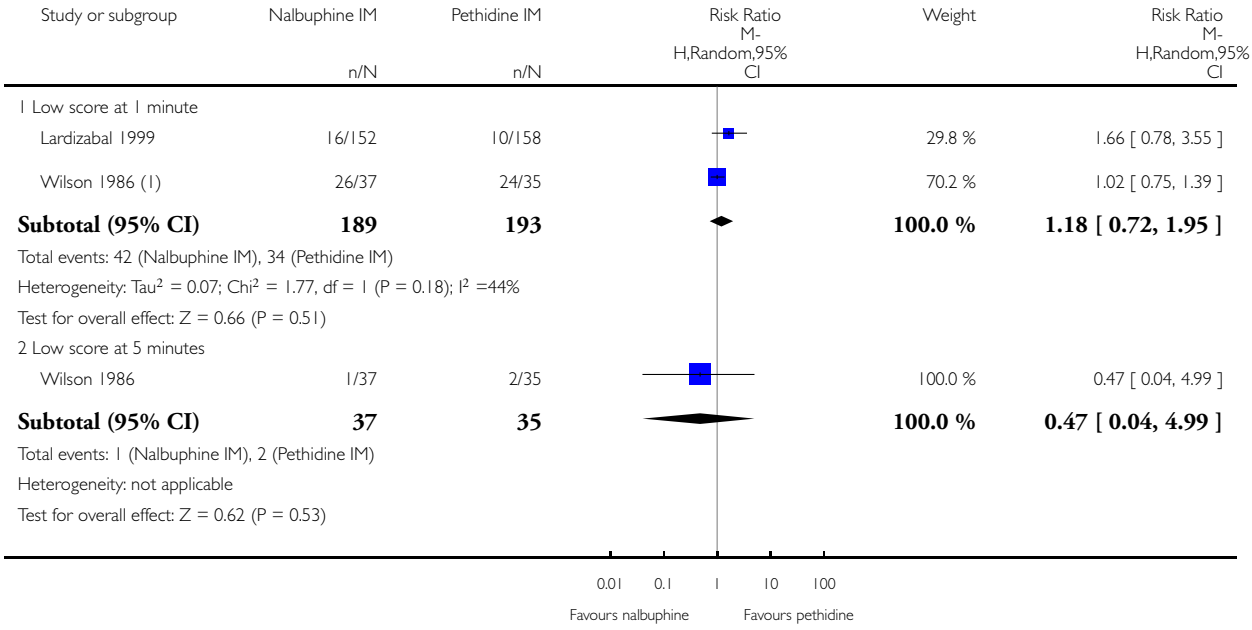


Analysis 10.12. Comparison 10 IM nalbuphine versus pethidine, Outcome 12 Apgar score ≤ 7 at 1 and 5 minutes.

Review: Parenteral opioids for maternal pain management in labour

Comparison: 10 IM nalbuphine versus pethidine

Outcome: 12 Apgar score ≤ 7 at 1 and 5 minutes



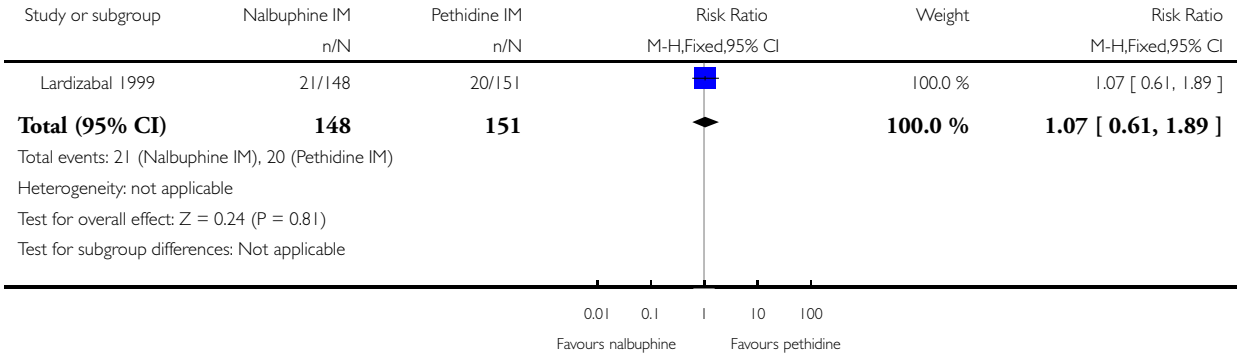
(1) Apgar modified: minus colour score

Analysis 10.13. Comparison 10 IM nalbuphine versus pethidine, Outcome 13 Admission to NICU.

Review: Parenteral opioids for maternal pain management in labour

Comparison: 10 IM nalbuphine versus pethidine

Outcome: 13 Admission to NICU

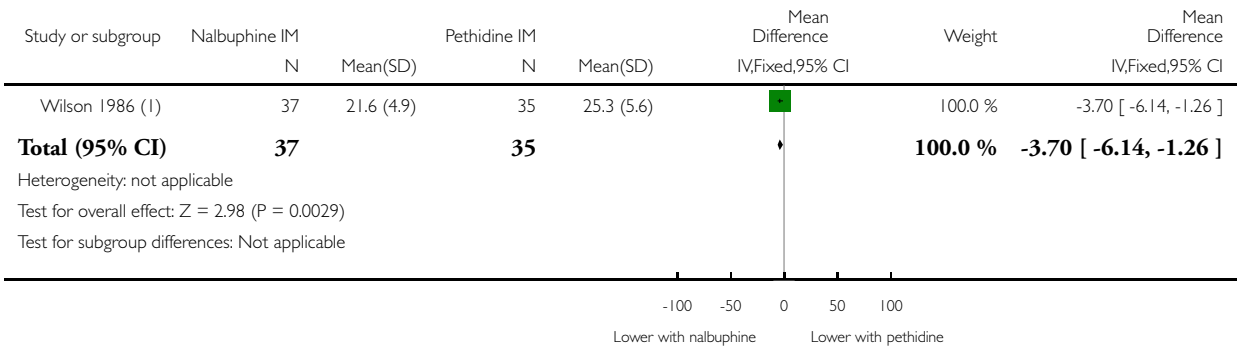


Analysis 10.14. Comparison 10 IM nalbuphine versus pethidine, Outcome 14 Neonatal neurobehavioural (Scanlon) 2-4 hours PN.

Review: Parenteral opioids for maternal pain management in labour

Comparison: 10 IM nalbuphine versus pethidine

Outcome: 14 Neonatal neurobehavioural (Scanlon) 2-4 hours PN



(1) Lower scores on Scanlon scale = poorer outcome

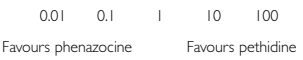
Analysis 11.1. Comparison 11 IM phenazocine versus pethidine, Outcome 1 Epidural.

Review: Parenteral opioids for maternal pain management in labour

Comparison: 11 IM phenazocine versus pethidine

Outcome: 1 Epidural

Study or subgroup	Phenazocine IM n/N	Pethidine IM n/N	Risk Ratio M-H,Fixed,95% CI	Weight	Risk Ratio M-H,Fixed,95% CI
Grant 1970	12/107	9/105		100.0 %	1.31 [0.58, 2.97]
Total (95% CI)	**107**	**105**		**100.0 %**	**1.31 [0.58, 2.97]**
Total events: 12 (Phenazocine IM), 9 (Pethidine IM)					
Heterogeneity: not applicable					
Test for overall effect: Z = 0.64 (P = 0.52)					
Test for subgroup differences: Not applicable					



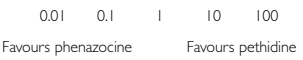
Analysis 11.2. Comparison 11 IM phenazocine versus pethidine, Outcome 2 Vomiting.

Review: Parenteral opioids for maternal pain management in labour

Comparison: 11 IM phenazocine versus pethidine

Outcome: 2 Vomiting

Study or subgroup	Phenazocine IM n/N	Pethidine IM n/N	Risk Ratio M-H,Fixed,95% CI	Weight	Risk Ratio M-H,Fixed,95% CI
Grant 1970	10/107	25/105		100.0 %	0.39 [0.20, 0.78]
Total (95% CI)	**107**	**105**		**100.0 %**	**0.39 [0.20, 0.78]**
Total events: 10 (Phenazocine IM), 25 (Pethidine IM)					
Heterogeneity: not applicable					
Test for overall effect: Z = 2.69 (P = 0.0072)					
Test for subgroup differences: Not applicable					



Analysis 12.1. Comparison 12 IM diamorphine/morphine versus pethidine, Outcome 1 Maternal satisfaction with analgesia (number of women satisfied or very satisfied).

Review: Parenteral opioids for maternal pain management in labour

Comparison: 12 IM diamorphine/morphine versus pethidine

Outcome: 1 Maternal satisfaction with analgesia (number of women satisfied or very satisfied)

Study or subgroup	Morphine IM n/N	Pethidine IM n/N	Risk Ratio M-H,Fixed,95% CI	Weight	Risk Ratio M-H,Fixed,95% CI
Wee 2014	196/244	170/240		100.0 %	1.13 [1.02, 1.26]
Total (95% CI)	**244**	**240**		**100.0 %**	**1.13 [1.02, 1.26]**
Total events: 196 (Morphine IM), 170 (Pethidine IM)					
Heterogeneity: not applicable					
Test for overall effect: Z = 2.41 (P = 0.016)					
Test for subgroup differences: Not applicable					

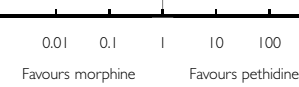
Analysis 12.2. Comparison 12 IM diamorphine/morphine versus pethidine, Outcome 2 Maternal satisfaction with analgesia measured during labour or during the postnatal period (Pain relief described as poor).

Review: Parenteral opioids for maternal pain management in labour

Comparison: 12 IM diamorphine/morphine versus pethidine

Outcome: 2 Maternal satisfaction with analgesia measured during labour or during the postnatal period (Pain relief described as poor)

Study or subgroup	Morphine IM n/N	Pethidine IM n/N	Risk Ratio M-H,Fixed,95% CI	Weight	Risk Ratio M-H,Fixed,95% CI
Prasertsawat 1986 (1)	11/45	9/45		100.0 %	1.22 [0.56, 2.66]
Total (95% CI)	**45**	**45**		**100.0 %**	**1.22 [0.56, 2.66]**
Total events: 11 (Morphine IM), 9 (Pethidine IM)					
Heterogeneity: not applicable					
Test for overall effect: Z = 0.51 (P = 0.61)					
Test for subgroup differences: Not applicable					



(1) Poor response after 1st dose.

Analysis 12.3. Comparison 12 IM diamorphine/morphine versus pethidine, Outcome 3 Maternal pain score or pain measured in labour (pain relief at 30 mins).

Review: Parenteral opioids for maternal pain management in labour

Comparison: 12 IM diamorphine/morphine versus pethidine

Outcome: 3 Maternal pain score or pain measured in labour (pain relief at 30 mins)

Study or subgroup	Morphine IM N	Mean(SD)	Pethidine IM N	Mean(SD)	Mean Difference IV,Fixed,95% CI	Weight	Mean Difference IV,Fixed,95% CI
Wee 2014	244	5.9 (2.3)	240	6.7 (2.6)		100.0 %	-0.80 [-1.24, -0.36]
Total (95% CI)	**244**		**240**			**100.0 %**	**-0.80 [-1.24, -0.36]**

Heterogeneity: not applicable

Test for overall effect: Z = 3.58 (P = 0.00034)

Test for subgroup differences: Not applicable

Analysis 12.4. Comparison 12 IM diamorphine/morphine versus pethidine, Outcome 4 Maternal pain score or pain measured in labour (pain relief at 60 mins).

Review: Parenteral opioids for maternal pain management in labour

Comparison: 12 IM diamorphine/morphine versus pethidine

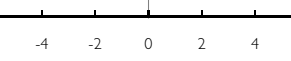
Outcome: 4 Maternal pain score or pain measured in labour (pain relief at 60 mins)

Study or subgroup	Morphine IM N	Mean(SD)	Pethidine IM N	Mean(SD)	Mean Difference IV,Fixed,95% CI	Weight	Mean Difference IV,Fixed,95% CI
Wee 2014	244	5.9 (2.5)	240	6.7 (2.7)		100.0 %	-0.80 [-1.26, -0.34]
Total (95% CI)	**244**		**240**			**100.0 %**	**-0.80 [-1.26, -0.34]**

Heterogeneity: not applicable

Test for overall effect: Z = 3.38 (P = 0.00072)

Test for subgroup differences: Not applicable

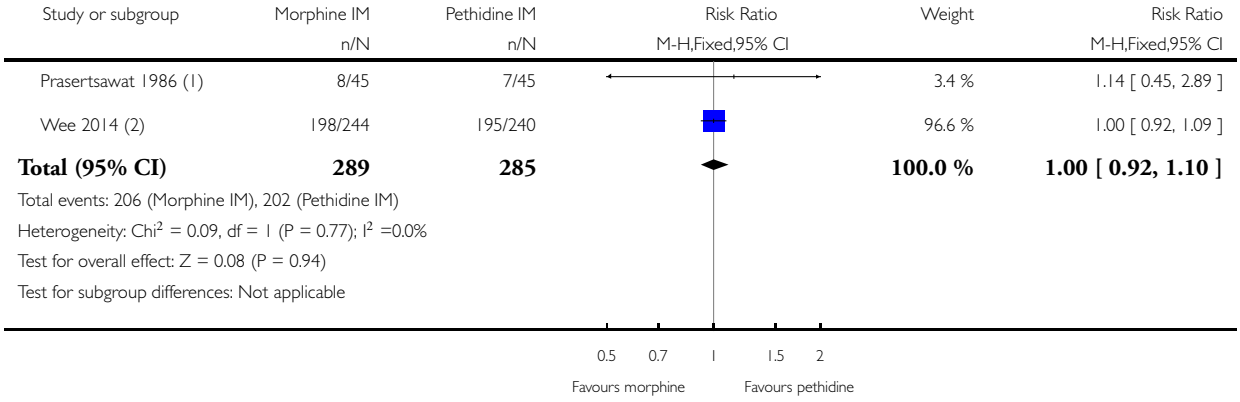


Analysis 12.5. Comparison 12 IM diamorphine/morphine versus pethidine, Outcome 5 Additional analgesia required.

Review: Parenteral opioids for maternal pain management in labour

Comparison: 12 IM diamorphine/morphine versus pethidine

Outcome: 5 Additional analgesia required



(1) 2nd dose of study drug but half initial amount

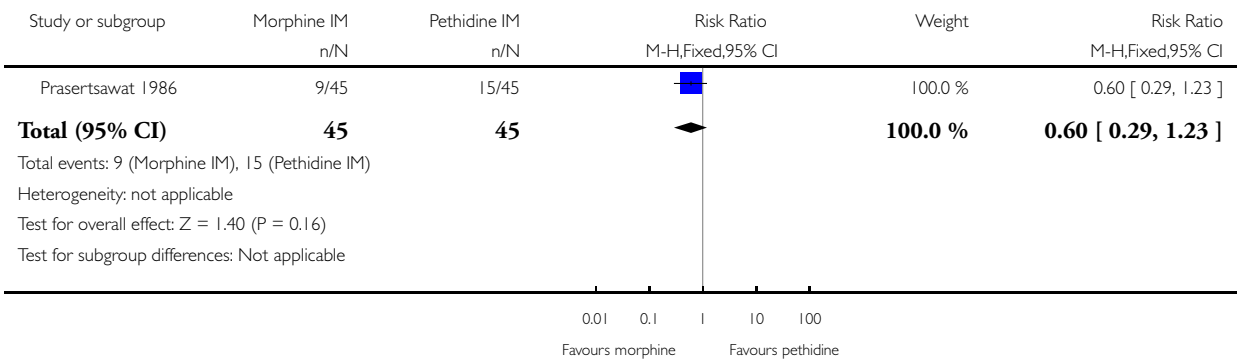
(2) Entonox

Analysis 12.6. Comparison 12 IM diamorphine/morphine versus pethidine, Outcome 6 Maternal sleepiness.

Review: Parenteral opioids for maternal pain management in labour

Comparison: 12 IM diamorphine/morphine versus pethidine

Outcome: 6 Maternal sleepiness

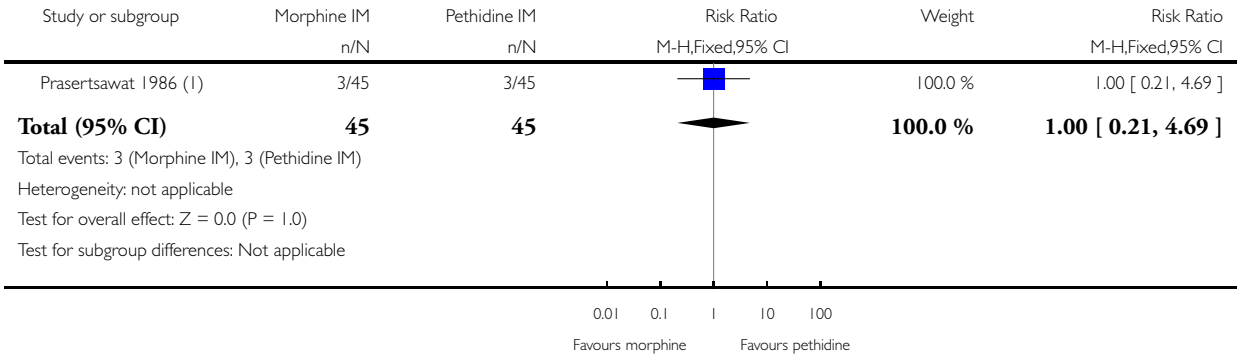


Analysis 12.7. Comparison 12 IM diamorphine/morphine versus pethidine, Outcome 7 Nausea and vomiting.

Review: Parenteral opioids for maternal pain management in labour

Comparison: 12 IM diamorphine/morphine versus pethidine

Outcome: 7 Nausea and vomiting



(1) Prasertsawat nausea - vomiting in 1/45 morphine and 2/45 pethidine.

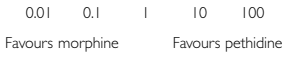
Analysis 12.8. Comparison 12 IM diamorphine/morphine versus pethidine, Outcome 8 Caesarean section.

Review: Parenteral opioids for maternal pain management in labour

Comparison: 12 IM diamorphine/morphine versus pethidine

Outcome: 8 Caesarean section

Study or subgroup	Morphine IM n/N	Pethidine IM n/N	Risk Ratio M-H,Fixed,95% CI	Weight	Risk Ratio M-H,Fixed,95% CI
Wee 2014	47/244	49/240		100.0 %	0.94 [0.66, 1.35]
Total (95% CI)	**244**	**240**		**100.0 %**	**0.94 [0.66, 1.35]**
Total events: 47 (Morphine IM), 49 (Pethidine IM)					
Heterogeneity: not applicable					
Test for overall effect: Z = 0.32 (P = 0.75)					
Test for subgroup differences: Not applicable					



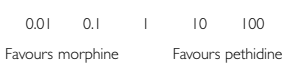
Analysis 12.9. Comparison 12 IM diamorphine/morphine versus pethidine, Outcome 9 Assisted vaginal birth.

Review: Parenteral opioids for maternal pain management in labour

Comparison: 12 IM diamorphine/morphine versus pethidine

Outcome: 9 Assisted vaginal birth

Study or subgroup	Morphine IM n/N	Pethidine IM n/N	Risk Ratio M-H,Fixed,95% CI	Weight	Risk Ratio M-H,Fixed,95% CI
Wee 2014	60/244	46/240		100.0 %	1.28 [0.91, 1.80]
Total (95% CI)	**244**	**240**		**100.0 %**	**1.28 [0.91, 1.80]**
Total events: 60 (Morphine IM), 46 (Pethidine IM)					
Heterogeneity: not applicable					
Test for overall effect: Z = 1.44 (P = 0.15)					
Test for subgroup differences: Not applicable					



Analysis 12.10. Comparison 12 IM diamorphine/morphine versus pethidine, Outcome 10 Naloxone administration.

Review: Parenteral opioids for maternal pain management in labour

Comparison: 12 IM diamorphine/morphine versus pethidine

Outcome: 10 Naloxone administration

Study or subgroup	Morphine IM n/N	Pethidine IM n/N	Risk Ratio M-H,Fixed,95% CI	Weight	Risk Ratio M-H,Fixed,95% CI
Wee 2014	3/244	3/240		100.0 %	0.98 [0.20, 4.83]
Total (95% CI)	**244**	**240**		**100.0 %**	**0.98 [0.20, 4.83]**

Total events: 3 (Morphine IM), 3 (Pethidine IM)

Heterogeneity: not applicable

Test for overall effect: Z = 0.02 (P = 0.98)

Test for subgroup differences: Not applicable

Analysis 12.11. Comparison 12 IM diamorphine/morphine versus pethidine, Outcome 11 Neonatal resuscitation.

Review: Parenteral opioids for maternal pain management in labour

Comparison: 12 IM diamorphine/morphine versus pethidine

Outcome: 11 Neonatal resuscitation

Study or subgroup	Morphine IM n/N	Pethidine IM n/N	Risk Ratio M-H,Fixed,95% CI	Weight	Risk Ratio M-H,Fixed,95% CI
Prasertsawat 1986	0/45	0/45			Not estimable
Wee 2014	43/244	44/240		100.0 %	0.96 [0.66, 1.41]
Total (95% CI)	**289**	**285**		**100.0 %**	**0.96 [0.66, 1.41]**

Total events: 43 (Morphine IM), 44 (Pethidine IM)

Heterogeneity: not applicable

Test for overall effect: Z = 0.20 (P = 0.84)

Test for subgroup differences: Not applicable

Analysis 12.12. Comparison 12 IM diamorphine/morphine versus pethidine, Outcome 12 Apgar < 7 at 1 minute.

Review: Parenteral opioids for maternal pain management in labour

Comparison: 12 IM diamorphine/morphine versus pethidine

Outcome: 12 Apgar < 7 at 1 minute

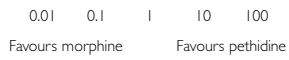
Study or subgroup	Morphine IM n/N	Pethidine IM n/N	Risk Ratio M-H,Fixed,95% CI	Weight	Risk Ratio M-H,Fixed,95% CI
Prasertsawat 1986	0/45	0/45			Not estimable
Wee 2014	42/244	36/240		100.0 %	1.15 [0.76, 1.73]
Total (95% CI)	**289**	**285**		**100.0 %**	**1.15 [0.76, 1.73]**

Total events: 42 (Morphine IM), 36 (Pethidine IM)

Heterogeneity: not applicable

Test for overall effect: Z = 0.66 (P = 0.51)

Test for subgroup differences: Not applicable



Analysis 12.13. Comparison 12 IM diamorphine/morphine versus pethidine, Outcome 13 Admission to NICU.

Review: Parenteral opioids for maternal pain management in labour

Comparison: 12 IM diamorphine/morphine versus pethidine

Outcome: 13 Admission to NICU

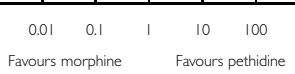
Study or subgroup	Morphine IM n/N	Pethidine IM n/N	Risk Ratio M-H,Fixed,95% CI	Weight	Risk Ratio M-H,Fixed,95% CI
Wee 2014	8/244	9/240		100.0 %	0.87 [0.34, 2.23]
Total (95% CI)	**244**	**240**		**100.0 %**	**0.87 [0.34, 2.23]**

Total events: 8 (Morphine IM), 9 (Pethidine IM)

Heterogeneity: not applicable

Test for overall effect: Z = 0.28 (P = 0.78)

Test for subgroup differences: Not applicable

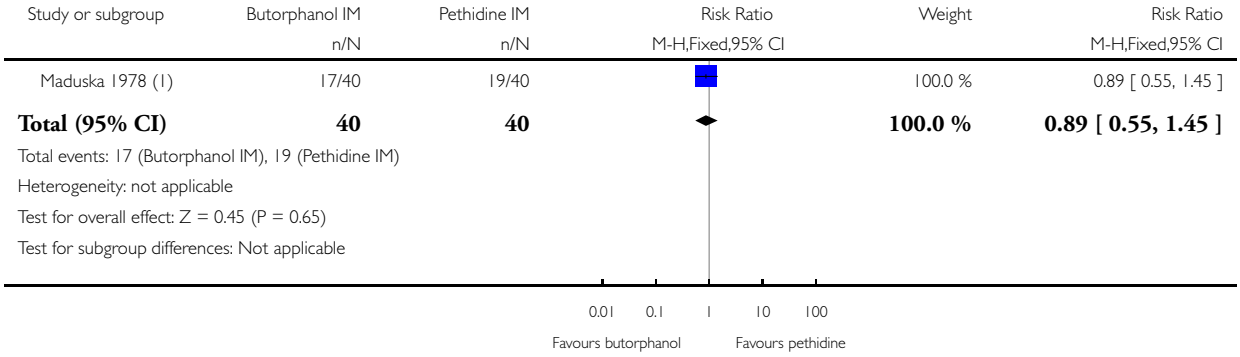


Analysis 13.1. Comparison 13 IM butorphanol versus pethidine, Outcome 1 Additional analgesia required.

Review: Parenteral opioids for maternal pain management in labour

Comparison: 13 IM butorphanol versus pethidine

Outcome: 1 Additional analgesia required



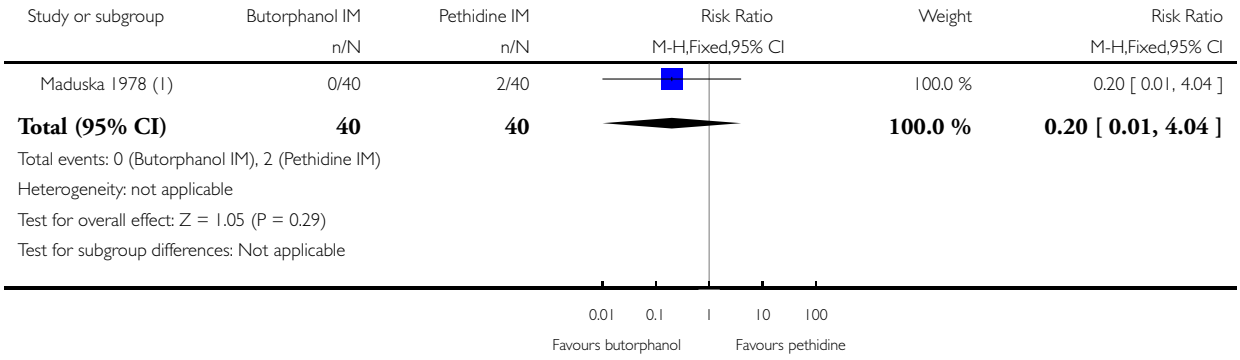
(1) 2nd dose of study drug

Analysis 13.2. Comparison 13 IM butorphanol versus pethidine, Outcome 2 Nausea.

Review: Parenteral opioids for maternal pain management in labour

Comparison: 13 IM butorphanol versus pethidine

Outcome: 2 Nausea



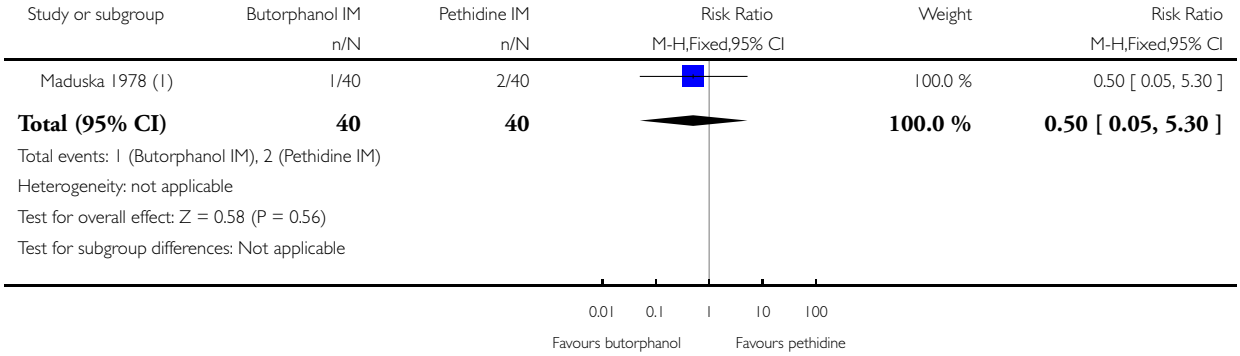
(1) Unclear when assessed

Analysis 13.3. Comparison 13 IM butorphanol versus pethidine, Outcome 3 Vomiting.

Review: Parenteral opioids for maternal pain management in labour

Comparison: 13 IM butorphanol versus pethidine

Outcome: 3 Vomiting



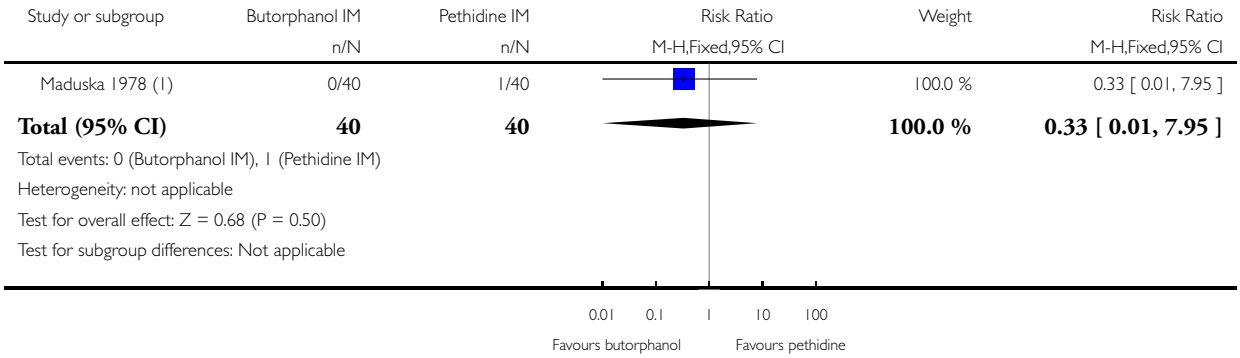
(1) Unclear when assessed

Analysis 13.4. Comparison 13 IM butorphanol versus pethidine, Outcome 4 Neonatal resuscitation.

Review: Parenteral opioids for maternal pain management in labour

Comparison: 13 IM butorphanol versus pethidine

Outcome: 4 Neonatal resuscitation



(1) received 2 doses of pethidine (40 mg x 2)

Analysis 13.5. Comparison 13 IM butorphanol versus pethidine, Outcome 5 Naloxone administration (neonatal).

Review: Parenteral opioids for maternal pain management in labour

Comparison: 13 IM butorphanol versus pethidine

Outcome: 5 Naloxone administration (neonatal)

Study or subgroup	Butorphanol IM n/N	Pethidine IM n/N	Risk Ratio M-H,Fixed,95% CI	Weight	Risk Ratio M-H,Fixed,95% CI
Maduska 1978 (1)	0/40	1/40		100.0 %	0.33 [0.01, 7.95]
Total (95% CI)	**40**	**40**		**100.0 %**	**0.33 [0.01, 7.95]**

Total events: 0 (Butorphanol IM), 1 (Pethidine IM)
Heterogeneity: not applicable
Test for overall effect: Z = 0.68 (P = 0.50)
Test for subgroup differences: Not applicable

(1) received 2 doses of pethidine (40 mg x 2)

Analysis 14.1. Comparison 14 IM Avacan® versus IM pentazocine, Outcome 1 Additional analgesia required - Entonox.

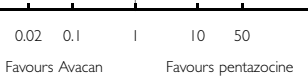
Review: Parenteral opioids for maternal pain management in labour

Comparison: 14 IM Avacan versus IM pentazocine

Outcome: 1 Additional analgesia required - Entonox

Study or subgroup	Avacan n/N	Pentazocine n/N	Risk Ratio M-H,Fixed,95% CI	Weight	Risk Ratio M-H,Fixed,95% CI
Hamann 1972	18/81	19/79		100.0 %	0.92 [0.53, 1.63]
Total (95% CI)	**81**	**79**		**100.0 %**	**0.92 [0.53, 1.63]**

Total events: 18 (Avacan), 19 (Pentazocine)
Heterogeneity: not applicable
Test for overall effect: Z = 0.27 (P = 0.78)
Test for subgroup differences: Not applicable



Analysis 14.2. Comparison 14 IM Avacan® versus IM pentazocine, Outcome 2 Additional analgesia required - pudendal-paracervical block.

Review: Parenteral opioids for maternal pain management in labour

Comparison: 14 IM Avacan versus IM pentazocine

Outcome: 2 Additional analgesia required - pudendal-paracervical block

Study or subgroup	Avacan n/N	Pentazocine n/N	Risk Ratio M-H,Fixed,95% CI	Weight	Risk Ratio M-H,Fixed,95% CI
Hamann 1972	29/81	14/79		100.0 %	2.02 [1.16, 3.53]
Total (95% CI)	**81**	**79**		**100.0 %**	**2.02 [1.16, 3.53]**
Total events: 29 (Avacan), 14 (Pentazocine)					
Heterogeneity: not applicable					
Test for overall effect: Z = 2.47 (P = 0.013)					
Test for subgroup differences: Not applicable					

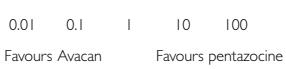
Analysis 14.3. Comparison 14 IM Avacan® versus IM pentazocine, Outcome 3 Caesarean section.

Review: Parenteral opioids for maternal pain management in labour

Comparison: 14 IM Avacan versus IM pentazocine

Outcome: 3 Caesarean section

Study or subgroup	Avacan n/N	Pentazocine n/N	Risk Ratio M-H,Fixed,95% CI	Weight	Risk Ratio M-H,Fixed,95% CI
Hamann 1972 (1)	5/92	8/92		100.0 %	0.63 [0.21, 1.84]
Total (95% CI)	**92**	**92**		**100.0 %**	**0.63 [0.21, 1.84]**
Total events: 5 (Avacan), 8 (Pentazocine)					
Heterogeneity: not applicable					
Test for overall effect: Z = 0.85 (P = 0.39)					
Test for subgroup differences: Not applicable					



(1) Denominators not clear (women having CS were excluded from analyses in study report).

Analysis 14.4. Comparison 14 IM Avacan® versus IM pentazocine, Outcome 4 Low Apgar score (< 7) "at birth".

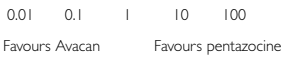
Review: Parenteral opioids for maternal pain management in labour

Comparison: 14 IM Avacan versus IM pentazocine

Outcome: 4 Low Apgar score (< 7) "at birth"

Study or subgroup	Avacan n/N	Pentazocine n/N	Risk Ratio M-H,Fixed,95% CI	Weight	Risk Ratio M-H,Fixed,95% CI
Hamann 1972	9/81	15/79		100.0 %	0.59 [0.27, 1.26]
Total (95% CI)	**81**	**79**		**100.0 %**	**0.59 [0.27, 1.26]**

Total events: 9 (Avacan), 15 (Pentazocine)
Heterogeneity: not applicable
Test for overall effect: Z = 1.37 (P = 0.17)
Test for subgroup differences: Not applicable



Analysis 15.1. Comparison 15 IM pentazocine versus IM Pethilorfan®, Outcome 1 Maternal pain score measured during labour (Pain relief (women NOT obtaining pain relief) at 1 hour).

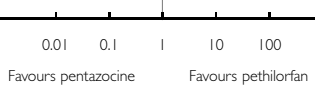
Review: Parenteral opioids for maternal pain management in labour

Comparison: 15 IM pentazocine versus IM Pethilorfan

Outcome: 1 Maternal pain score measured during labour (Pain relief (women NOT obtaining pain relief) at 1 hour)

Study or subgroup	Pentazocine n/N	Pethilorfan n/N	Risk Ratio M-H,Fixed,95% CI	Weight	Risk Ratio M-H,Fixed,95% CI
O'Dwyer 1971 (1)	18/32	17/37		100.0 %	1.22 [0.77, 1.95]
Total (95% CI)	**32**	**37**		**100.0 %**	**1.22 [0.77, 1.95]**

Total events: 18 (Pentazocine), 17 (Pethilorfan)
Heterogeneity: not applicable
Test for overall effect: Z = 0.85 (P = 0.39)
Test for subgroup differences: Not applicable



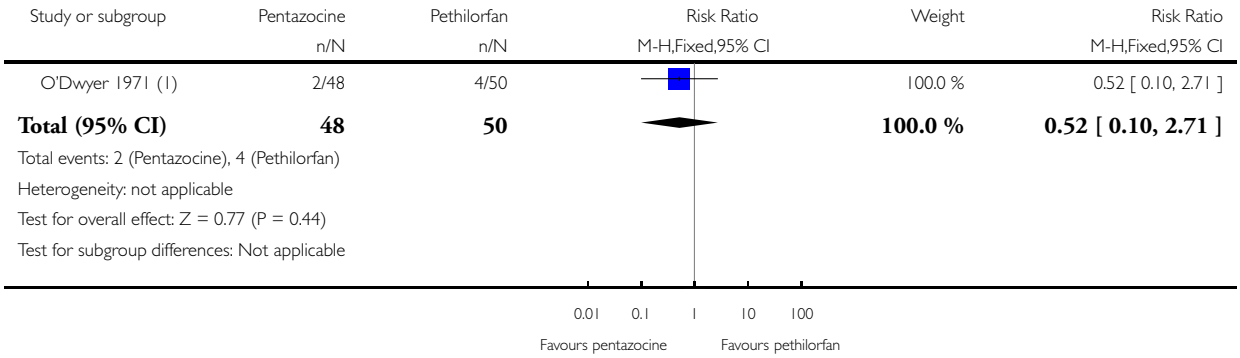
(1) After 1st dose only

Analysis 15.2. Comparison 15 IM pentazocine versus IM Pethilorfan®, Outcome 2 Additional analgesia required.

Review: Parenteral opioids for maternal pain management in labour

Comparison: 15 IM pentazocine versus IM Pethilorfan

Outcome: 2 Additional analgesia required



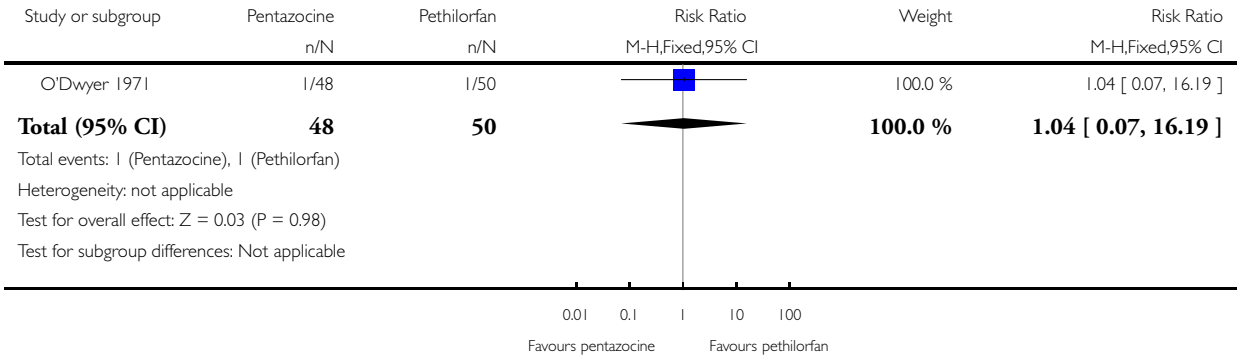
(1) 2nd dose of study drug

Analysis 15.3. Comparison 15 IM pentazocine versus IM Pethilorfan®, Outcome 3 Assisted vaginal birth.

Review: Parenteral opioids for maternal pain management in labour

Comparison: 15 IM pentazocine versus IM Pethilorfan

Outcome: 3 Assisted vaginal birth



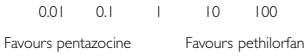
Analysis 15.4. Comparison 15 IM pentazocine versus IM Pethilorfan®, Outcome 4 Apgar < 8 at 1 minute (non pre-specified).

Review: Parenteral opioids for maternal pain management in labour

Comparison: 15 IM pentazocine versus IM Pethilorfan

Outcome: 4 Apgar < 8 at 1 minute (non pre-specified)

Study or subgroup	Pentazocine n/N	Pethilorfan n/N	Risk Ratio M-H,Fixed,95% CI	Weight	Risk Ratio M-H,Fixed,95% CI
O'Dwyer 1971	6/42	1/40		100.0 %	5.71 [0.72, 45.39]
Total (95% CI)	**42**	**40**		**100.0 %**	**5.71 [0.72, 45.39]**
Total events: 6 (Pentazocine), 1 (Pethilorfan)					
Heterogeneity: not applicable					
Test for overall effect: Z = 1.65 (P = 0.099)					
Test for subgroup differences: Not applicable					



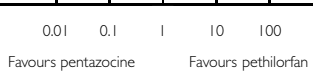
Analysis 15.5. Comparison 15 IM pentazocine versus IM Pethilorfan®, Outcome 5 Apgar < 8 at 5 minutes (non pre-specified).

Review: Parenteral opioids for maternal pain management in labour

Comparison: 15 IM pentazocine versus IM Pethilorfan

Outcome: 5 Apgar < 8 at 5 minutes (non pre-specified)

Study or subgroup	Pentazocine n/N	Pethilorfan n/N	Risk Ratio M-H,Fixed,95% CI	Weight	Risk Ratio M-H,Fixed,95% CI
O'Dwyer 1971	0/42	0/40			Not estimable
Total (95% CI)	**42**	**40**			**Not estimable**
Total events: 0 (Pentazocine), 0 (Pethilorfan)					
Heterogeneity: not applicable					
Test for overall effect: not applicable					
Test for subgroup differences: Not applicable					

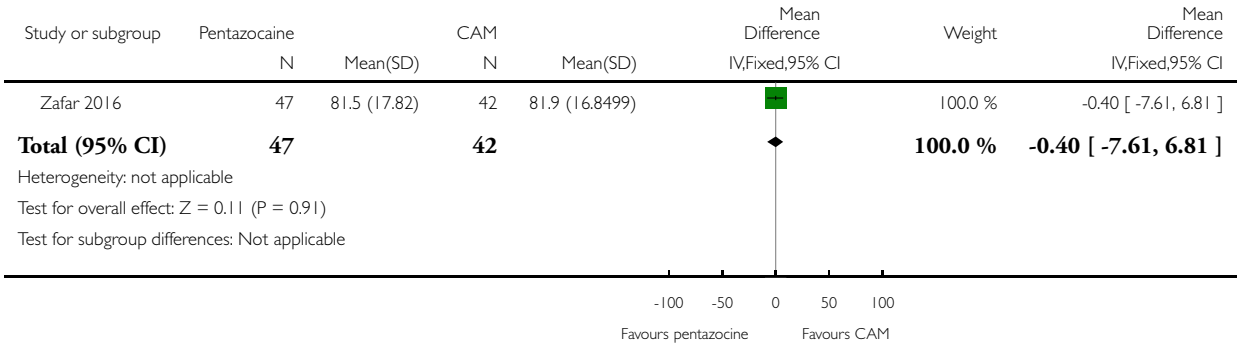


Analysis 16.1. Comparison 16 IM pentazocine versus complementary and alternate medicine (CAM), Outcome 1 Maternal pain score measured during labour.

Review: Parenteral opioids for maternal pain management in labour

Comparison: 16 IM pentazocine versus complementary and alternate medicine (CAM)

Outcome: 1 Maternal pain score measured during labour

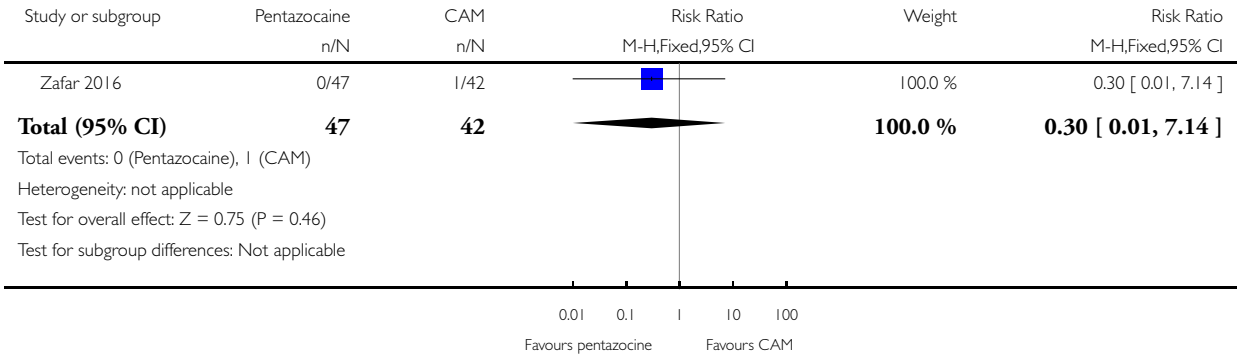


Analysis 16.2. Comparison 16 IM pentazocine versus complementary and alternate medicine (CAM), Outcome 2 Nausea and vomiting.

Review: Parenteral opioids for maternal pain management in labour

Comparison: 16 IM pentazocine versus complementary and alternate medicine (CAM)

Outcome: 2 Nausea and vomiting

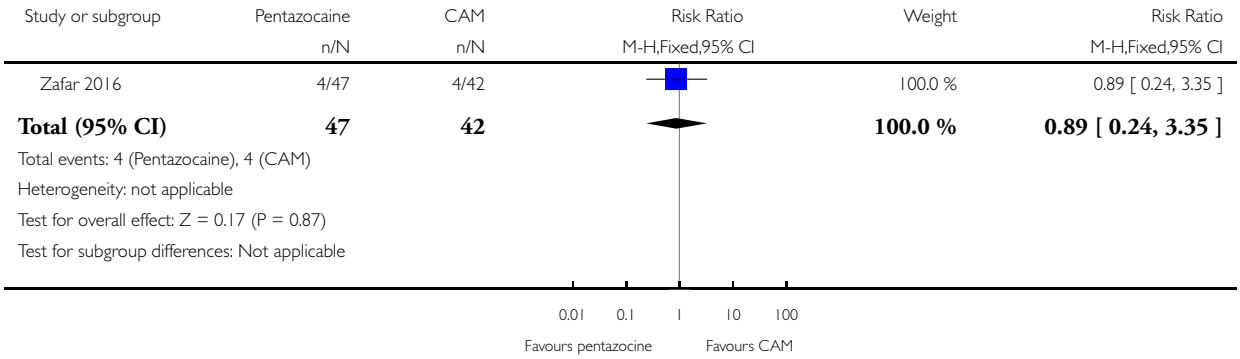


Analysis 16.3. Comparison 16 IM pentazocine versus complementary and alternate medicine (CAM), Outcome 3 Caesarean section.

Review: Parenteral opioids for maternal pain management in labour

Comparison: 16 IM pentazocine versus complementary and alternate medicine (CAM)

Outcome: 3 Caesarean section

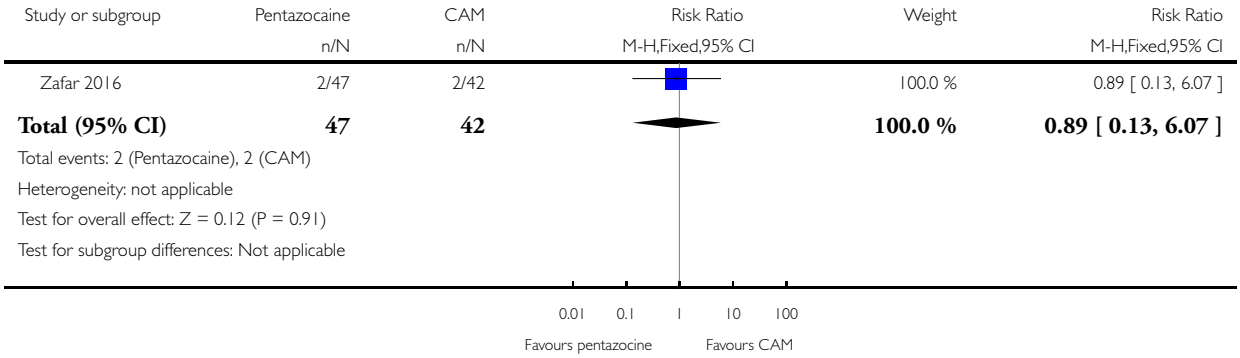


Analysis 16.4. Comparison 16 IM pentazocine versus complementary and alternate medicine (CAM), Outcome 4 Assisted vaginal delivery.

Review: Parenteral opioids for maternal pain management in labour

Comparison: 16 IM pentazocine versus complementary and alternate medicine (CAM)

Outcome: 4 Assisted vaginal delivery



Analysis 17.1. Comparison 17 IM pentazocine versus IM tramadol, Outcome 1 Maternal satisfaction with analgesia measured during labour (pain relief after 30 mins).

Review: Parenteral opioids for maternal pain management in labour

Comparison: 17 IM pentazocine versus IM tramadol

Outcome: 1 Maternal satisfaction with analgesia measured during labour (pain relief after 30 mins)

Study or subgroup	Pentazocine n/N	Tramadol n/N	Risk Ratio M-H,Fixed,95% CI	Weight	Risk Ratio M-H,Fixed,95% CI
Kuti 2008	24/50	10/50		100.0 %	2.40 [1.28, 4.48]
Total (95% CI)	**50**	**50**		**100.0 %**	**2.40 [1.28, 4.48]**
Total events: 24 (Pentazocine), 10 (Tramadol)					
Heterogeneity: not applicable					
Test for overall effect: Z = 2.75 (P = 0.0060)					
Test for subgroup differences: Not applicable					

Analysis 17.2. Comparison 17 IM pentazocine versus IM tramadol, Outcome 2 Maternal satisfaction with analgesia measured during labour (pain after 60 mins).

Review: Parenteral opioids for maternal pain management in labour

Comparison: 17 IM pentazocine versus IM tramadol

Outcome: 2 Maternal satisfaction with analgesia measured during labour (pain after 60 mins)

Study or subgroup	Pentazocine n/N	Tramadol n/N	Risk Ratio M-H,Fixed,95% CI	Weight	Risk Ratio M-H,Fixed,95% CI
Kuti 2008	21/50	13/50		100.0 %	1.62 [0.91, 2.86]
Total (95% CI)	**50**	**50**		**100.0 %**	**1.62 [0.91, 2.86]**
Total events: 21 (Pentazocine), 13 (Tramadol)					
Heterogeneity: not applicable					
Test for overall effect: Z = 1.65 (P = 0.099)					
Test for subgroup differences: Not applicable					

Analysis 17.3. Comparison 17 IM pentazocine versus IM tramadol, Outcome 3 Maternal pain score or pain measured in labour (moderate or severe at 30 mins).

Review: Parenteral opioids for maternal pain management in labour

Comparison: 17 IM pentazocine versus IM tramadol

Outcome: 3 Maternal pain score or pain measured in labour (moderate or severe at 30 mins)

Study or subgroup	Pentazocine n/N	Tramadol n/N	Risk Ratio M-H,Fixed,95% CI	Weight	Risk Ratio M-H,Fixed,95% CI
Kuti 2008	27/50	36/50		100.0 %	0.75 [0.55, 1.02]
Total (95% CI)	**50**	**50**		**100.0 %**	**0.75 [0.55, 1.02]**
Total events: 27 (Pentazocine), 36 (Tramadol)					
Heterogeneity: not applicable					
Test for overall effect: Z = 1.83 (P = 0.068)					
Test for subgroup differences: Not applicable					

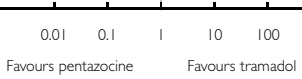
Analysis 17.4. Comparison 17 IM pentazocine versus IM tramadol, Outcome 4 Maternal pain score or pain measured in labour (moderate or severe at 60 mins).

Review: Parenteral opioids for maternal pain management in labour

Comparison: 17 IM pentazocine versus IM tramadol

Outcome: 4 Maternal pain score or pain measured in labour (moderate or severe at 60 mins)

Study or subgroup	Pentazocine n/N	Tramadol n/N	Risk Ratio M-H,Fixed,95% CI	Weight	Risk Ratio M-H,Fixed,95% CI
Kuti 2008	29/50	36/50		100.0 %	0.81 [0.60, 1.08]
Total (95% CI)	**50**	**50**		**100.0 %**	**0.81 [0.60, 1.08]**
Total events: 29 (Pentazocine), 36 (Tramadol)					
Heterogeneity: not applicable					
Test for overall effect: Z = 1.45 (P = 0.15)					
Test for subgroup differences: Not applicable					



Analysis 17.5. Comparison 17 IM pentazocine versus IM tramadol, Outcome 5 Maternal sleepiness during labour.

Review: Parenteral opioids for maternal pain management in labour

Comparison: 17 IM pentazocine versus IM tramadol

Outcome: 5 Maternal sleepiness during labour

Study or subgroup	Pentazocine n/N	Tramadol n/N	Risk Ratio M-H,Fixed,95% CI	Weight	Risk Ratio M-H,Fixed,95% CI
Kuti 2008	10/50	6/50		100.0 %	1.67 [0.66, 4.24]
Total (95% CI)	**50**	**50**		**100.0 %**	**1.67 [0.66, 4.24]**

Total events: 10 (Pentazocine), 6 (Tramadol)
Heterogeneity: not applicable
Test for overall effect: Z = 1.07 (P = 0.28)
Test for subgroup differences: Not applicable

Analysis 17.6. Comparison 17 IM pentazocine versus IM tramadol, Outcome 6 Nausea and vomiting.

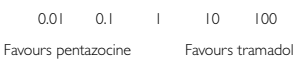
Review: Parenteral opioids for maternal pain management in labour

Comparison: 17 IM pentazocine versus IM tramadol

Outcome: 6 Nausea and vomiting

Study or subgroup	Pentazocine n/N	Tramadol n/N	Risk Ratio M-H,Fixed,95% CI	Weight	Risk Ratio M-H,Fixed,95% CI
Kuti 2008	1/50	1/50		100.0 %	1.00 [0.06, 15.55]
Total (95% CI)	**50**	**50**		**100.0 %**	**1.00 [0.06, 15.55]**

Total events: 1 (Pentazocine), 1 (Tramadol)
Heterogeneity: not applicable
Test for overall effect: Z = 0.0 (P = 1.0)
Test for subgroup differences: Not applicable



Analysis 17.7. Comparison 17 IM pentazocine versus IM tramadol, Outcome 7 Caesarean section.

Review: Parenteral opioids for maternal pain management in labour

Comparison: 17 IM pentazocine versus IM tramadol

Outcome: 7 Caesarean section

Study or subgroup	Pentazocine n/N	Tramadol n/N	Risk Ratio M-H,Fixed,95% CI	Weight	Risk Ratio M-H,Fixed,95% CI
Kuti 2008	6/50	4/50		100.0 %	1.50 [0.45, 4.99]
Total (95% CI)	**50**	**50**		**100.0 %**	**1.50 [0.45, 4.99]**
Total events: 6 (Pentazocine), 4 (Tramadol)					
Heterogeneity: not applicable					
Test for overall effect: Z = 0.66 (P = 0.51)					
Test for subgroup differences: Not applicable					

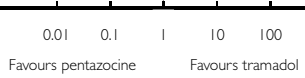
Analysis 17.8. Comparison 17 IM pentazocine versus IM tramadol, Outcome 8 Assisted vaginal delivery.

Review: Parenteral opioids for maternal pain management in labour

Comparison: 17 IM pentazocine versus IM tramadol

Outcome: 8 Assisted vaginal delivery

Study or subgroup	Pentazocine n/N	Tramadol n/N	Risk Ratio M-H,Fixed,95% CI	Weight	Risk Ratio M-H,Fixed,95% CI
Kuti 2008	2/50	1/50		100.0 %	2.00 [0.19, 21.36]
Total (95% CI)	**50**	**50**		**100.0 %**	**2.00 [0.19, 21.36]**
Total events: 2 (Pentazocine), 1 (Tramadol)					
Heterogeneity: not applicable					
Test for overall effect: Z = 0.57 (P = 0.57)					
Test for subgroup differences: Not applicable					



Analysis 17.9. Comparison 17 IM pentazocine versus IM tramadol, Outcome 9 Apgar score < 7 at 1 minute.

Review: Parenteral opioids for maternal pain management in labour

Comparison: 17 IM pentazocine versus IM tramadol

Outcome: 9 Apgar score < 7 at 1 minute

Study or subgroup	Pentazocine n/N	Tramadol n/N	Risk Ratio M-H,Fixed,95% CI	Weight	Risk Ratio M-H,Fixed,95% CI
Kuti 2008	5/50	3/50		100.0 %	1.67 [0.42, 6.60]
Total (95% CI)	**50**	**50**		**100.0 %**	**1.67 [0.42, 6.60]**
Total events: 5 (Pentazocine), 3 (Tramadol)					
Heterogeneity: not applicable					
Test for overall effect: Z = 0.73 (P = 0.47)					
Test for subgroup differences: Not applicable					

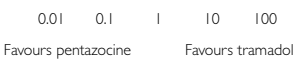
Analysis 17.10. Comparison 17 IM pentazocine versus IM tramadol, Outcome 10 Apgar score < 7 at 5 minutes.

Review: Parenteral opioids for maternal pain management in labour

Comparison: 17 IM pentazocine versus IM tramadol

Outcome: 10 Apgar score < 7 at 5 minutes

Study or subgroup	Pentazocine n/N	Tramadol n/N	Risk Ratio M-H,Fixed,95% CI	Weight	Risk Ratio M-H,Fixed,95% CI
Kuti 2008	1/50	0/50		100.0 %	3.00 [0.13, 71.92]
Total (95% CI)	**50**	**50**		**100.0 %**	**3.00 [0.13, 71.92]**
Total events: 1 (Pentazocine), 0 (Tramadol)					
Heterogeneity: not applicable					
Test for overall effect: Z = 0.68 (P = 0.50)					
Test for subgroup differences: Not applicable					

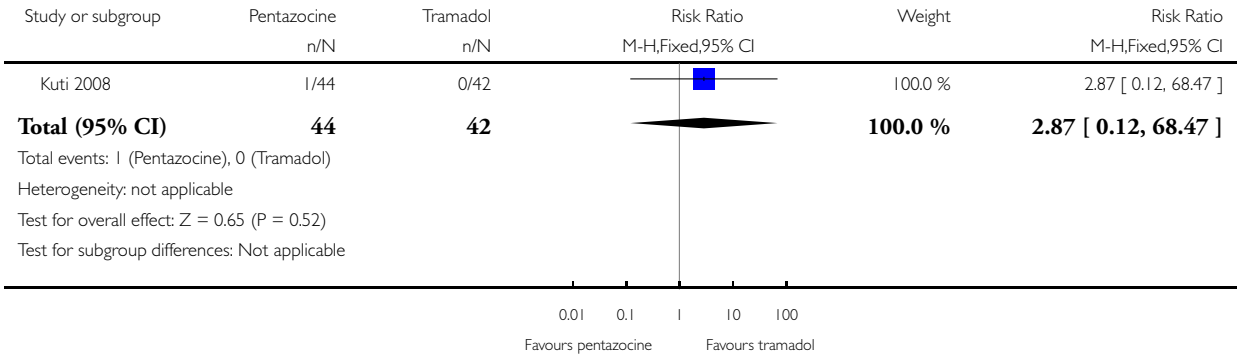


Analysis 17.11. Comparison 17 IM pentazocine versus IM tramadol, Outcome 11 Admission to NICU.

Review: Parenteral opioids for maternal pain management in labour

Comparison: 17 IM pentazocine versus IM tramadol

Outcome: 11 Admission to NICU

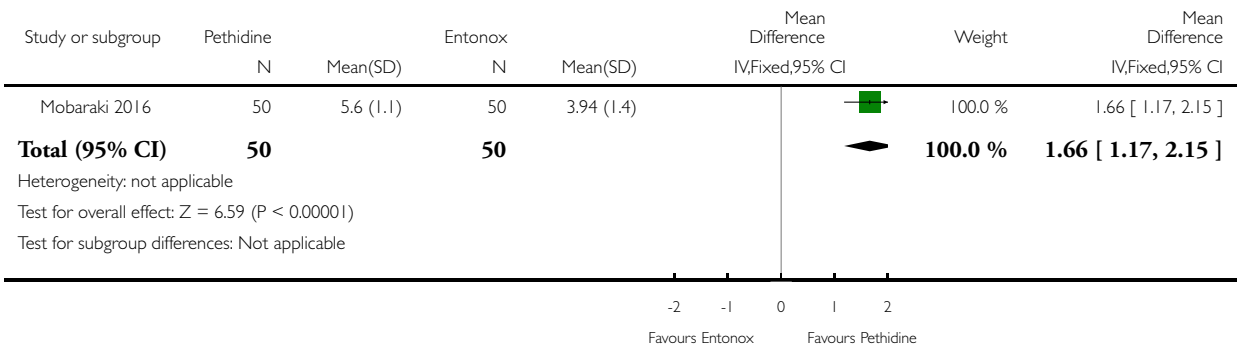


Analysis 18.1. Comparison 18 IM pethidine versus Entonox, Outcome 1 Maternal pain score or pain measured in labour (after 30 mins).

Review: Parenteral opioids for maternal pain management in labour

Comparison: 18 IM pethidine versus Entonox

Outcome: 1 Maternal pain score or pain measured in labour (after 30 mins)

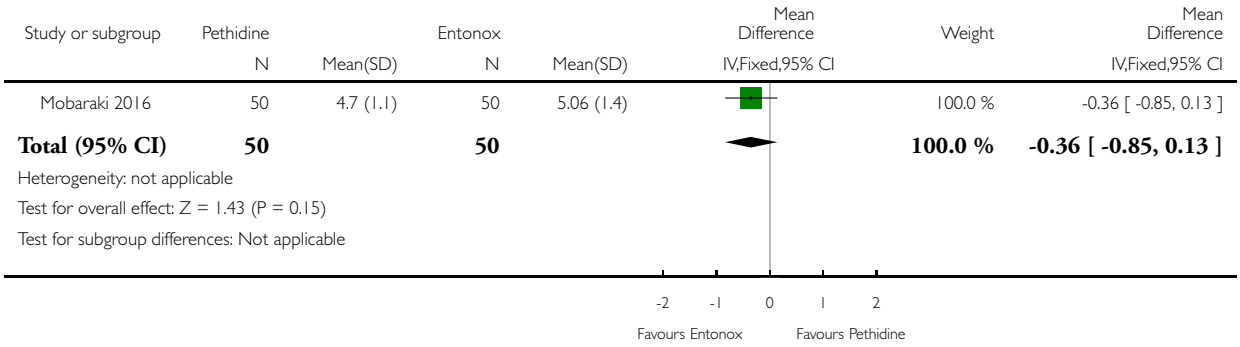


Analysis 18.2. Comparison 18 IM pethidine versus Entonox, Outcome 2 Maternal pain score or pain measured in labour (after 60 mins).

Review: Parenteral opioids for maternal pain management in labour

Comparison: 18 IM pethidine versus Entonox

Outcome: 2 Maternal pain score or pain measured in labour (after 60 mins)

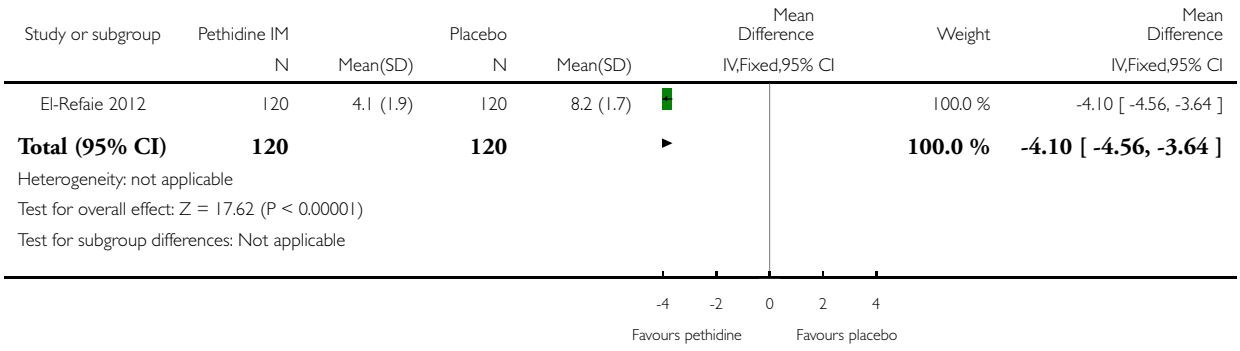


Analysis 19.1. Comparison 19 IV pethidine versus placebo, Outcome 1 Maternal pain score or pain measured in labour (Pain score 30 mins post analgesia).

Review: Parenteral opioids for maternal pain management in labour

Comparison: 19 IV pethidine versus placebo

Outcome: 1 Maternal pain score or pain measured in labour (Pain score 30 mins post analgesia)

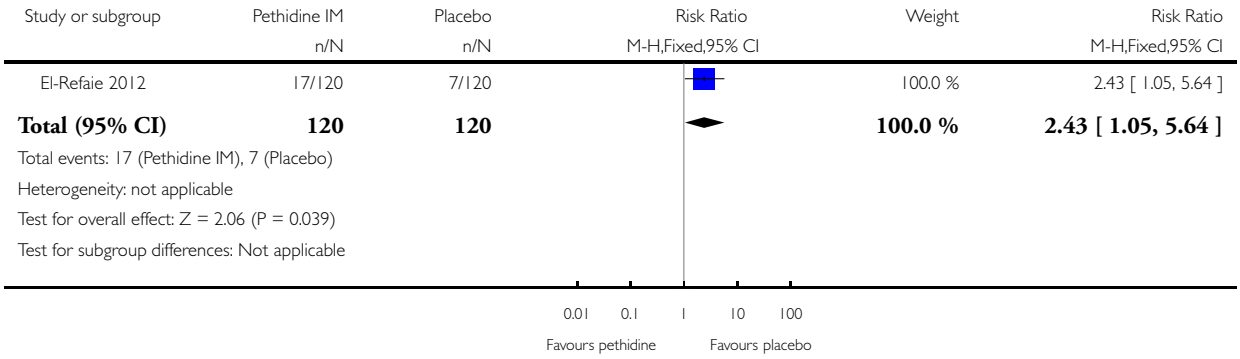


Analysis 19.2. Comparison 19 IV pethidine versus placebo, Outcome 2 Nausea and vomiting.

Review: Parenteral opioids for maternal pain management in labour

Comparison: 19 IV pethidine versus placebo

Outcome: 2 Nausea and vomiting

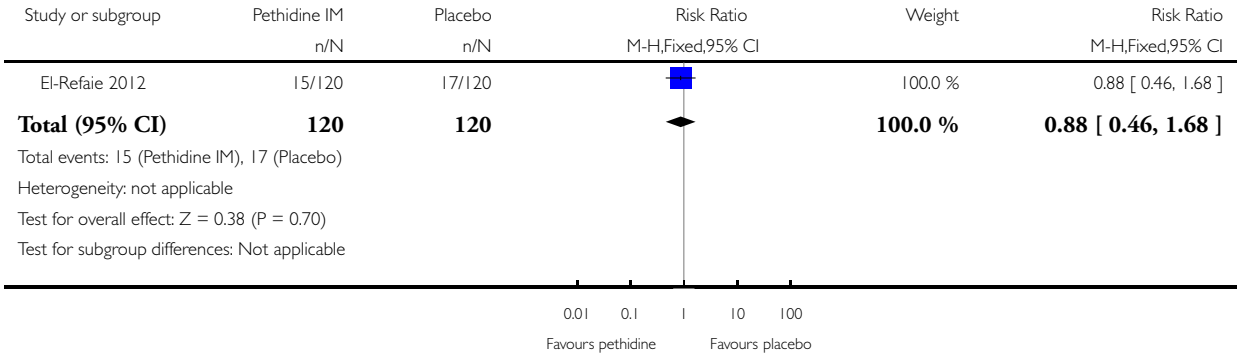


Analysis 19.3. Comparison 19 IV pethidine versus placebo, Outcome 3 Caesarean section.

Review: Parenteral opioids for maternal pain management in labour

Comparison: 19 IV pethidine versus placebo

Outcome: 3 Caesarean section

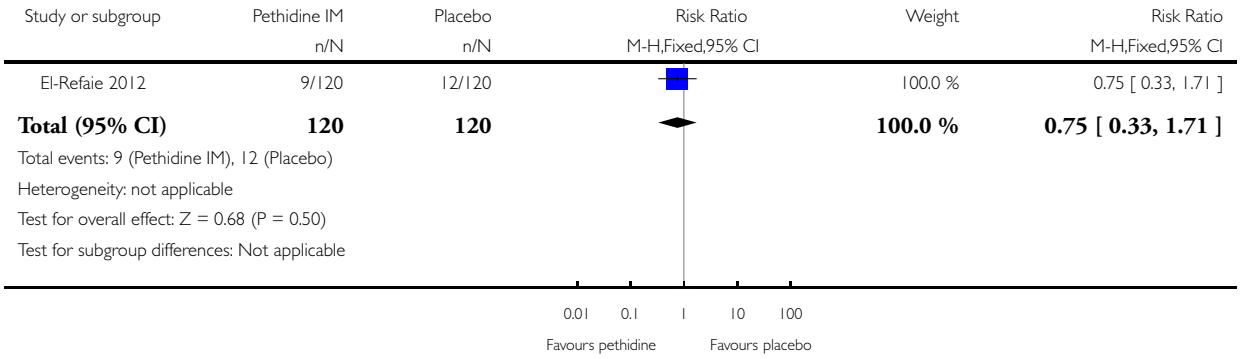


Analysis 19.4. Comparison 19 IV pethidine versus placebo, Outcome 4 Assisted vaginal birth.

Review: Parenteral opioids for maternal pain management in labour

Comparison: 19 IV pethidine versus placebo

Outcome: 4 Assisted vaginal birth

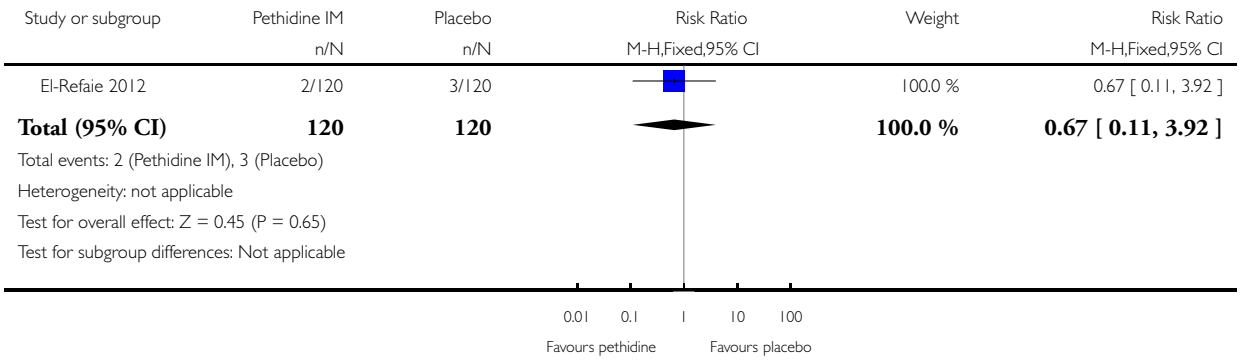


Analysis 19.5. Comparison 19 IV pethidine versus placebo, Outcome 5 Admission to NICU.

Review: Parenteral opioids for maternal pain management in labour

Comparison: 19 IV pethidine versus placebo

Outcome: 5 Admission to NICU



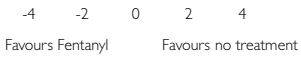
Analysis 20.1. Comparison 20 IV fentanyl versus no treatment, Outcome 1 Maternal pain score or pain measured in labour (Pain score 1 hour post-analgesia).

Review: Parenteral opioids for maternal pain management in labour

Comparison: 20 IV fentanyl versus no treatment

Outcome: 1 Maternal pain score or pain measured in labour (Pain score 1 hour post-analgesia)

Study or subgroup	Fentanyl N	Mean(SD)	No treatment N	Mean(SD)	Mean Difference IV,Fixed,95% CI	Weight	Mean Difference IV,Fixed,95% CI
Jahani 2013	35	3 (1)	35	8 (1)		100.0 %	-5.00 [-5.47, -4.53]
Total (95% CI)	**35**		**35**			**100.0 %**	**-5.00 [-5.47, -4.53]**
Heterogeneity: not applicable							
Test for overall effect: Z = 20.92 (P < 0.00001)							
Test for subgroup differences: Not applicable							



Analysis 20.2. Comparison 20 IV fentanyl versus no treatment, Outcome 2 Maternal pain score or pain measured in labour (Pain intensity (Severe) after 1 hour).

Review: Parenteral opioids for maternal pain management in labour

Comparison: 20 IV fentanyl versus no treatment

Outcome: 2 Maternal pain score or pain measured in labour (Pain intensity (Severe) after 1 hour)

Study or subgroup	Fentanyl n/N	No treatment n/N	Risk Ratio M-H,Fixed,95% CI	Weight	Risk Ratio M-H,Fixed,95% CI
Jahani 2013	0/35	31/35		100.0 %	0.02 [0.00, 0.25]
Total (95% CI)	**35**	**35**		**100.0 %**	**0.02 [0.00, 0.25]**
Total events: 0 (Fentanyl), 31 (No treatment)					
Heterogeneity: not applicable					
Test for overall effect: Z = 2.95 (P = 0.0032)					
Test for subgroup differences: Not applicable					

Analysis 20.3. Comparison 20 IV fentanyl versus no treatment, Outcome 3 Caesarean section.

Review: Parenteral opioids for maternal pain management in labour

Comparison: 20 IV fentanyl versus no treatment

Outcome: 3 Caesarean section

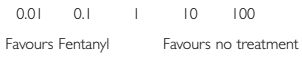
Study or subgroup	Fentanyl n/N	No treatment n/N	Risk Ratio M-H,Fixed,95% CI	Weight	Risk Ratio M-H,Fixed,95% CI
Jahani 2013	3/35	2/35		100.0 %	1.50 [0.27, 8.43]
Total (95% CI)	**35**	**35**		**100.0 %**	**1.50 [0.27, 8.43]**

Total events: 3 (Fentanyl), 2 (No treatment)

Heterogeneity: not applicable

Test for overall effect: Z = 0.46 (P = 0.65)

Test for subgroup differences: Not applicable



Analysis 21.1. Comparison 21 IV fentanyl versus IV pethidine, Outcome 1 Maternal pain score or pain measured in labour (Pain score 1 hour after drug administration).

Review: Parenteral opioids for maternal pain management in labour

Comparison: 21 IV fentanyl versus IV pethidine

Outcome: 1 Maternal pain score or pain measured in labour (Pain score 1 hour after drug administration)

Study or subgroup	Fentanyl N	Mean(SD)	Pethidine N	Mean(SD)	Mean Difference IV,Fixed,95% CI	Weight	Mean Difference IV,Fixed,95% CI
Rayburn 1989a (1)	49	5.9 (2.8)	56	6.1 (2.245)		100.0 %	-0.20 [-1.18, 0.78]
Total (95% CI)	**49**		**56**			**100.0 %**	**-0.20 [-1.18, 0.78]**

Heterogeneity: not applicable

Test for overall effect: Z = 0.40 (P = 0.69)

Test for subgroup differences: Not applicable

(1) Pain score at 4-7cm dilatation (SD/SE not clear)

Analysis 21.2. Comparison 21 IV fentanyl versus IV pethidine, Outcome 2 Mean doses of analgesia (non pre-specified).

Review: Parenteral opioids for maternal pain management in labour

Comparison: 21 IV fentanyl versus IV pethidine

Outcome: 2 Mean doses of analgesia (non pre-specified)

Study or subgroup	Fentanyl N	Mean(SD)	Pethidine N	Mean(SD)	Mean Difference IV,Fixed,95% CI	Weight	Mean Difference IV,Fixed,95% CI
Rayburn 1989a	49	2.3 (0.8)	56	1.9 (0.5)		100.0 %	0.40 [0.14, 0.66]
Total (95% CI)	**49**		**56**			**100.0 %**	**0.40 [0.14, 0.66]**

Heterogeneity: not applicable

Test for overall effect: Z = 3.02 (P = 0.0025)

Test for subgroup differences: Not applicable

Analysis 21.3. Comparison 21 IV fentanyl versus IV pethidine, Outcome 3 Maternal sleepiness in labour (sedation).

Review: Parenteral opioids for maternal pain management in labour

Comparison: 21 IV fentanyl versus IV pethidine

Outcome: 3 Maternal sleepiness in labour (sedation)

Study or subgroup	Fentanyl n/N	Pethidine n/N	Risk Ratio M-H,Fixed,95% CI	Weight	Risk Ratio M-H,Fixed,95% CI
Rayburn 1989a	0/49	11/56		100.0 %	0.05 [0.00, 0.82]
Total (95% CI)	**49**	**56**		**100.0 %**	**0.05 [0.00, 0.82]**

Total events: 0 (Fentanyl), 11 (Pethidine)

Heterogeneity: not applicable

Test for overall effect: Z = 2.10 (P = 0.036)

Test for subgroup differences: Not applicable

Analysis 21.4. Comparison 21 IV fentanyl versus IV pethidine, Outcome 4 Nausea and/or vomiting.

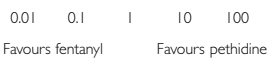
Review: Parenteral opioids for maternal pain management in labour

Comparison: 21 IV fentanyl versus IV pethidine

Outcome: 4 Nausea and/or vomiting

Study or subgroup	Fentanyl n/N	Pethidine n/N	Risk Ratio M-H,Fixed,95% CI	Weight	Risk Ratio M-H,Fixed,95% CI
Rayburn 1989a	4/49	9/56		100.0 %	0.51 [0.17, 1.55]
Total (95% CI)	**49**	**56**		**100.0 %**	**0.51 [0.17, 1.55]**

Total events: 4 (Fentanyl), 9 (Pethidine)
Heterogeneity: not applicable
Test for overall effect: Z = 1.19 (P = 0.23)
Test for subgroup differences: Not applicable



Analysis 21.5. Comparison 21 IV fentanyl versus IV pethidine, Outcome 5 Anti-emetic required (non pre-specified).

Review: Parenteral opioids for maternal pain management in labour

Comparison: 21 IV fentanyl versus IV pethidine

Outcome: 5 Anti-emetic required (non pre-specified)

Study or subgroup	Fentanyl n/N	Pethidine n/N	Risk Ratio M-H,Fixed,95% CI	Weight	Risk Ratio M-H,Fixed,95% CI
Rayburn 1989a	0/49	6/56		100.0 %	0.09 [0.01, 1.52]
Total (95% CI)	**49**	**56**		**100.0 %**	**0.09 [0.01, 1.52]**

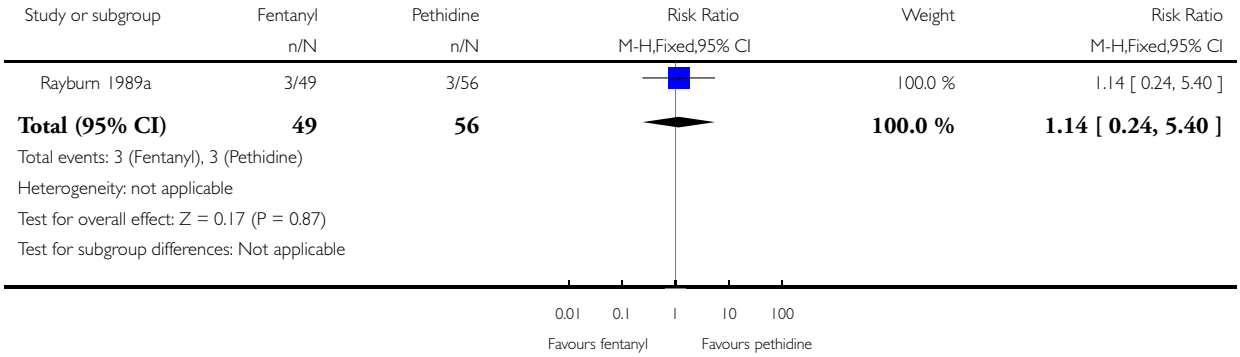
Total events: 0 (Fentanyl), 6 (Pethidine)
Heterogeneity: not applicable
Test for overall effect: Z = 1.67 (P = 0.094)
Test for subgroup differences: Not applicable

Analysis 21.6. Comparison 21 IV fentanyl versus IV pethidine, Outcome 6 Caesarean section.

Review: Parenteral opioids for maternal pain management in labour

Comparison: 21 IV fentanyl versus IV pethidine

Outcome: 6 Caesarean section

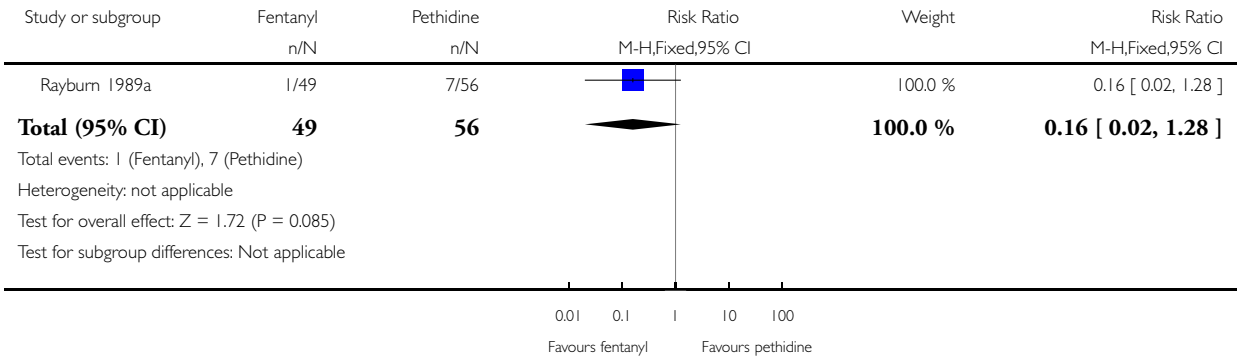


Analysis 21.7. Comparison 21 IV fentanyl versus IV pethidine, Outcome 7 Naloxone administered.

Review: Parenteral opioids for maternal pain management in labour

Comparison: 21 IV fentanyl versus IV pethidine

Outcome: 7 Naloxone administered



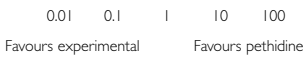
Analysis 21.8. Comparison 21 IV fentanyl versus IV pethidine, Outcome 8 Babies requiring resuscitation/ventilatory support.

Review: Parenteral opioids for maternal pain management in labour

Comparison: 21 IV fentanyl versus IV pethidine

Outcome: 8 Babies requiring resuscitation/ventilatory support

Study or subgroup	Experimental n/N	Pethidine n/N	Risk Ratio M-H,Fixed,95% CI	Weight	Risk Ratio M-H,Fixed,95% CI
Rayburn 1989a	9/49	10/56		100.0 %	1.03 [0.46, 2.32]
Total (95% CI)	**49**	**56**		**100.0 %**	**1.03 [0.46, 2.32]**
Total events: 9 (Experimental), 10 (Pethidine)					
Heterogeneity: not applicable					
Test for overall effect: Z = 0.07 (P = 0.95)					
Test for subgroup differences: Not applicable					



Analysis 21.9. Comparison 21 IV fentanyl versus IV pethidine, Outcome 9 Apgar score < 7 at 1 minute.

Review: Parenteral opioids for maternal pain management in labour

Comparison: 21 IV fentanyl versus IV pethidine

Outcome: 9 Apgar score < 7 at 1 minute

Study or subgroup	Fentanyl n/N	Pethidine n/N	Risk Ratio M-H,Fixed,95% CI	Weight	Risk Ratio M-H,Fixed,95% CI
Rayburn 1989a	5/49	9/56			0.63 [0.23, 1.77]

Analysis 21.10. Comparison 21 IV fentanyl versus IV pethidine, Outcome 10 Apgar score < 7 at 5 minutes.

Review: Parenteral opioids for maternal pain management in labour

Comparison: 21 IV fentanyl versus IV pethidine

Outcome: 10 Apgar score < 7 at 5 minutes

Study or subgroup	Fentanyl n/N	Pethidine n/N	Risk Ratio M-H,Fixed,95% CI	Weight	Risk Ratio M-H,Fixed,95% CI
Rayburn 1989a	0/49	1/56			0.38 [0.02, 9.12]

Analysis 21.11. Comparison 21 IV fentanyl versus IV pethidine, Outcome 11 Neurobehavioural score (1 - 2 hours after delivery).

Review: Parenteral opioids for maternal pain management in labour

Comparison: 21 IV fentanyl versus IV pethidine

Outcome: 11 Neurobehavioural score (1 - 2 hours after delivery)

Study or subgroup	Fentanyl N	Mean(SD)	Pethidine N	Mean(SD)	Mean Difference IV,Fixed,95% CI	Weight	Mean Difference IV,Fixed,95% CI
Rayburn 1989a (1)	49	33.2 (2.9)	56	31.9 (3.1)		100.0 %	1.30 [0.15, 2.45]
Total (95% CI)	**49**		**56**			**100.0 %**	**1.30 [0.15, 2.45]**

Heterogeneity: not applicable

Test for overall effect: Z = 2.22 (P = 0.026)

Test for subgroup differences: Not applicable

(1) Neurologic and Adaptive Capacity Score - 40 maximum score, >30 reassuring. High scores = positive result

Analysis 21.12. Comparison 21 IV fentanyl versus IV pethidine, Outcome 12 Neurobehavioural score (2 hours - 24 hours).

Review: Parenteral opioids for maternal pain management in labour

Comparison: 21 IV fentanyl versus IV pethidine

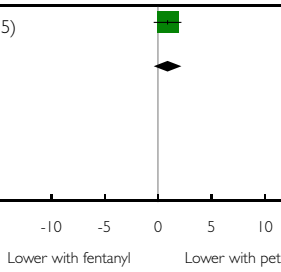
Outcome: 12 Neurobehavioural score (2 hours - 24 hours)

Study or subgroup	Fentanyl N	Mean(SD)	Pethidine N	Mean(SD)	Mean Difference IV,Fixed,95% CI	Weight	Mean Difference IV,Fixed,95% CI
Rayburn 1989a (1)	49	35.7 (3.4)	56	34.8 (3.5)		100.0 %	0.90 [-0.42, 2.22]
Total (95% CI)	**49**		**56**			**100.0 %**	**0.90 [-0.42, 2.22]**

Heterogeneity: not applicable

Test for overall effect: Z = 1.33 (P = 0.18)

Test for subgroup differences: Not applicable



(1) Neurologic and Adaptive Capacity Score - 40 maximum score, >30 reassuring. High scores = positive result

Analysis 22.1. Comparison 22 IV nalbuphine versus IV pethidine, Outcome 1 Caesarean section.

Review: Parenteral opioids for maternal pain management in labour

Comparison: 22 IV nalbuphine versus IV pethidine

Outcome: 1 Caesarean section

Study or subgroup	Nalbuphine n/N	Pethidine n/N	Risk Ratio M-H,Fixed,95% CI	Weight	Risk Ratio M-H,Fixed,95% CI
Giannina 1995	2/14	0/14		100.0 %	5.00 [0.26, 95.61]
Total (95% CI)	**14**	**14**		**100.0 %**	**5.00 [0.26, 95.61]**

Total events: 2 (Nalbuphine), 0 (Pethidine)

Heterogeneity: not applicable

Test for overall effect: Z = 1.07 (P = 0.29)

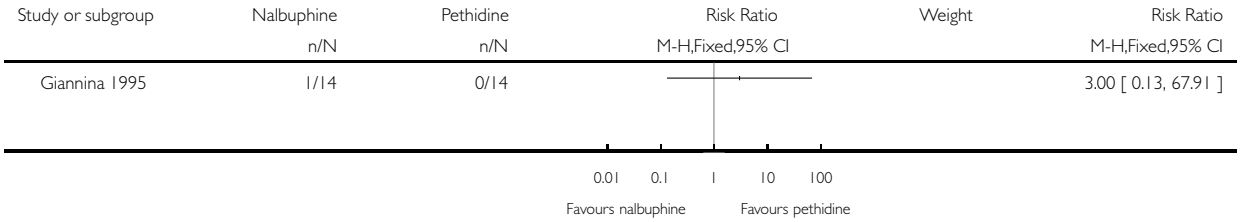
Test for subgroup differences: Not applicable

Analysis 22.2. Comparison 22 IV nalbuphine versus IV pethidine, Outcome 2 Apgar score < 7 at 1 minute.

Review: Parenteral opioids for maternal pain management in labour

Comparison: 22 IV nalbuphine versus IV pethidine

Outcome: 2 Apgar score < 7 at 1 minute

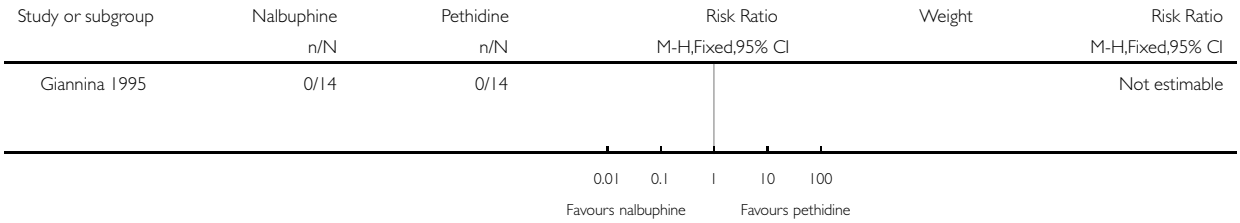


Analysis 22.3. Comparison 22 IV nalbuphine versus IV pethidine, Outcome 3 Apgar score < 7 at 5 minutes.

Review: Parenteral opioids for maternal pain management in labour

Comparison: 22 IV nalbuphine versus IV pethidine

Outcome: 3 Apgar score < 7 at 5 minutes



Analysis 23.1. Comparison 23 IV phenazocine versus IV pethidine, Outcome 1 Maternal satisfaction with analgesia measured during labour (women with fair or poor relief).

Review: Parenteral opioids for maternal pain management in labour

Comparison: 23 IV phenazocine versus IV pethidine

Outcome: 1 Maternal satisfaction with analgesia measured during labour (women with fair or poor relief)

Study or subgroup	Phenazocine n/N	Pethidine n/N	Risk Ratio M-H,Fixed,95% CI	Weight	Risk Ratio M-H,Fixed,95% CI
Olson 1964	26/97	36/97		100.0 %	0.72 [0.48, 1.10]
Total (95% CI)	**97**	**97**		**100.0 %**	**0.72 [0.48, 1.10]**
Total events: 26 (Phenazocine), 36 (Pethidine)					
Heterogeneity: not applicable					
Test for overall effect: Z = 1.52 (P = 0.13)					
Test for subgroup differences: Not applicable					

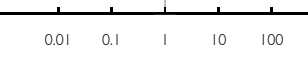
Analysis 23.2. Comparison 23 IV phenazocine versus IV pethidine, Outcome 2 Nausea with vomiting.

Review: Parenteral opioids for maternal pain management in labour

Comparison: 23 IV phenazocine versus IV pethidine

Outcome: 2 Nausea with vomiting

Study or subgroup	Phenazocine n/N	Pethidine n/N	Risk Ratio M-H,Fixed,95% CI	Weight	Risk Ratio M-H,Fixed,95% CI
Olson 1964	2/97	5/97		100.0 %	0.40 [0.08, 2.01]
Total (95% CI)	**97**	**97**		**100.0 %**	**0.40 [0.08, 2.01]**
Total events: 2 (Phenazocine), 5 (Pethidine)					
Heterogeneity: not applicable					
Test for overall effect: Z = 1.11 (P = 0.27)					
Test for subgroup differences: Not applicable					



Analysis 23.3. Comparison 23 IV phenazocine versus IV pethidine, Outcome 3 Perinatal death.

Review: Parenteral opioids for maternal pain management in labour

Comparison: 23 IV phenazocine versus IV pethidine

Outcome: 3 Perinatal death

Study or subgroup	Phenazocine n/N	Pethidine n/N	Risk Ratio M-H,Fixed,95% CI	Weight	Risk Ratio M-H,Fixed,95% CI
Olson 1964	0/97	0/97			Not estimable
Total (95% CI)	**97**	**97**			**Not estimable**
Total events: 0 (Phenazocine), 0 (Pethidine)					
Heterogeneity: not applicable					
Test for overall effect: not applicable					
Test for subgroup differences: Not applicable					

Analysis 23.4. Comparison 23 IV phenazocine versus IV pethidine, Outcome 4 Apgar score < 7 at 1 minute.

Review: Parenteral opioids for maternal pain management in labour

Comparison: 23 IV phenazocine versus IV pethidine

Outcome: 4 Apgar score < 7 at 1 minute

Study or subgroup	Phenazocine n/N	Pethidine n/N	Risk Ratio M-H,Fixed,95% CI	Weight	Risk Ratio M-H,Fixed,95% CI
Olson 1964	0/97	0/97			Not estimable
Total (95% CI)	**97**	**97**			**Not estimable**
Total events: 0 (Phenazocine), 0 (Pethidine)					
Heterogeneity: not applicable					
Test for overall effect: not applicable					
Test for subgroup differences: Not applicable					

Analysis 24.1. Comparison 24 IV butorphanol versus IV pethidine, Outcome 1 Maternal pain score or pain measured in labour (Pain relief score).

Review: Parenteral opioids for maternal pain management in labour

Comparison: 24 IV butorphanol versus IV pethidine

Outcome: 1 Maternal pain score or pain measured in labour (Pain relief score)

Study or subgroup	Butorphanol N	Mean(SD)	Pethidine N	Mean(SD)	Mean Difference IV,Fixed,95% CI	Weight	Mean Difference IV,Fixed,95% CI
Quilligan 1980	40	1.7 (1.01)	40	1.03 (0.89)		100.0 %	0.67 [0.25, 1.09]
Total (95% CI)	**40**		**40**			**100.0 %**	**0.67 [0.25, 1.09]**

Heterogeneity: not applicable

Test for overall effect: Z = 3.15 (P = 0.0016)

Test for subgroup differences: Not applicable

Analysis 24.2. Comparison 24 IV butorphanol versus IV pethidine, Outcome 2 Maternal pain score or pain measured in labour (Pain score (1 hour after drug administration)).

Review: Parenteral opioids for maternal pain management in labour

Comparison: 24 IV butorphanol versus IV pethidine

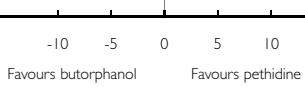
Outcome: 2 Maternal pain score or pain measured in labour (Pain score (1 hour after drug administration))

Study or subgroup	Butorphanol N	Mean(SD)	Pethidine N	Mean(SD)	Mean Difference IV,Fixed,95% CI	Weight	Mean Difference IV,Fixed,95% CI
Quilligan 1980	40	2.1 (1.01)	40	2.7 (0.89)		100.0 %	-0.60 [-1.02, -0.18]
Total (95% CI)	**40**		**40**			**100.0 %**	**-0.60 [-1.02, -0.18]**

Heterogeneity: not applicable

Test for overall effect: Z = 2.82 (P = 0.0048)

Test for subgroup differences: Not applicable



Analysis 24.3. Comparison 24 IV butorphanol versus IV pethidine, Outcome 3 Additional analgesia required.

Review: Parenteral opioids for maternal pain management in labour

Comparison: 24 IV butorphanol versus IV pethidine

Outcome: 3 Additional analgesia required

Study or subgroup	Butorphanol n/N	Pethidine n/N	Risk Ratio M-H,Fixed,95% CI	Weight	Risk Ratio M-H,Fixed,95% CI
Quilligan 1980 (1)	23/50	24/50		100.0 %	0.96 [0.63, 1.45]
Total (95% CI)	**50**	**50**		**100.0 %**	**0.96 [0.63, 1.45]**
Total events: 23 (Butorphanol), 24 (Pethidine)					
Heterogeneity: not applicable					
Test for overall effect: Z = 0.20 (P = 0.84)					
Test for subgroup differences: Not applicable					

(1) 2nd dose required

Analysis 24.4. Comparison 24 IV butorphanol versus IV pethidine, Outcome 4 Epidural.

Review: Parenteral opioids for maternal pain management in labour

Comparison: 24 IV butorphanol versus IV pethidine

Outcome: 4 Epidural

Study or subgroup	Butorphanol n/N	Pethidine n/N	Risk Ratio M-H,Fixed,95% CI	Weight	Risk Ratio M-H,Fixed,95% CI
Hodgkinson 1979	5/100	5/100		100.0 %	1.00 [0.30, 3.35]
Total (95% CI)	**100**	**100**		**100.0 %**	**1.00 [0.30, 3.35]**
Total events: 5 (Butorphanol), 5 (Pethidine)					
Heterogeneity: not applicable					
Test for overall effect: Z = 0.0 (P = 1.0)					
Test for subgroup differences: Not applicable					

Analysis 24.5. Comparison 24 IV butorphanol versus IV pethidine, Outcome 5 Nausea and/or vomiting.

Review: Parenteral opioids for maternal pain management in labour

Comparison: 24 IV butorphanol versus IV pethidine

Outcome: 5 Nausea and/or vomiting

Study or subgroup	Butorphanol n/N	Pethidine n/N	Risk Ratio M-H,Fixed,95% CI	Weight	Risk Ratio M-H,Fixed,95% CI
Hodgkinson 1979	0/100	12/100		100.0 %	0.04 [0.00, 0.67]
Total (95% CI)	**100**	**100**		**100.0 %**	**0.04 [0.00, 0.67]**
Total events: 0 (Butorphanol), 12 (Pethidine)					
Heterogeneity: not applicable					
Test for overall effect: Z = 2.24 (P = 0.025)					
Test for subgroup differences: Not applicable					

Analysis 24.6. Comparison 24 IV butorphanol versus IV pethidine, Outcome 6 Caesarean section.

Review: Parenteral opioids for maternal pain management in labour

Comparison: 24 IV butorphanol versus IV pethidine

Outcome: 6 Caesarean section

Study or subgroup	Butorphanol n/N	Pethidine n/N	Risk Ratio M-H,Fixed,95% CI	Weight	Risk Ratio M-H,Fixed,95% CI
Hodgkinson 1979	4/100	5/100		100.0 %	0.80 [0.22, 2.89]
Total (95% CI)	**100**	**100**		**100.0 %**	**0.80 [0.22, 2.89]**
Total events: 4 (Butorphanol), 5 (Pethidine)					
Heterogeneity: not applicable					
Test for overall effect: Z = 0.34 (P = 0.73)					
Test for subgroup differences: Not applicable					

Analysis 24.7. Comparison 24 IV butorphanol versus IV pethidine, Outcome 7 Assisted vaginal birth.

Review: Parenteral opioids for maternal pain management in labour

Comparison: 24 IV butorphanol versus IV pethidine

Outcome: 7 Assisted vaginal birth

Study or subgroup	Butorphanol n/N	Pethidine n/N	Risk Ratio M-H,Fixed,95% CI	Weight	Risk Ratio M-H,Fixed,95% CI
Hodgkinson 1979	13/100	10/100		100.0 %	1.30 [0.60, 2.83]
Total (95% CI)	**100**	**100**		**100.0 %**	**1.30 [0.60, 2.83]**

Total events: 13 (Butorphanol), 10 (Pethidine)
Heterogeneity: not applicable
Test for overall effect: Z = 0.66 (P = 0.51)
Test for subgroup differences: Not applicable

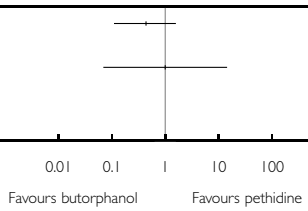
Analysis 24.8. Comparison 24 IV butorphanol versus IV pethidine, Outcome 8 Apgar score < 7 at 1 minute.

Review: Parenteral opioids for maternal pain management in labour

Comparison: 24 IV butorphanol versus IV pethidine

Outcome: 8 Apgar score < 7 at 1 minute

Study or subgroup	Butorphanol n/N	Pethidine n/N	Risk Ratio M-H,Fixed,95% CI	Weight	Risk Ratio M-H,Fixed,95% CI
Hodgkinson 1979	3/100	7/100			0.43 [0.11, 1.61]
Nelson 2005	1/15	1/15			1.00 [0.07, 14.55]



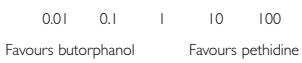
Analysis 24.9. Comparison 24 IV butorphanol versus IV pethidine, Outcome 9 Apgar score < 7 at 5 minutes.

Review: Parenteral opioids for maternal pain management in labour

Comparison: 24 IV butorphanol versus IV pethidine

Outcome: 9 Apgar score < 7 at 5 minutes

Study or subgroup	Butorphanol n/N	Pethidine n/N	Risk Ratio M-H,Fixed,95% CI	Weight	Risk Ratio M-H,Fixed,95% CI
Hodgkinson 1979	1/100	1/100			1.00 [0.06, 15.77]
Nelson 2005	0/15	0/15			Not estimable



Analysis 25.1. Comparison 25 IV morphine versus IV pethidine, Outcome 1 Maternal satisfaction with analgesia (assessed 3 days postpartum).

Review: Parenteral opioids for maternal pain management in labour

Comparison: 25 IV morphine versus IV pethidine

Outcome: 1 Maternal satisfaction with analgesia (assessed 3 days postpartum)

Study or subgroup	Experimental n/N	Pethidine n/N	Risk Ratio M-H,Fixed,95% CI	Weight	Risk Ratio M-H,Fixed,95% CI
Campbell 1961	60/72	66/69		100.0 %	0.87 [0.78, 0.98]
Total (95% CI)	**72**	**69**		**100.0 %**	**0.87 [0.78, 0.98]**
Total events: 60 (Experimental), 66 (Pethidine)					
Heterogeneity: not applicable					
Test for overall effect: Z = 2.35 (P = 0.019)					
Test for subgroup differences: Not applicable					

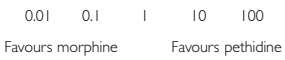
Analysis 25.2. Comparison 25 IV morphine versus IV pethidine, Outcome 2 Additional analgesia required.

Review: Parenteral opioids for maternal pain management in labour

Comparison: 25 IV morphine versus IV pethidine

Outcome: 2 Additional analgesia required

Study or subgroup	Morphine n/N	Pethidine n/N	Risk Ratio M-H,Fixed,95% CI	Weight	Risk Ratio M-H,Fixed,95% CI
Campbell 1961 (1)	38/72	11/71		100.0 %	3.41 [1.90, 6.12]
Total (95% CI)	**72**	**71**		**100.0 %**	**3.41 [1.90, 6.12]**
Total events: 38 (Morphine), 11 (Pethidine)					
Heterogeneity: not applicable					
Test for overall effect: Z = 4.10 (P = 0.000041)					
Test for subgroup differences: Not applicable					



(1) Further dose of study analgesia required

Analysis 25.3. Comparison 25 IV morphine versus IV pethidine, Outcome 3 Nausea and vomiting.

Review: Parenteral opioids for maternal pain management in labour

Comparison: 25 IV morphine versus IV pethidine

Outcome: 3 Nausea and vomiting

Study or subgroup	Morphine n/N	Pethidine n/N	Risk Ratio M-H,Fixed,95% CI	Weight	Risk Ratio M-H,Fixed,95% CI
1 Nausea					
Olofsson 1996	1/10	6/10		100.0 %	0.17 [0.02, 1.14]
Subtotal (95% CI)	**10**	**10**		**100.0 %**	**0.17 [0.02, 1.14]**
Total events: 1 (Morphine), 6 (Pethidine)					
Heterogeneity: not applicable					
Test for overall effect: Z = 1.82 (P = 0.068)					
2 Vomiting					
Olofsson 1996	1/10	4/10		100.0 %	0.25 [0.03, 1.86]
Subtotal (95% CI)	**10**	**10**		**100.0 %**	**0.25 [0.03, 1.86]**
Total events: 1 (Morphine), 4 (Pethidine)					
Heterogeneity: not applicable					
Test for overall effect: Z = 1.35 (P = 0.18)					

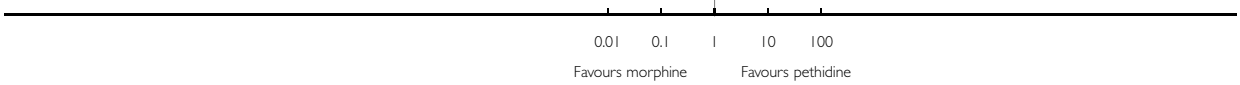
Analysis 25.4. Comparison 25 IV morphine versus IV pethidine, Outcome 4 Caesarean section.

Review: Parenteral opioids for maternal pain management in labour

Comparison: 25 IV morphine versus IV pethidine

Outcome: 4 Caesarean section

Study or subgroup	Morphine n/N	Pethidine n/N	Risk Ratio M-H,Fixed,95% CI	Weight	Risk Ratio M-H,Fixed,95% CI
Olofsson 1996	0/10	0/10			Not estimable
Total (95% CI)	**10**	**10**			**Not estimable**
Total events: 0 (Morphine), 0 (Pethidine)					
Heterogeneity: not applicable					
Test for overall effect: not applicable					
Test for subgroup differences: Not applicable					

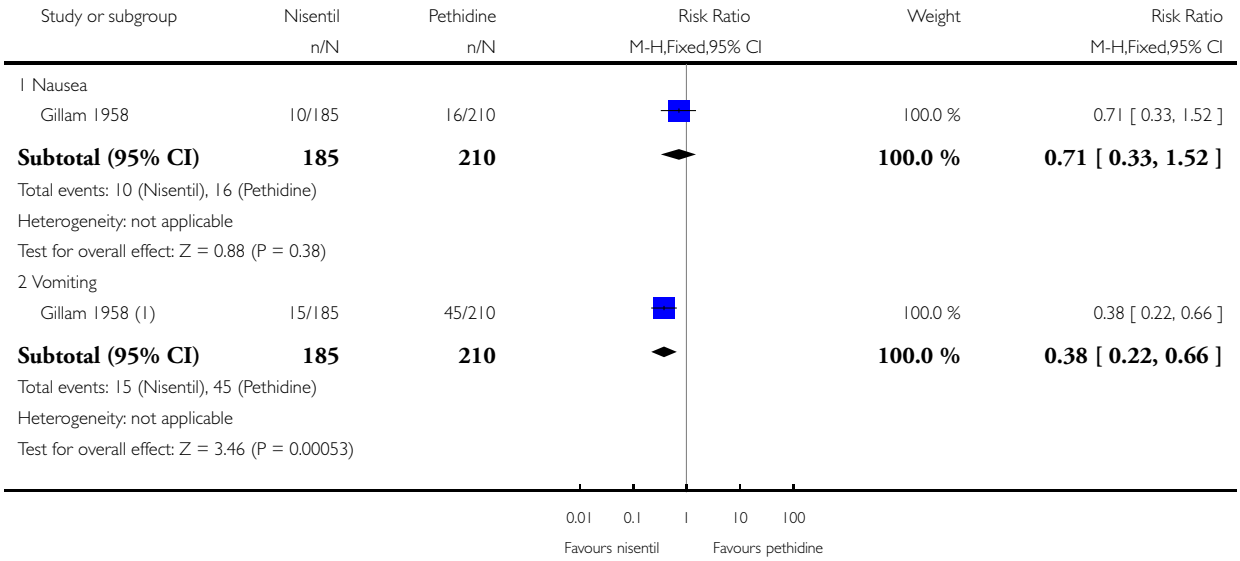


Analysis 26.1. Comparison 26 IV Nisentil versus IV pethidine, Outcome 1 Nausea and vomiting.

Review: Parenteral opioids for maternal pain management in labour

Comparison: 26 IV Nisentil versus IV pethidine

Outcome: 1 Nausea and vomiting



(1) Both groups also received scopolamine

Analysis 26.2. Comparison 26 IV Nisentil versus IV pethidine, Outcome 2 Neonatal resuscitation/ventilatory support.

Review: Parenteral opioids for maternal pain management in labour

Comparison: 26 IV Nisentil versus IV pethidine

Outcome: 2 Neonatal resuscitation/ventilatory support

Study or subgroup	Nisentil n/N	Pethidine n/N	Risk Ratio M-H,Fixed,95% CI	Weight	Risk Ratio M-H,Fixed,95% CI
Gillam 1958	14/185	8/210		100.0 %	1.99 [0.85, 4.63]
Total (95% CI)	**185**	**210**		**100.0 %**	**1.99 [0.85, 4.63]**
Total events: 14 (Nisentil), 8 (Pethidine)					
Heterogeneity: not applicable					
Test for overall effect: Z = 1.59 (P = 0.11)					
Test for subgroup differences: Not applicable					

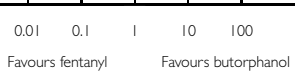
Analysis 27.1. Comparison 27 IV fentanyl versus IV butorphanol, Outcome 1 Additional analgesia required.

Review: Parenteral opioids for maternal pain management in labour

Comparison: 27 IV fentanyl versus IV butorphanol

Outcome: 1 Additional analgesia required

Study or subgroup	Fentanyl n/N	Butorphanol n/N	Risk Ratio M-H,Fixed,95% CI	Weight	Risk Ratio M-H,Fixed,95% CI
Atkinson 1994 (1)	39/50	28/50		100.0 %	1.39 [1.05, 1.85]
Total (95% CI)	**50**	**50**		**100.0 %**	**1.39 [1.05, 1.85]**
Total events: 39 (Fentanyl), 28 (Butorphanol)					
Heterogeneity: not applicable					
Test for overall effect: Z = 2.27 (P = 0.023)					
Test for subgroup differences: Not applicable					



(1) Two or more doses

Analysis 27.2. Comparison 27 IV fentanyl versus IV butorphanol, Outcome 2 Epidural.

Review: Parenteral opioids for maternal pain management in labour

Comparison: 27 IV fentanyl versus IV butorphanol

Outcome: 2 Epidural

Study or subgroup	Fentanyl n/N	Butorphanol n/N	Risk Ratio M-H,Fixed,95% CI	Weight	Risk Ratio M-H,Fixed,95% CI
Atkinson 1994	18/50	9/50		100.0 %	2.00 [1.00, 4.02]
Total (95% CI)	**50**	**50**		**100.0 %**	**2.00 [1.00, 4.02]**
Total events: 18 (Fentanyl), 9 (Butorphanol)					
Heterogeneity: not applicable					
Test for overall effect: Z = 1.95 (P = 0.051)					
Test for subgroup differences: Not applicable					

Analysis 27.3. Comparison 27 IV fentanyl versus IV butorphanol, Outcome 3 Matenal sleepiness (required tactile rousing).

Review: Parenteral opioids for maternal pain management in labour

Comparison: 27 IV fentanyl versus IV butorphanol

Outcome: 3 Matenal sleepiness (required tactile rousing)

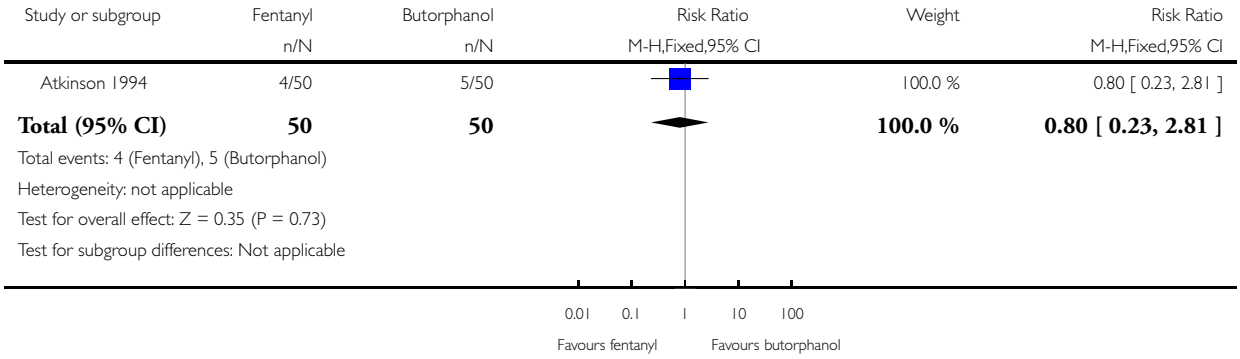
Study or subgroup	Fentanyl n/N	Butorphanol n/N	Risk Ratio M-H,Fixed,95% CI	Weight	Risk Ratio M-H,Fixed,95% CI
Atkinson 1994	6/50	2/50		100.0 %	3.00 [0.64, 14.16]
Total (95% CI)	**50**	**50**		**100.0 %**	**3.00 [0.64, 14.16]**
Total events: 6 (Fentanyl), 2 (Butorphanol)					
Heterogeneity: not applicable					
Test for overall effect: Z = 1.39 (P = 0.17)					
Test for subgroup differences: Not applicable					

Analysis 27.4. Comparison 27 IV fentanyl versus IV butorphanol, Outcome 4 Caesarean section.

Review: Parenteral opioids for maternal pain management in labour

Comparison: 27 IV fentanyl versus IV butorphanol

Outcome: 4 Caesarean section

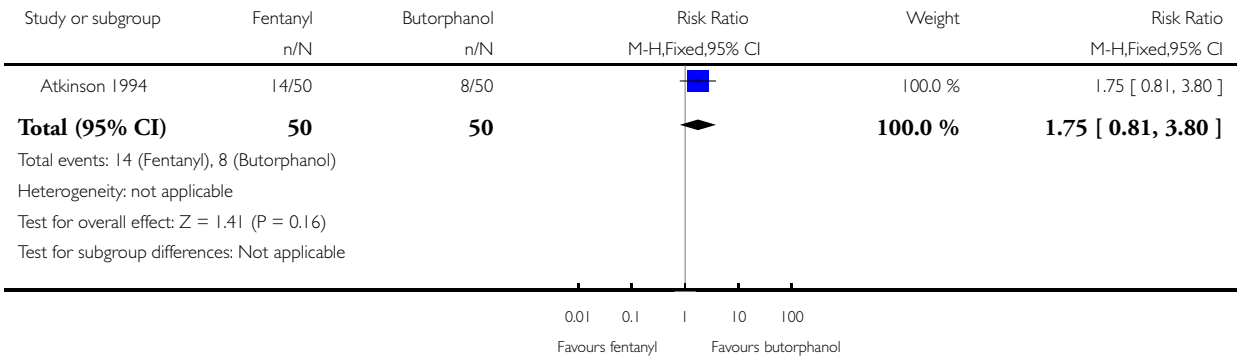


Analysis 27.5. Comparison 27 IV fentanyl versus IV butorphanol, Outcome 5 Naloxone required.

Review: Parenteral opioids for maternal pain management in labour

Comparison: 27 IV fentanyl versus IV butorphanol

Outcome: 5 Naloxone required



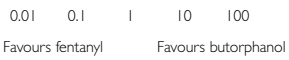
Analysis 27.6. Comparison 27 IV fentanyl versus IV butorphanol, Outcome 6 Neonatal resuscitation (Babies requiring ventilatory support).

Review: Parenteral opioids for maternal pain management in labour

Comparison: 27 IV fentanyl versus IV butorphanol

Outcome: 6 Neonatal resuscitation (Babies requiring ventilatory support)

Study or subgroup	Fentanyl n/N	Butorphanol n/N	Risk Ratio M-H,Fixed,95% CI	Weight	Risk Ratio M-H,Fixed,95% CI
Atkinson 1994	5/50	0/50		100.0 %	11.00 [0.62, 193.80]
Total (95% CI)	**50**	**50**		**100.0 %**	**11.00 [0.62, 193.80]**
Total events: 5 (Fentanyl), 0 (Butorphanol)					
Heterogeneity: not applicable					
Test for overall effect: Z = 1.64 (P = 0.10)					
Test for subgroup differences: Not applicable					



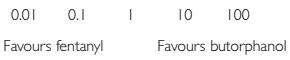
Analysis 27.7. Comparison 27 IV fentanyl versus IV butorphanol, Outcome 7 Apgar score < 7 at 5 minutes.

Review: Parenteral opioids for maternal pain management in labour

Comparison: 27 IV fentanyl versus IV butorphanol

Outcome: 7 Apgar score < 7 at 5 minutes

Study or subgroup	Fentanyl n/N	Butorphanol n/N	Risk Ratio M-H,Fixed,95% CI	Weight	Risk Ratio M-H,Fixed,95% CI
Atkinson 1994	6/50	5/50		100.0 %	1.20 [0.39, 3.68]
Total (95% CI)	**50**	**50**		**100.0 %**	**1.20 [0.39, 3.68]**
Total events: 6 (Fentanyl), 5 (Butorphanol)					
Heterogeneity: not applicable					
Test for overall effect: Z = 0.32 (P = 0.75)					
Test for subgroup differences: Not applicable					



Analysis 27.8. Comparison 27 IV fentanyl versus IV butorphanol, Outcome 8 Newborn neurobehavioural score at 2-4 hours.

Review: Parenteral opioids for maternal pain management in labour

Comparison: 27 IV fentanyl versus IV butorphanol

Outcome: 8 Newborn neurobehavioural score at 2-4 hours

Study or subgroup	Fentanyl N	Mean(SD)	Butorphanol N	Mean(SD)	Mean Difference IV,Fixed,95% CI	Weight	Mean Difference IV,Fixed,95% CI
Atkinson 1994	50	28.4 (3.7)	50	28.4 (4.5)		100.0 %	0.0 [-1.61, 1.61]
Total (95% CI)	**50**		**50**			**100.0 %**	**0.0 [-1.61, 1.61]**

Heterogeneity: not applicable

Test for overall effect: Z = 0.0 (P = 1.0)

Test for subgroup differences: Not applicable

Analysis 27.9. Comparison 27 IV fentanyl versus IV butorphanol, Outcome 9 Newborn neurobehavioural score at 24-36 hours.

Review: Parenteral opioids for maternal pain management in labour

Comparison: 27 IV fentanyl versus IV butorphanol

Outcome: 9 Newborn neurobehavioural score at 24-36 hours

Study or subgroup	Fentanyl N	Mean(SD)	Butorphanol N	Mean(SD)	Mean Difference IV,Fixed,95% CI	Weight	Mean Difference IV,Fixed,95% CI
Atkinson 1994	50	31.7 (2.9)	50	32.2 (2.8)		100.0 %	-0.50 [-1.62, 0.62]
Total (95% CI)	**50**		**50**			**100.0 %**	**-0.50 [-1.62, 0.62]**

Heterogeneity: not applicable

Test for overall effect: Z = 0.88 (P = 0.38)

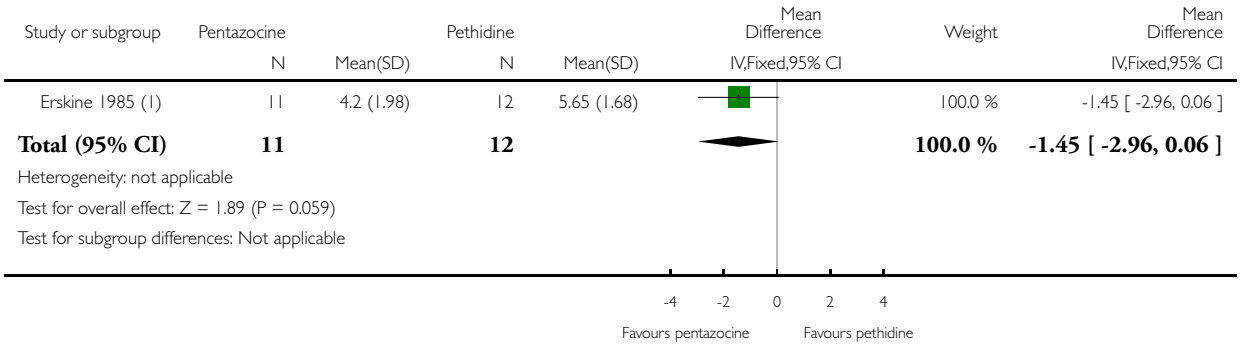
Test for subgroup differences: Not applicable

Analysis 28.1. Comparison 28 PCA pentazocine versus PCA pethidine, Outcome 1 Maternal pan score or pain measured in labour.

Review: Parenteral opioids for maternal pain management in labour

Comparison: 28 PCA pentazocine versus PCA pethidine

Outcome: 1 Maternal pan score or pain measured in labour



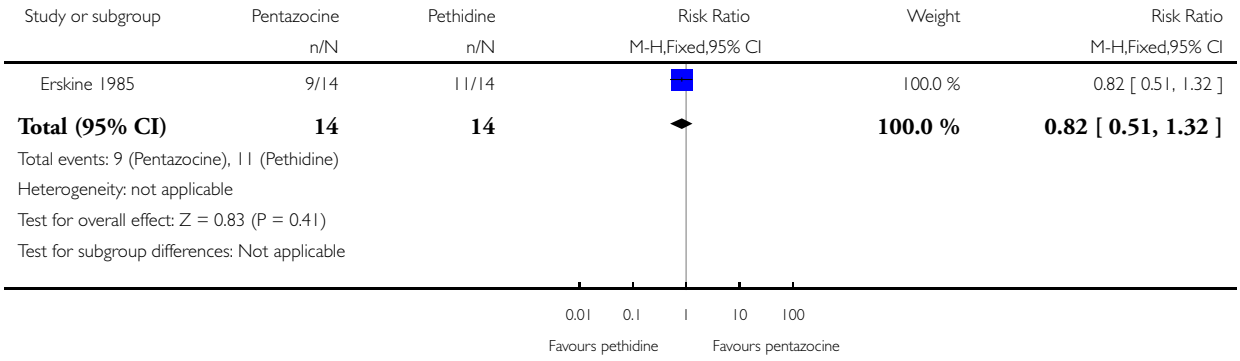
(1) Recorded just after delivery

Analysis 28.2. Comparison 28 PCA pentazocine versus PCA pethidine, Outcome 2 Maternal pan score or pain measured in labour (rated as good one day after birth).

Review: Parenteral opioids for maternal pain management in labour

Comparison: 28 PCA pentazocine versus PCA pethidine

Outcome: 2 Maternal pan score or pain measured in labour (rated as good one day after birth)



Analysis 28.3. Comparison 28 PCA pentazocine versus PCA pethidine, Outcome 3 Epidural.

Review: Parenteral opioids for maternal pain management in labour

Comparison: 28 PCA pentazocine versus PCA pethidine

Outcome: 3 Epidural

Study or subgroup	Pentazocine n/N	Pethidine n/N	Risk Ratio M-H,Fixed,95% CI	Weight	Risk Ratio M-H,Fixed,95% CI
Erskine 1985	3/14	2/14		100.0 %	1.50 [0.29, 7.65]
Total (95% CI)	**14**	**14**		**100.0 %**	**1.50 [0.29, 7.65]**
Total events: 3 (Pentazocine), 2 (Pethidine)					
Heterogeneity: not applicable					
Test for overall effect: Z = 0.49 (P = 0.63)					
Test for subgroup differences: Not applicable					

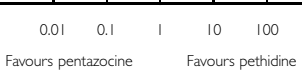
Analysis 28.4. Comparison 28 PCA pentazocine versus PCA pethidine, Outcome 4 Nausea and vomiting.

Review: Parenteral opioids for maternal pain management in labour

Comparison: 28 PCA pentazocine versus PCA pethidine

Outcome: 4 Nausea and vomiting

Study or subgroup	Pentazocine n/N	Pethidine n/N	Risk Ratio M-H,Fixed,95% CI	Weight	Risk Ratio M-H,Fixed,95% CI
Erskine 1985	0/14	5/15		100.0 %	0.10 [0.01, 1.61]
Total (95% CI)	**14**	**15**		**100.0 %**	**0.10 [0.01, 1.61]**
Total events: 0 (Pentazocine), 5 (Pethidine)					
Heterogeneity: not applicable					
Test for overall effect: Z = 1.63 (P = 0.10)					
Test for subgroup differences: Not applicable					



Analysis 28.5. Comparison 28 PCA pentazocine versus PCA pethidine, Outcome 5 Maternal sleepiness during labour (Sedation).

Review: Parenteral opioids for maternal pain management in labour

Comparison: 28 PCA pentazocine versus PCA pethidine

Outcome: 5 Maternal sleepiness during labour (Sedation)

Study or subgroup	Pentazocine n/N	Pethidine n/N	Risk Ratio M-H,Fixed,95% CI	Weight	Risk Ratio M-H,Fixed,95% CI
Erskine 1985	0/14	2/15		100.0 %	0.21 [0.01, 4.09]
Total (95% CI)	**14**	**15**		**100.0 %**	**0.21 [0.01, 4.09]**

Total events: 0 (Pentazocine), 2 (Pethidine)

Heterogeneity: not applicable

Test for overall effect: Z = 1.03 (P = 0.31)

Test for subgroup differences: Not applicable

Analysis 28.6. Comparison 28 PCA pentazocine versus PCA pethidine, Outcome 6 Caesarean section.

Review: Parenteral opioids for maternal pain management in labour

Comparison: 28 PCA pentazocine versus PCA pethidine

Outcome: 6 Caesarean section

Study or subgroup	Pentazocine n/N	Pethidine n/N	Risk Ratio M-H,Fixed,95% CI	Weight	Risk Ratio M-H,Fixed,95% CI
Erskine 1985	0/14	1/15		100.0 %	0.36 [0.02, 8.07]
Total (95% CI)	**14**	**15**		**100.0 %**	**0.36 [0.02, 8.07]**

Total events: 0 (Pentazocine), 1 (Pethidine)

Heterogeneity: not applicable

Test for overall effect: Z = 0.65 (P = 0.52)

Test for subgroup differences: Not applicable

Analysis 28.7. Comparison 28 PCA pentazocine versus PCA pethidine, Outcome 7 Breastfeeding at discharge.

Review: Parenteral opioids for maternal pain management in labour

Comparison: 28 PCA pentazocine versus PCA pethidine

Outcome: 7 Breastfeeding at discharge

Study or subgroup	Pentazocine n/N	Pethidine n/N	Risk Ratio M-H,Fixed,95% CI	Weight	Risk Ratio M-H,Fixed,95% CI
Erskine 1985	11/11	12/12		100.0 %	1.00 [0.85, 1.17]
Total (95% CI)	**11**	**12**		**100.0 %**	**1.00 [0.85, 1.17]**
Total events: 11 (Pentazocine), 12 (Pethidine)					
Heterogeneity: not applicable					
Test for overall effect: Z = 0.0 (P = 1.0)					
Test for subgroup differences: Not applicable					

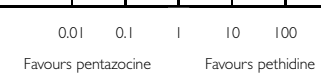
Analysis 28.8. Comparison 28 PCA pentazocine versus PCA pethidine, Outcome 8 Apgar score < 7 at 5 minutes.

Review: Parenteral opioids for maternal pain management in labour

Comparison: 28 PCA pentazocine versus PCA pethidine

Outcome: 8 Apgar score < 7 at 5 minutes

Study or subgroup	Pentazocine n/N	Pethidine n/N	Risk Ratio M-H,Fixed,95% CI	Weight	Risk Ratio M-H,Fixed,95% CI
Erskine 1985	0/14	0/15			Not estimable
Total (95% CI)	**14**	**15**			**Not estimable**
Total events: 0 (Pentazocine), 0 (Pethidine)					
Heterogeneity: not applicable					
Test for overall effect: not applicable					
Test for subgroup differences: Not applicable					



Analysis 29.1. Comparison 29 PCA remifentanil versus PCA pethidine, Outcome 1 Maternal pain score in labour.

Review: Parenteral opioids for maternal pain management in labour

Comparison: 29 PCA remifentanil versus PCA pethidine

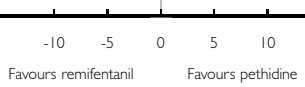
Outcome: 1 Maternal pain score in labour

Study or subgroup	Remifentanil N	Mean(SD)	Pethidine N	Mean(SD)	Mean Difference IV,Random,95% CI	Weight	Mean Difference IV,Random,95% CI
Douma 2010	52	4.56 (2.4)	53	6.61 (2.3)		68.8 %	-2.05 [-2.95, -1.15]
Volikas 2001	9	28 (28)	8	51 (25)		31.2 %	-23.00 [-48.19, 2.19]
Total (95% CI)	**61**		**61**			**100.0 %**	**-8.59 [-27.61, 10.44]**

Heterogeneity: $Tau^2 = 136.73$; $Chi^2 = 2.65$, df = 1 (P = 0.10); $I^2 = 62\%$

Test for overall effect: Z = 0.88 (P = 0.38)

Test for subgroup differences: Not applicable



Analysis 29.2. Comparison 29 PCA remifentanil versus PCA pethidine, Outcome 2 Additional analgesia required.

Review: Parenteral opioids for maternal pain management in labour

Comparison: 29 PCA remifentanil versus PCA pethidine

Outcome: 2 Additional analgesia required

Study or subgroup	Remifentanil n/N	Pethidine n/N	Risk Ratio M-H,Fixed,95% CI	Weight	Risk Ratio M-H,Fixed,95% CI
Blair 2005 (1)	18/20	19/19		79.0 %	0.90 [0.76, 1.07]
Volikas 2001 (2)	4/9	5/8		21.0 %	0.71 [0.29, 1.76]
Total (95% CI)	**29**	**27**		**100.0 %**	**0.86 [0.69, 1.08]**
Total events: 22 (Remifentanil), 24 (Pethidine)					
Heterogeneity: Chi^2 = 0.45, df = 1 (P = 0.50); I^2 =0.0%					
Test for overall effect: Z = 1.30 (P = 0.19)					
Test for subgroup differences: Not applicable					

(1) Entonox

(2) Entonox

Analysis 29.3. Comparison 29 PCA remifentanil versus PCA pethidine, Outcome 3 Epidural.

Review: Parenteral opioids for maternal pain management in labour

Comparison: 29 PCA remifentanil versus PCA pethidine

Outcome: 3 Epidural

Study or subgroup	Remifentanil n/N	Pethidine n/N	Risk Ratio M-H,Fixed,95% CI	Weight	Risk Ratio M-H,Fixed,95% CI
Douma 2010	7/52	18/53		94.4 %	0.40 [0.18, 0.87]
Volikas 2001	1/9	1/8		5.6 %	0.89 [0.07, 12.00]
Total (95% CI)	**61**	**61**		**100.0 %**	**0.42 [0.20, 0.89]**
Total events: 8 (Remifentanil), 19 (Pethidine)					
Heterogeneity: Chi^2 = 0.34, df = 1 (P = 0.56); I^2 =0.0%					
Test for overall effect: Z = 2.25 (P = 0.024)					
Test for subgroup differences: Not applicable					

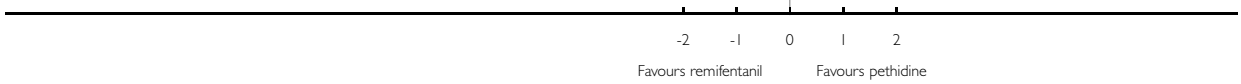
Analysis 29.4. Comparison 29 PCA remifentanil versus PCA pethidine, Outcome 4 Maternal sleepiness during labour.

Review: Parenteral opioids for maternal pain management in labour

Comparison: 29 PCA remifentanil versus PCA pethidine

Outcome: 4 Maternal sleepiness during labour

Study or subgroup	Remifentanil N	Mean(SD)	Pethidine N	Mean(SD)	Mean Difference IV,Fixed,95% CI	Weight	Mean Difference IV,Fixed,95% CI
Douma 2010	52	1.85 (0.8)	53	1.45 (0.5)		100.0 %	0.40 [0.14, 0.66]
Total (95% CI)	**52**		**53**			**100.0 %**	**0.40 [0.14, 0.66]**
Heterogeneity: not applicable							
Test for overall effect: Z = 3.07 (P = 0.0022)							
Test for subgroup differences: Not applicable							



Analysis 29.5. Comparison 29 PCA remifentanil versus PCA pethidine, Outcome 5 Nausea and vomiting.

Review: Parenteral opioids for maternal pain management in labour

Comparison: 29 PCA remifentanil versus PCA pethidine

Outcome: 5 Nausea and vomiting

Study or subgroup	Remifentanil n/N	Pethidine n/N	Risk Ratio M-H,Fixed,95% CI	Weight	Risk Ratio M-H,Fixed,95% CI
Douma 2010	20/51	23/51		97.8 %	0.87 [0.55, 1.37]
Volikas 2001 (1)	2/9	0/8		2.2 %	4.50 [0.25, 81.76]
Total (95% CI)	**60**	**59**		**100.0 %**	**0.95 [0.61, 1.49]**

Total events: 22 (Remifentanil), 23 (Pethidine)

Heterogeneity: Chi^2 = 1.25, df = 1 (P = 0.26); I^2 =20%

Test for overall effect: Z = 0.22 (P = 0.83)

Test for subgroup differences: Not applicable

(1) Anti-emetic required

Analysis 29.6. Comparison 29 PCA remifentanil versus PCA pethidine, Outcome 6 Caesarean section.

Review: Parenteral opioids for maternal pain management in labour

Comparison: 29 PCA remifentanil versus PCA pethidine

Outcome: 6 Caesarean section

Study or subgroup	Remifentanil n/N	Pethidine n/N	Risk Ratio M-H,Fixed,95% CI	Weight	Risk Ratio M-H,Fixed,95% CI
Douma 2010	7/45	3/35		76.1 %	1.81 [0.51, 6.52]
Volikas 2001	2/9	1/8		23.9 %	1.78 [0.20, 16.10]
Total (95% CI)	**54**	**43**		**100.0 %**	**1.81 [0.60, 5.46]**

Total events: 9 (Remifentanil), 4 (Pethidine)

Heterogeneity: Chi^2 = 0.00, df = 1 (P = 0.99); I^2 =0.0%

Test for overall effect: Z = 1.05 (P = 0.30)

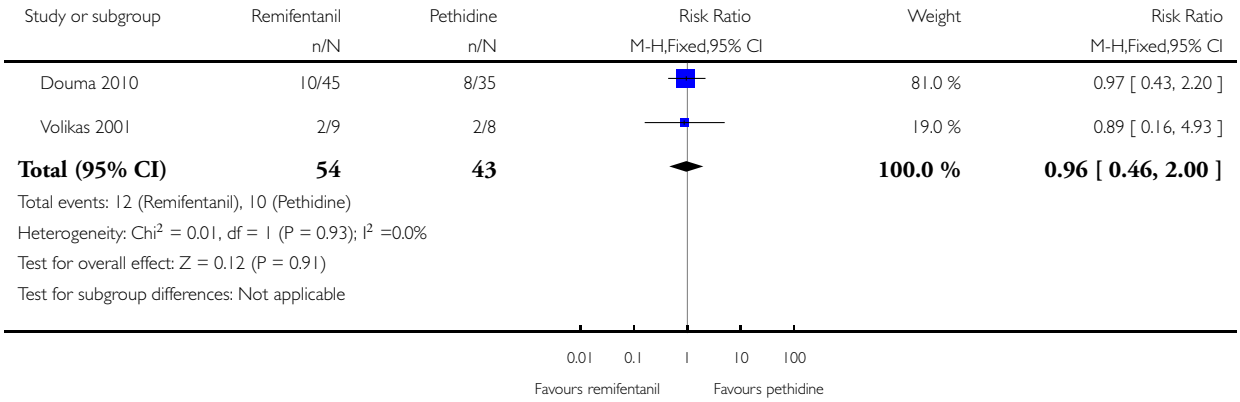
Test for subgroup differences: Not applicable

Analysis 29.7. Comparison 29 PCA remifentanil versus PCA pethidine, Outcome 7 Assisted vaginal birth.

Review: Parenteral opioids for maternal pain management in labour

Comparison: 29 PCA remifentanil versus PCA pethidine

Outcome: 7 Assisted vaginal birth

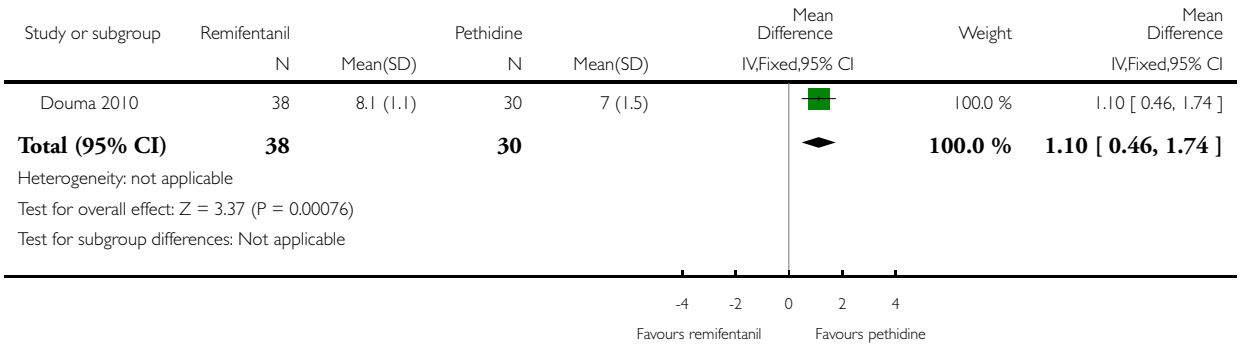


Analysis 29.8. Comparison 29 PCA remifentanil versus PCA pethidine, Outcome 8 Satisfaction with childbirth experience.

Review: Parenteral opioids for maternal pain management in labour

Comparison: 29 PCA remifentanil versus PCA pethidine

Outcome: 8 Satisfaction with childbirth experience

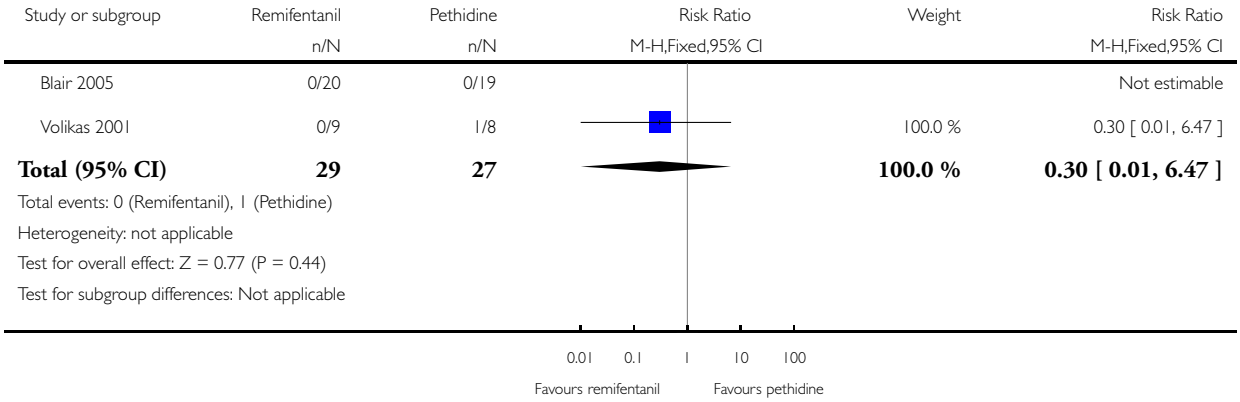


Analysis 29.9. Comparison 29 PCA remifentanil versus PCA pethidine, Outcome 9 Naloxone administered.

Review: Parenteral opioids for maternal pain management in labour

Comparison: 29 PCA remifentanil versus PCA pethidine

Outcome: 9 Naloxone administered

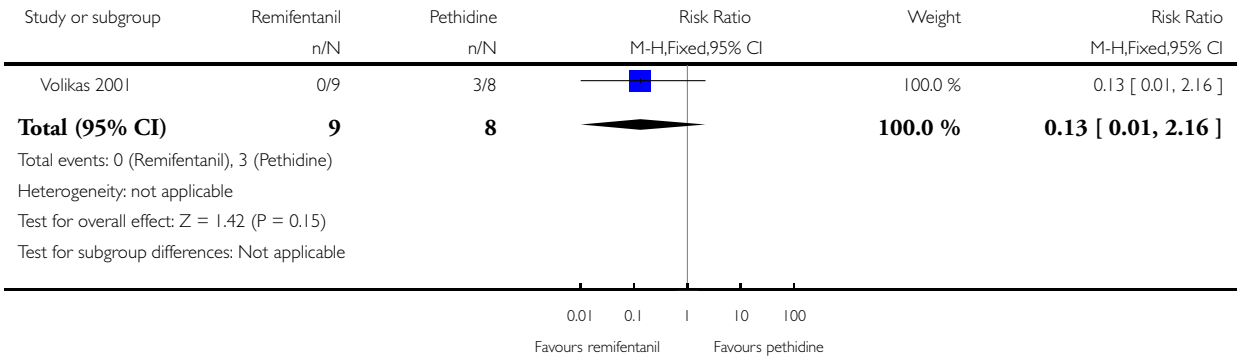


Analysis 29.10. Comparison 29 PCA remifentanil versus PCA pethidine, Outcome 10 Apgar score < 7 at 5 minutes.

Review: Parenteral opioids for maternal pain management in labour

Comparison: 29 PCA remifentanil versus PCA pethidine

Outcome: 10 Apgar score < 7 at 5 minutes

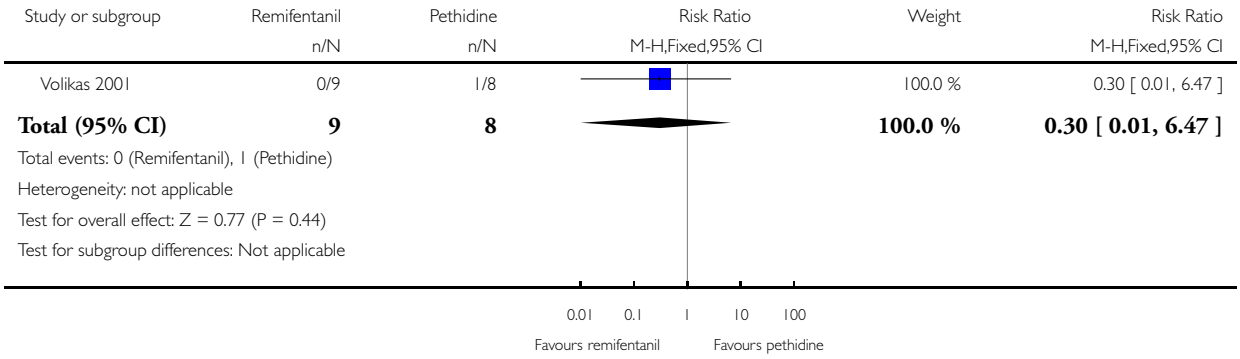


Analysis 29.11. Comparison 29 PCA remifentanil versus PCA pethidine, Outcome 11 Admission to NICU.

Review: Parenteral opioids for maternal pain management in labour

Comparison: 29 PCA remifentanil versus PCA pethidine

Outcome: 11 Admission to NICU

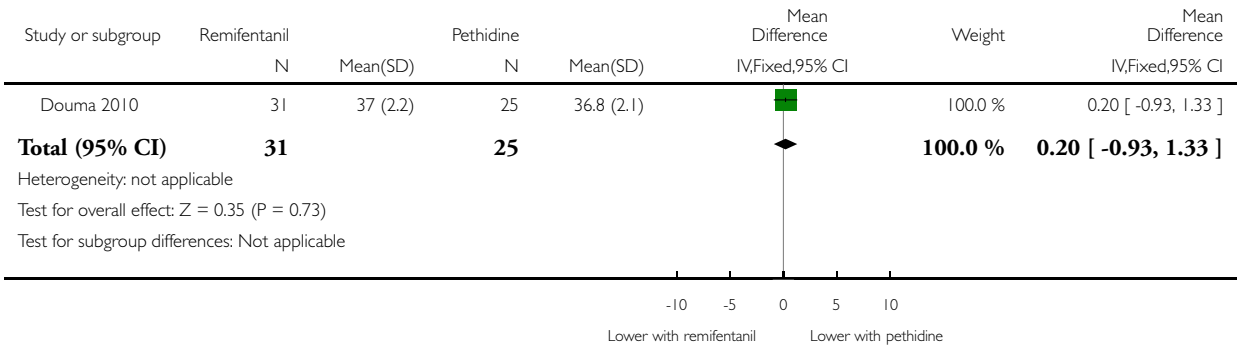


Analysis 29.12. Comparison 29 PCA remifentanil versus PCA pethidine, Outcome 12 Newborn neurobehavioural score (15 minutes post delivery).

Review: Parenteral opioids for maternal pain management in labour

Comparison: 29 PCA remifentanil versus PCA pethidine

Outcome: 12 Newborn neurobehavioural score (15 minutes post delivery)

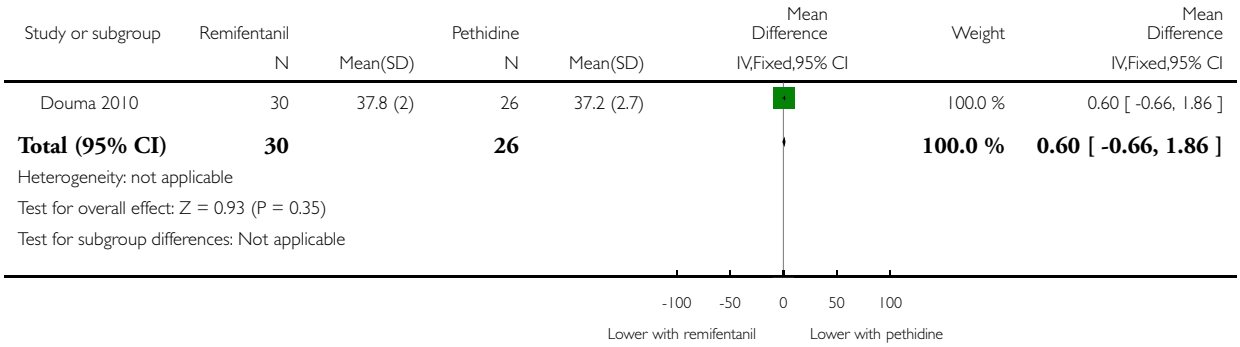


Analysis 29.13. Comparison 29 PCA remifentanil versus PCA pethidine, Outcome 13 Newborn neurobehavioural score (2 hours post delivery).

Review: Parenteral opioids for maternal pain management in labour

Comparison: 29 PCA remifentanil versus PCA pethidine

Outcome: 13 Newborn neurobehavioural score (2 hours post delivery)

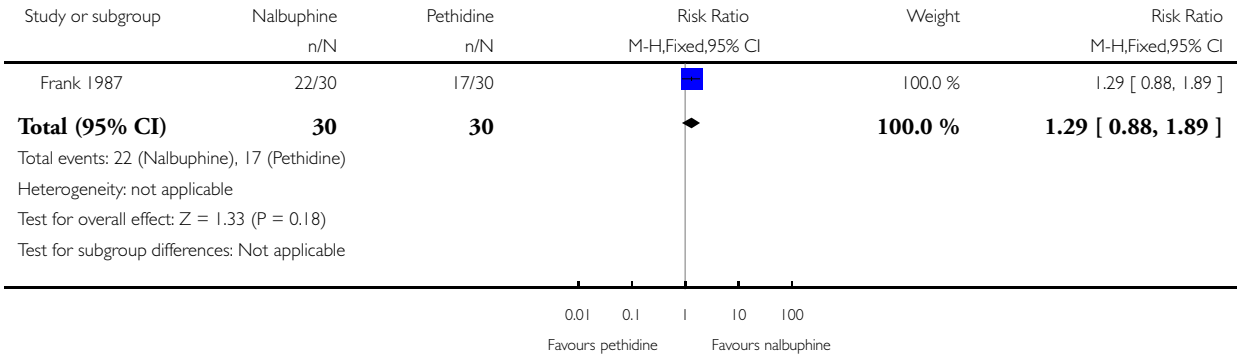


Analysis 30.1. Comparison 30 PCA nalbuphine versus PCA pethidine, Outcome 1 Maternal satisfaction with analgesia in labour measured during the postnatal period (rated good or excellent).

Review: Parenteral opioids for maternal pain management in labour

Comparison: 30 PCA nalbuphine versus PCA pethidine

Outcome: 1 Maternal satisfaction with analgesia in labour measured during the postnatal period (rated good or excellent)



Analysis 30.2. Comparison 30 PCA nalbuphine versus PCA pethidine, Outcome 2 Maternal satisfaction with analgesia in labour measured during the postnatal period (Would use the same pain relief again).

Review: Parenteral opioids for maternal pain management in labour

Comparison: 30 PCA nalbuphine versus PCA pethidine

Outcome: 2 Maternal satisfaction with analgesia in labour measured during the postnatal period (Would use the same pain relief again)

Study or subgroup	Nalbuphine n/N	Pethidine n/N	Risk Ratio M-H,Fixed,95% CI	Weight	Risk Ratio M-H,Fixed,95% CI
Frank 1987	23/30	21/29		100.0 %	1.06 [0.79, 1.43]
Total (95% CI)	**30**	**29**		**100.0 %**	**1.06 [0.79, 1.43]**
Total events: 23 (Nalbuphine), 21 (Pethidine)					
Heterogeneity: not applicable					
Test for overall effect: Z = 0.37 (P = 0.71)					
Test for subgroup differences: Not applicable					

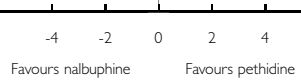
Analysis 30.3. Comparison 30 PCA nalbuphine versus PCA pethidine, Outcome 3 Maternal pain score or pain measured in labour.

Review: Parenteral opioids for maternal pain management in labour

Comparison: 30 PCA nalbuphine versus PCA pethidine

Outcome: 3 Maternal pain score or pain measured in labour

Study or subgroup	Nalbuphine N	Mean(SD)	Pethidine N	Mean(SD)	Mean Difference IV,Fixed,95% CI	Weight	Mean Difference IV,Fixed,95% CI
Frank 1987 (1)	30	2.1 (0.774)	30	2.5 (0.774)		100.0 %	-0.40 [-0.79, -0.01]
Total (95% CI)	**30**		**30**			**100.0 %**	**-0.40 [-0.79, -0.01]**
Heterogeneity: not applicable							
Test for overall effect: Z = 2.00 (P = 0.045)							
Test for subgroup differences: Not applicable							



(1) SD estimated from P value 0.05

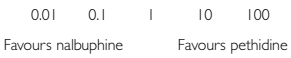
Analysis 30.4. Comparison 30 PCA nalbuphine versus PCA pethidine, Outcome 4 Additional analgesia required.

Review: Parenteral opioids for maternal pain management in labour

Comparison: 30 PCA nalbuphine versus PCA pethidine

Outcome: 4 Additional analgesia required

Study or subgroup	Nalbuphine n/N	Pethidine n/N	Risk Ratio M-H,Fixed,95% CI	Weight	Risk Ratio M-H,Fixed,95% CI
Frank 1987 (1)	12/30	14/29		100.0 %	0.83 [0.46, 1.48]
Total (95% CI)	**30**	**29**		**100.0 %**	**0.83 [0.46, 1.48]**
Total events: 12 (Nalbuphine), 14 (Pethidine)					
Heterogeneity: not applicable					
Test for overall effect: Z = 0.64 (P = 0.52)					
Test for subgroup differences: Not applicable					



(1) Entonox

Analysis 30.5. Comparison 30 PCA nalbuphine versus PCA pethidine, Outcome 5 Nausea and vomiting.

Review: Parenteral opioids for maternal pain management in labour

Comparison: 30 PCA nalbuphine versus PCA pethidine

Outcome: 5 Nausea and vomiting

Study or subgroup	Nalbuphine n/N	Pethidine n/N	Risk Ratio M-H,Fixed,95% CI	Weight	Risk Ratio M-H,Fixed,95% CI
Frank 1987	7/30	10/29		100.0 %	0.68 [0.30, 1.54]
Total (95% CI)	**30**	**29**		**100.0 %**	**0.68 [0.30, 1.54]**
Total events: 7 (Nalbuphine), 10 (Pethidine)					
Heterogeneity: not applicable					
Test for overall effect: Z = 0.93 (P = 0.35)					
Test for subgroup differences: Not applicable					

Analysis 30.6. Comparison 30 PCA nalbuphine versus PCA pethidine, Outcome 6 Apgar score < 7 at 5 minutes.

Review: Parenteral opioids for maternal pain management in labour

Comparison: 30 PCA nalbuphine versus PCA pethidine

Outcome: 6 Apgar score < 7 at 5 minutes

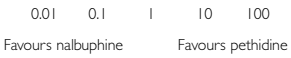
Study or subgroup	Nalbuphine n/N	Pethidine n/N	Risk Ratio M-H,Fixed,95% CI	Weight	Risk Ratio M-H,Fixed,95% CI
Frank 1987 (1)	0/18	1/23		100.0 %	0.42 [0.02, 9.76]
Total (95% CI)	**18**	**23**		**100.0 %**	**0.42 [0.02, 9.76]**

Total events: 0 (Nalbuphine), 1 (Pethidine)

Heterogeneity: not applicable

Test for overall effect: Z = 0.54 (P = 0.59)

Test for subgroup differences: Not applicable



(1) Those babies delivered within 4 hrs of medication only

Analysis 31.1. Comparison 31 PCA fentanyl versus PCA alfentanil, Outcome 1 Maternal satisfaction with analgesia in labour measured during the postnatal period (described as adequate).

Review: Parenteral opioids for maternal pain management in labour

Comparison: 31 PCA fentanyl versus PCA alfentanil

Outcome: 1 Maternal satisfaction with analgesia in labour measured during the postnatal period (described as adequate)

Study or subgroup	Fentanyl n/N	Alfentanil n/N	Risk Ratio M-H,Fixed,95% CI	Weight	Risk Ratio M-H,Fixed,95% CI
Morley-Forster 2000	10/11	7/12		100.0 %	1.56 [0.93, 2.60]
Total (95% CI)	**11**	**12**		**100.0 %**	**1.56 [0.93, 2.60]**

Total events: 10 (Fentanyl), 7 (Alfentanil)

Heterogeneity: not applicable

Test for overall effect: Z = 1.69 (P = 0.090)

Test for subgroup differences: Not applicable

Analysis 31.2. Comparison 31 PCA fentanyl versus PCA alfentanil, Outcome 2 Maternal pain score or pain measured in labour (Pain score at 4-6 cm cervical dilatation).

Review: Parenteral opioids for maternal pain management in labour

Comparison: 31 PCA fentanyl versus PCA alfentanil

Outcome: 2 Maternal pain score or pain measured in labour (Pain score at 4-6 cm cervical dilatation)

Study or subgroup	Fentanyl N	Mean(SD)	Alfentanil N	Mean(SD)	Mean Difference IV,Fixed,95% CI	Weight	Mean Difference IV,Fixed,95% CI
Morley-Forster 2000	11	54.9 (24.9)	10	67.7 (20.2)		100.0 %	-12.80 [-32.12, 6.52]
Total (95% CI)	**11**		**10**			**100.0 %**	**-12.80 [-32.12, 6.52]**

Heterogeneity: not applicable

Test for overall effect: Z = 1.30 (P = 0.19)

Test for subgroup differences: Not applicable

Analysis 31.3. Comparison 31 PCA fentanyl versus PCA alfentanil, Outcome 3 Nausea.

Review: Parenteral opioids for maternal pain management in labour

Comparison: 31 PCA fentanyl versus PCA alfentanil

Outcome: 3 Nausea

Study or subgroup	Fentanyl n/N	Alfentanil n/N	Risk Ratio M-H,Fixed,95% CI	Weight	Risk Ratio M-H,Fixed,95% CI
Morley-Forster 2000	5/11	2/12		100.0 %	2.73 [0.66, 11.30]
Total (95% CI)	**11**	**12**		**100.0 %**	**2.73 [0.66, 11.30]**

Total events: 5 (Fentanyl), 2 (Alfentanil)

Heterogeneity: not applicable

Test for overall effect: Z = 1.38 (P = 0.17)

Test for subgroup differences: Not applicable

Analysis 31.4. Comparison 31 PCA fentanyl versus PCA alfentanil, Outcome 4 Caesarean section.

Review: Parenteral opioids for maternal pain management in labour

Comparison: 31 PCA fentanyl versus PCA alfentanil

Outcome: 4 Caesarean section

Study or subgroup	Fentanyl n/N	Alfentanil n/N	Risk Ratio M-H,Fixed,95% CI	Weight	Risk Ratio M-H,Fixed,95% CI
Morley-Forster 2000	3/11	2/12		100.0 %	1.64 [0.33, 8.03]
Total (95% CI)	**11**	**12**		**100.0 %**	**1.64 [0.33, 8.03]**
Total events: 3 (Fentanyl), 2 (Alfentanil)					
Heterogeneity: not applicable					
Test for overall effect: Z = 0.61 (P = 0.54)					
Test for subgroup differences: Not applicable					

Analysis 31.5. Comparison 31 PCA fentanyl versus PCA alfentanil, Outcome 5 Naloxone required.

Review: Parenteral opioids for maternal pain management in labour

Comparison: 31 PCA fentanyl versus PCA alfentanil

Outcome: 5 Naloxone required

Study or subgroup	Fentanyl n/N	Alfentanil n/N	Risk Ratio M-H,Fixed,95% CI	Weight	Risk Ratio M-H,Fixed,95% CI
Morley-Forster 2000	4/11	2/13		100.0 %	2.36 [0.53, 10.55]
Total (95% CI)	**11**	**13**		**100.0 %**	**2.36 [0.53, 10.55]**
Total events: 4 (Fentanyl), 2 (Alfentanil)					
Heterogeneity: not applicable					
Test for overall effect: Z = 1.13 (P = 0.26)					
Test for subgroup differences: Not applicable					

Analysis 32.1. Comparison 32 PCA fentanyl versus PCA pethidine, Outcome 1 Maternla pain score measured in labour.

Review: Parenteral opioids for maternal pain management in labour

Comparison: 32 PCA fentanyl versus PCA pethidine

Outcome: 1 Maternla pain score measured in labour

Study or subgroup	Fentanyl N	Mean(SD)	Pethidine N	Mean(SD)	Mean Difference IV,Fixed,95% CI	Weight	Mean Difference IV,Fixed,95% CI
Douma 2010	54	5.96 (2.5)	53	6.61 (2.3)		100.0 %	-0.65 [-1.56, 0.26]
Total (95% CI)	**54**		**53**			**100.0 %**	**-0.65 [-1.56, 0.26]**

Heterogeneity: not applicable

Test for overall effect: Z = 1.40 (P = 0.16)

Test for subgroup differences: Not applicable

Analysis 32.2. Comparison 32 PCA fentanyl versus PCA pethidine, Outcome 2 Epidural.

Review: Parenteral opioids for maternal pain management in labour

Comparison: 32 PCA fentanyl versus PCA pethidine

Outcome: 2 Epidural

Study or subgroup	Fentanyl n/N	Pethidine n/N	Risk Ratio M-H,Fixed,95% CI	Weight	Risk Ratio M-H,Fixed,95% CI
Douma 2010	8/54	18/53		100.0 %	0.44 [0.21, 0.92]
Total (95% CI)	**54**	**53**		**100.0 %**	**0.44 [0.21, 0.92]**

Total events: 8 (Fentanyl), 18 (Pethidine)

Heterogeneity: not applicable

Test for overall effect: Z = 2.19 (P = 0.028)

Test for subgroup differences: Not applicable

Analysis 32.3. Comparison 32 PCA fentanyl versus PCA pethidine, Outcome 3 Maternal sleepiness during labour.

Review: Parenteral opioids for maternal pain management in labour

Comparison: 32 PCA fentanyl versus PCA pethidine

Outcome: 3 Maternal sleepiness during labour

Study or subgroup	Fentanyl N	Mean(SD)	Pethidine N	Mean(SD)	Mean Difference IV,Fixed,95% CI	Weight	Mean Difference IV,Fixed,95% CI
Douma 2010	54	1.39 (0.5)	53	1.45 (0.5)		100.0 %	-0.06 [-0.25, 0.13]
Total (95% CI)	**54**		**53**			**100.0 %**	**-0.06 [-0.25, 0.13]**

Heterogeneity: not applicable

Test for overall effect: Z = 0.62 (P = 0.53)

Test for subgroup differences: Not applicable

Analysis 32.4. Comparison 32 PCA fentanyl versus PCA pethidine, Outcome 4 Nausea and vomiting.

Review: Parenteral opioids for maternal pain management in labour

Comparison: 32 PCA fentanyl versus PCA pethidine

Outcome: 4 Nausea and vomiting

Study or subgroup	Fentanyl n/N	Pethidine n/N	Risk Ratio M-H,Fixed,95% CI	Weight	Risk Ratio M-H,Fixed,95% CI
Douma 2010	20/51	23/51		100.0 %	0.87 [0.55, 1.37]
Total (95% CI)	**51**	**51**		**100.0 %**	**0.87 [0.55, 1.37]**

Total events: 20 (Fentanyl), 23 (Pethidine)

Heterogeneity: not applicable

Test for overall effect: Z = 0.60 (P = 0.55)

Test for subgroup differences: Not applicable

Analysis 32.5. Comparison 32 PCA fentanyl versus PCA pethidine, Outcome 5 Caesarean section.

Review: Parenteral opioids for maternal pain management in labour

Comparison: 32 PCA fentanyl versus PCA pethidine

Outcome: 5 Caesarean section

Study or subgroup	Fentanyl n/N	Pethidine n/N	Risk Ratio M-H,Fixed,95% CI	Weight	Risk Ratio M-H,Fixed,95% CI
Douma 2010	1/46	3/35		100.0 %	0.25 [0.03, 2.34]
Total (95% CI)	**46**	**35**		**100.0 %**	**0.25 [0.03, 2.34]**

Total events: 1 (Fentanyl), 3 (Pethidine)
Heterogeneity: not applicable
Test for overall effect: Z = 1.21 (P = 0.23)
Test for subgroup differences: Not applicable

Analysis 32.6. Comparison 32 PCA fentanyl versus PCA pethidine, Outcome 6 Assisted vaginal birth.

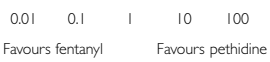
Review: Parenteral opioids for maternal pain management in labour

Comparison: 32 PCA fentanyl versus PCA pethidine

Outcome: 6 Assisted vaginal birth

Study or subgroup	Fentanyl n/N	Pethidine n/N	Risk Ratio M-H,Fixed,95% CI	Weight	Risk Ratio M-H,Fixed,95% CI
Douma 2010	6/46	8/35		100.0 %	0.57 [0.22, 1.49]
Total (95% CI)	**46**	**35**		**100.0 %**	**0.57 [0.22, 1.49]**

Total events: 6 (Fentanyl), 8 (Pethidine)
Heterogeneity: not applicable
Test for overall effect: Z = 1.14 (P = 0.25)
Test for subgroup differences: Not applicable



Analysis 32.7. Comparison 32 PCA fentanyl versus PCA pethidine, Outcome 7 Newborn neurobehavioural score (15 minutes post delivery).

Review: Parenteral opioids for maternal pain management in labour

Comparison: 32 PCA fentanyl versus PCA pethidine

Outcome: 7 Newborn neurobehavioural score (15 minutes post delivery)

Study or subgroup	Fentanyl N	Mean(SD)	Pethidine N	Mean(SD)	Mean Difference IV,Fixed,95% CI	Weight	Mean Difference IV,Fixed,95% CI
Douma 2010 (1)	38	35.9 (3.6)	25	36.8 (2.1)		100.0 %	-0.90 [-2.31, 0.51]
Total (95% CI)	**38**		**25**			**100.0 %**	**-0.90 [-2.31, 0.51]**

Heterogeneity: not applicable

Test for overall effect: Z = 1.25 (P = 0.21)

Test for subgroup differences: Not applicable

(1) Neurologic and Adaptive Capacity Score - 40 maximum score, >30 reassuring. High scores = positive result

Analysis 32.8. Comparison 32 PCA fentanyl versus PCA pethidine, Outcome 8 Newborn neurobehavioural score (2 hours post delivery).

Review: Parenteral opioids for maternal pain management in labour

Comparison: 32 PCA fentanyl versus PCA pethidine

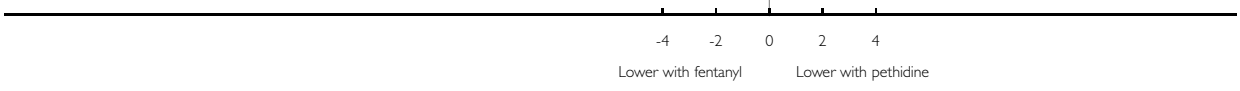
Outcome: 8 Newborn neurobehavioural score (2 hours post delivery)

Study or subgroup	Fentanyl N	Mean(SD)	Pethidine N	Mean(SD)	Mean Difference IV,Fixed,95% CI	Weight	Mean Difference IV,Fixed,95% CI
Douma 2010 (1)	38	36.7 (3.2)	26	37.2 (2.7)		100.0 %	-0.50 [-1.95, 0.95]
Total (95% CI)	**38**		**26**			**100.0 %**	**-0.50 [-1.95, 0.95]**

Heterogeneity: not applicable

Test for overall effect: Z = 0.67 (P = 0.50)

Test for subgroup differences: Not applicable



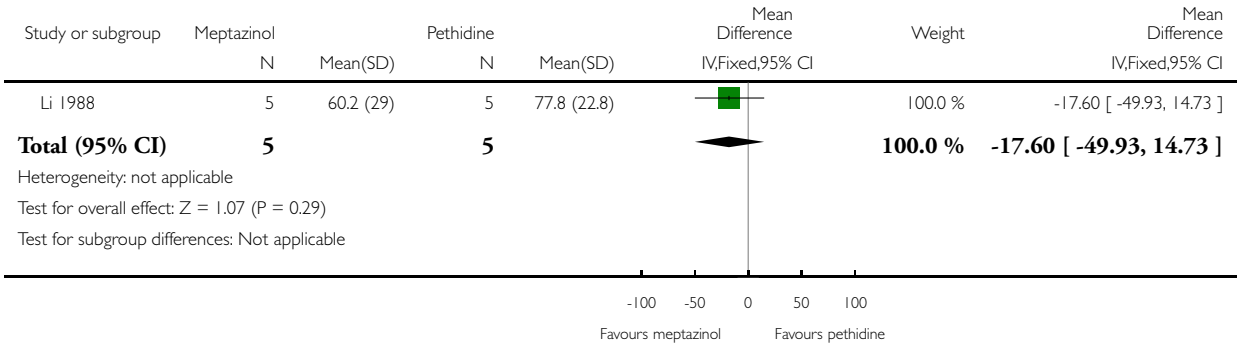
(1) Neurologic and Adaptive Capacity Score - 40 maximum score, >30 reassuring. High scores = positive result

Analysis 33.1. Comparison 33 PCA (IM) meptazinol versus PCA (IM) pethidine, Outcome 1 Maternal pain score or pain measured in labour (measured 1 day after delivery).

Review: Parenteral opioids for maternal pain management in labour

Comparison: 33 PCA (IM) meptazinol versus PCA (IM) pethidine

Outcome: 1 Maternal pain score or pain measured in labour (measured 1 day after delivery)

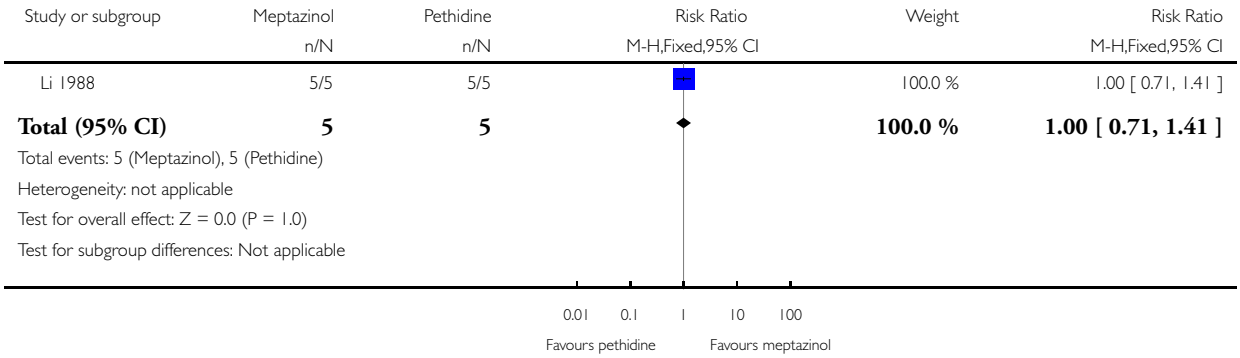


Analysis 33.2. Comparison 33 PCA (IM) meptazinol versus PCA (IM) pethidine, Outcome 2 Satisfied with mode of administration (PCA IM) (non pre-specified).

Review: Parenteral opioids for maternal pain management in labour

Comparison: 33 PCA (IM) meptazinol versus PCA (IM) pethidine

Outcome: 2 Satisfied with mode of administration (PCA IM) (non pre-specified)

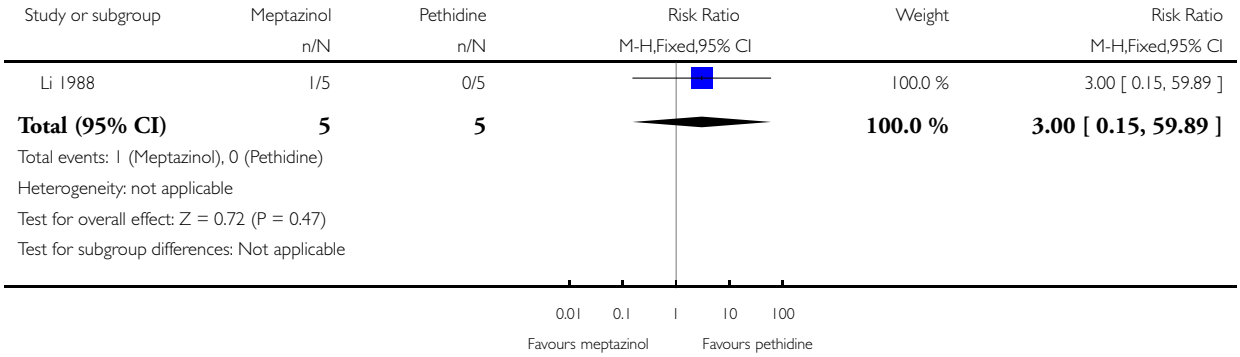


Analysis 33.3. Comparison 33 PCA (IM) meptazinol versus PCA (IM) pethidine, Outcome 3 Epidural.

Review: Parenteral opioids for maternal pain management in labour

Comparison: 33 PCA (IM) meptazinol versus PCA (IM) pethidine

Outcome: 3 Epidural

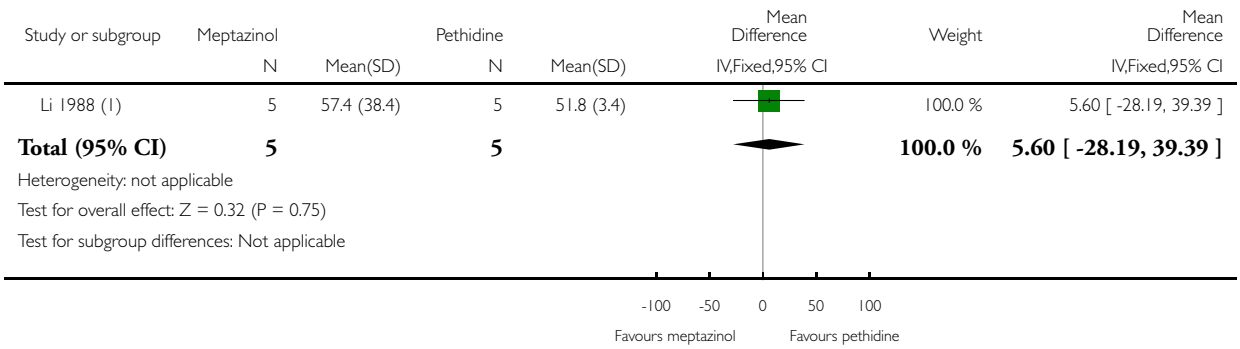


Analysis 33.4. Comparison 33 PCA (IM) meptazinol versus PCA (IM) pethidine, Outcome 4 Maternal sleepiness in labour (Drowsiness score in labour rated 1 day after delivery).

Review: Parenteral opioids for maternal pain management in labour

Comparison: 33 PCA (IM) meptazinol versus PCA (IM) pethidine

Outcome: 4 Maternal sleepiness in labour (Drowsiness score in labour rated 1 day after delivery)



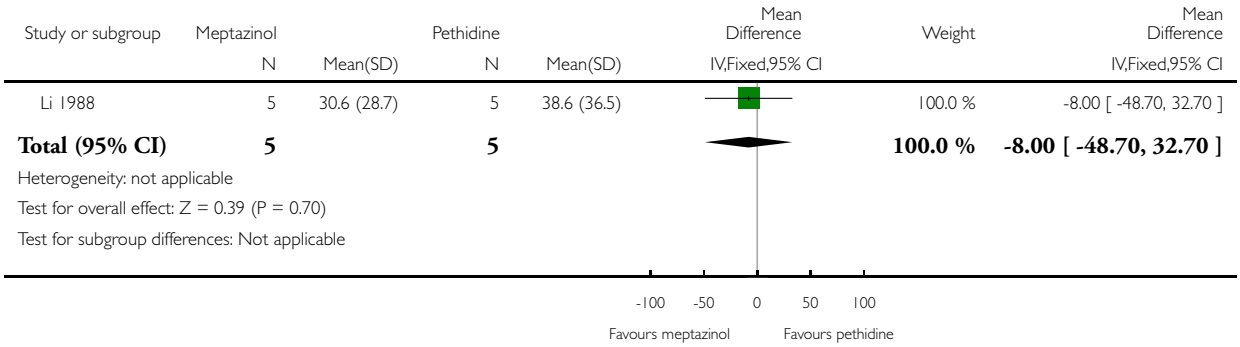
(1) SD in pethidine group as reported in published paper (extremely small)

Analysis 33.5. Comparison 33 PCA (IM) meptazinol versus PCA (IM) pethidine, Outcome 5 Nausea (score in labour rated 1 day after delivery).

Review: Parenteral opioids for maternal pain management in labour

Comparison: 33 PCA (IM) meptazinol versus PCA (IM) pethidine

Outcome: 5 Nausea (score in labour rated 1 day after delivery)

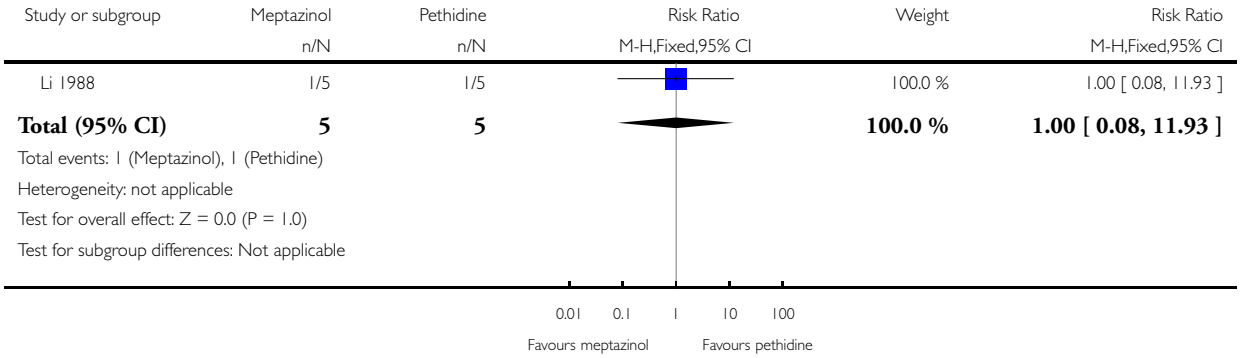


Analysis 33.6. Comparison 33 PCA (IM) meptazinol versus PCA (IM) pethidine, Outcome 6 Naloxone administered.

Review: Parenteral opioids for maternal pain management in labour

Comparison: 33 PCA (IM) meptazinol versus PCA (IM) pethidine

Outcome: 6 Naloxone administered



Analysis 34.1. Comparison 34 Opioids versus TENS, Outcome 1 Maternal satisfaction with analgesia measured post delivery (rated as good).

Review: Parenteral opioids for maternal pain management in labour

Comparison: 34 Opioids versus TENS

Outcome: 1 Maternal satisfaction with analgesia measured post delivery (rated as good)

Study or subgroup	Opioids n/N	TENS n/N	Risk Ratio M-H,Fixed,95% CI	Weight	Risk Ratio M-H,Fixed,95% CI
Neumark 1978	2/5	2/9		7.2 %	1.80 [0.35, 9.16]
Tawfik 1982	28/55	15/35		92.8 %	1.19 [0.75, 1.89]
Total (95% CI)	**60**	**44**		**100.0 %**	**1.23 [0.79, 1.92]**

Total events: 30 (Opioids), 17 (TENS)

Heterogeneity: Chi^2 = 0.23, df = 1 (P = 0.63); I^2 =0.0%

Test for overall effect: Z = 0.92 (P = 0.36)

Test for subgroup differences: Not applicable

Analysis 34.2. Comparison 34 Opioids versus TENS, Outcome 2 Maternal pain score measured during labour.

Review: Parenteral opioids for maternal pain management in labour

Comparison: 34 Opioids versus TENS

Outcome: 2 Maternal pain score measured during labour

Study or subgroup	Opioids n/N	TENS n/N	Risk Ratio M-H,Random,95% CI	Weight	Risk Ratio M-H,Random,95% CI
Tawfik 1982	38/55	17/35		38.5 %	1.42 [0.97, 2.09]
Thakur 2004	70/100	70/100		61.5 %	1.00 [0.83, 1.20]
Total (95% CI)	**155**	**135**		**100.0 %**	**1.15 [0.81, 1.61]**

Total events: 108 (Opioids), 87 (TENS)

Heterogeneity: Tau^2 = 0.04; Chi^2 = 2.76, df = 1 (P = 0.10); I^2 =64%

Test for overall effect: Z = 0.77 (P = 0.44)

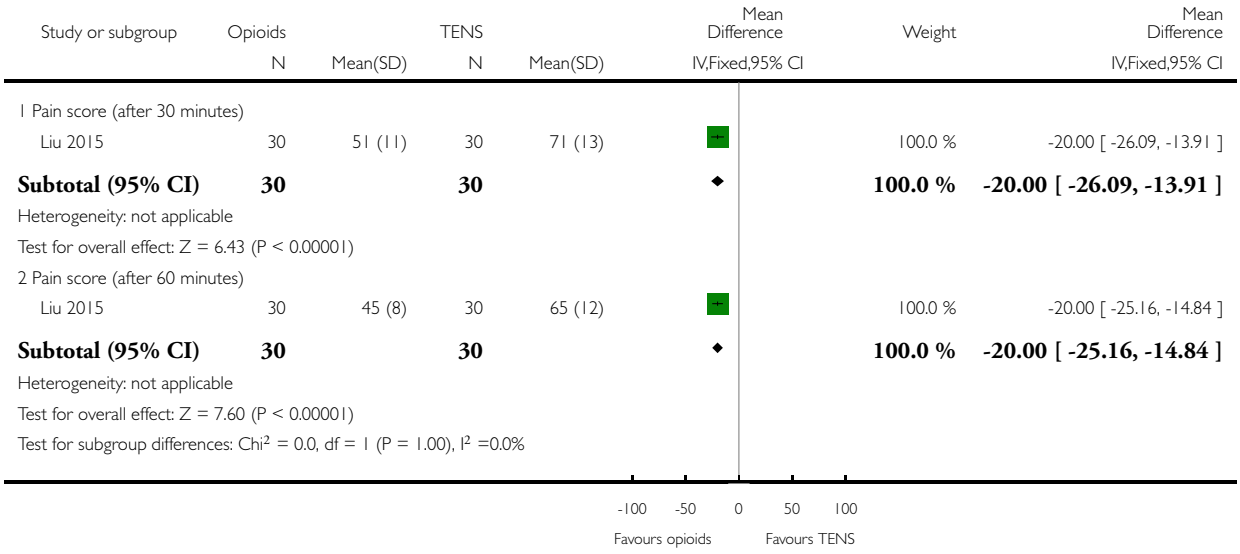
Test for subgroup differences: Not applicable

Analysis 34.3. Comparison 34 Opioids versus TENS, Outcome 3 Maternal pain score in labour.

Review: Parenteral opioids for maternal pain management in labour

Comparison: 34 Opioids versus TENS

Outcome: 3 Maternal pain score in labour



Analysis 34.4. Comparison 34 Opioids versus TENS, Outcome 4 Maternal sleepiness during labour (Drowsiness).

Review: Parenteral opioids for maternal pain management in labour

Comparison: 34 Opioids versus TENS

Outcome: 4 Maternal sleepiness during labour (Drowsiness)

Study or subgroup	Opioids n/N	TENS n/N	Risk Ratio M-H,Fixed,95% CI	Weight	Risk Ratio M-H,Fixed,95% CI
Tawfik 1982	9/55	0/35		54.9 %	12.21 [0.73, 203.45]
Thakur 2004	2/100	0/100		45.1 %	5.00 [0.24, 102.85]
Total (95% CI)	**155**	**135**		**100.0 %**	**8.96 [1.13, 71.07]**

Total events: 11 (Opioids), 0 (TENS)

Heterogeneity: $Chi^2 = 0.19$, df = 1 (P = 0.66); $I^2 = 0.0\%$

Test for overall effect: Z = 2.08 (P = 0.038)

Test for subgroup differences: Not applicable

Analysis 34.5. Comparison 34 Opioids versus TENS, Outcome 5 Nausea and vomiting.

Review: Parenteral opioids for maternal pain management in labour

Comparison: 34 Opioids versus TENS

Outcome: 5 Nausea and vomiting

Study or subgroup	Opioids n/N	TENS n/N	Risk Ratio M-H,Fixed,95% CI	Weight	Risk Ratio M-H,Fixed,95% CI
Liu 2015	6/30	0/30		31.1 %	13.00 [0.76, 220.96]
Tawfik 1982	6/55	0/35		37.8 %	8.36 [0.49, 143.87]
Thakur 2004	10/100	0/100		31.1 %	21.00 [1.25, 353.58]
Total (95% CI)	**185**	**165**		**100.0 %**	**13.73 [2.72, 69.24]**

Total events: 22 (Opioids), 0 (TENS)

Heterogeneity: $Chi^2 = 0.21$, df = 2 (P = 0.90); $I^2 = 0.0\%$

Test for overall effect: Z = 3.17 (P = 0.0015)

Test for subgroup differences: Not applicable

Analysis 34.6. Comparison 34 Opioids versus TENS, Outcome 6 Caesarean section.

Review: Parenteral opioids for maternal pain management in labour

Comparison: 34 Opioids versus TENS

Outcome: 6 Caesarean section

Study or subgroup	Opioids n/N	TENS n/N	Risk Ratio M-H,Fixed,95% CI	Weight	Risk Ratio M-H,Fixed,95% CI
Liu 2015	2/30	1/30		100.0 %	2.00 [0.19, 20.90]
Thakur 2004	0/100	0/100			Not estimable
Total (95% CI)	**130**	**130**		**100.0 %**	**2.00 [0.19, 20.90]**

Total events: 2 (Opioids), 1 (TENS)

Heterogeneity: not applicable

Test for overall effect: Z = 0.58 (P = 0.56)

Test for subgroup differences: Not applicable

Analysis 34.7. Comparison 34 Opioids versus TENS, Outcome 7 Assisted vaginal birth.

Review: Parenteral opioids for maternal pain management in labour

Comparison: 34 Opioids versus TENS

Outcome: 7 Assisted vaginal birth

Study or subgroup	Opioids n/N	TENS n/N	Risk Ratio M-H,Fixed,95% CI	Weight	Risk Ratio M-H,Fixed,95% CI
Liu 2015	2/30	2/30		80.0 %	1.00 [0.15, 6.64]
Thakur 2004	2/100	0/100		20.0 %	5.00 [0.24, 102.85]
Total (95% CI)	**130**	**130**		**100.0 %**	**1.80 [0.40, 8.18]**

Total events: 4 (Opioids), 2 (TENS)

Heterogeneity: Chi² = 0.81, df = 1 (P = 0.37); I² =0.0%

Test for overall effect: Z = 0.76 (P = 0.45)

Test for subgroup differences: Not applicable

Analysis 34.8. Comparison 34 Opioids versus TENS, Outcome 8 Fetal heart rate changes in labour (Fetal distress).

Review: Parenteral opioids for maternal pain management in labour

Comparison: 34 Opioids versus TENS

Outcome: 8 Fetal heart rate changes in labour (Fetal distress)

Study or subgroup	Opioids n/N	TENS n/N	Risk Ratio M-H,Fixed,95% CI	Weight	Risk Ratio M-H,Fixed,95% CI
Thakur 2004	2/100	0/100		100.0 %	5.00 [0.24, 102.85]
Total (95% CI)	**100**	**100**		**100.0 %**	**5.00 [0.24, 102.85]**

Total events: 2 (Opioids), 0 (TENS)

Heterogeneity: not applicable

Test for overall effect: Z = 1.04 (P = 0.30)

Test for subgroup differences: Not applicable

APPENDICES

Appendix 1. Search terms for ICTRP and ClinicalTrials.gov

(intravenous OR intramuscular OR opioids or opioid) AND (birth OR labour OR labor)

WHAT'S NEW

Date	Event	Description
11 May 2017	New search has been performed	Search updated, 70 new reports assessed. 'Summary of findings' tables have been incorporated in this update
11 May 2017	New citation required but conclusions have not changed	We included 13 new trials in this update. We also excluded a further 34 trials, identified five ongoing studies and added two to the awaiting classification section. Altogether, the review now includes 70 trials

HISTORY

Protocol first published: Issue 4, 2008

Review first published: Issue 9, 2010

Date	Event	Description
21 June 2011	New search has been performed	Search updated. We have included data from three new studies (Douma 2010; Tawfik 1982; Thakur 2004). These changes have not altered the conclusions of the review New outcome added - see Differences between protocol and review.

CONTRIBUTIONS OF AUTHORS

In this 2017 version of the review, Anna Cuthbert and Lesley Smith assessed eligibility and carried out data extraction. Lesley Smith and Ethel Burns updated the background and discussion.

DECLARATIONS OF INTEREST

Lesley A Smith: none known.

Ethel Burns: none known.

Anna Cuthbert: is supported by a grant to her Institution from WHO to work on this review, and has received support via an NIHR grant to her Institution to work on other Cochrane reviews.

SOURCES OF SUPPORT

Internal sources

- (AC) The University of Liverpool, UK.

External sources

- National Institute for Health Research, UK.

2010 Update - NIHR NHS Cochrane Collaboration Programme Grant Scheme award for NHS-prioritised centrally-managed, pregnancy and childbirth systematic reviews:CPGS02

- 2017 Update - WHO UNDP-UNFPA-UNICEF-WHO-World Bank Special Programme of Research, Development and Research Training in Human Reproduction (HRP), Department of Reproductive Health and Research (RHR), World Health Organization, Switzerland.

DIFFERENCES BETWEEN PROTOCOL AND REVIEW

The Background section of the review has been updated and amended since publication of the protocol and has been revised for this update.

The focus of some of the reports we identified using the search strategy was on the route of administration, rather than on the effectiveness of opioids compared with placebo or other opioids. That is, in several trials, women in both arms received the same opioid and the same dose but the drug was given by a different route (e.g. intravenous (staff administered) versus patient-controlled analgesia, or intramuscular versus intravenous). Although in the original protocol we had specified that we would examine different routes, in retrospect we thought that including such comparisons would add several more potentially large sections to the review (each report requiring a different comparison) and would throw little light on the main review questions: whether opioids are effective for pain relief in labour without causing unpleasant side effects or harm to mothers and babies. Studies focusing on route of administration will be examined in the future in a separate, related Cochrane review.

For the 2017 update, we split the outcome "Additional analgesia: Epidural" into two separate outcomes: "Additional analgesia required" and "Epidural". This meant we were able to capture second doses of study drugs that were already reported in the previous update. The review now includes GRADE methods and one new 'Summary of findings' table. Given the nature of this review, with many different comparisons and small sample sizes, we also added an additional table with GRADE including all outcomes relating to pain.

The previous update of this review was one of a series of reviews included in an overview of reviews examining methods of pain management in labour Jones 2012. It has been updated to follow the generic protocol developed in 2011 for reviews contributing to the overview (Jones 2011), as a result of which we have added a new comparison (opioids versus TENS).

For the 2017 update, we added in a search of ClinicalTrials.gov and the WHO International Clinical Trials Registry Platform (ICTRP).

INDEX TERMS

Medical Subject Headings (MeSH)

Analgesia, Obstetrical [*methods]; Analgesics, Opioid [*administration & dosage; adverse effects]; Injections, Intramuscular; Injections, Intravenous; Labor Pain [*drug therapy]; Meperidine [administration & dosage]; Randomized Controlled Trials as Topic; Transcutaneous Electric Nerve Stimulation

MeSH check words

Female; Humans; Pregnancy