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Parenteral opioids for maternal pain management in labour (Review)

Ullman R, Smith LA, Burns E, Mori R, Dowswell T



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[Intervention Review]

Parenteral opioids for maternal pain management in labour

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ABSTRACT

Background

Parenteral opioids are used for pain relief in labour in many countries throughout the world.

Objectives

To assess the acceptability, effectiveness and safety of different types, doses and modes of administration of parenteral opioids given to women in labour.

Search methods

We searched the Cochrane Pregnancy and Childbirth Group's Trials Register (30 April 2011) 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. We looked at studies comparing an opioid with another opioid, placebo, other non-pharmacological interventions (TENS) or inhaled analgesia.

Data collection and analysis

At least two review authors independently assessed study eligibility, collected data and assessed risk of bias.

Main results

We included 57 studies involving more than 7000 women that compared an opioid with placebo, another opioid administered intramuscularly or intravenously or compared with TENS to the back. The 57 studies reported on 29 different comparisons, and for many outcomes only one study contributed data. Overall, the evidence was of poor quality regarding the analgesic effect of opioids, satisfaction with analgesia, adverse effects and harm to women and babies. There were few statistically significant results. Many of the studies had small sample sizes, and low statistical power. Overall findings indicated that parenteral opioids provided some pain relief and moderate satisfaction with analgesia in labour, although up to two-thirds of women who received opioids reported moderate or severe pain and/or poor or moderate pain relief one or two hours after administration. Opioid drugs were associated with maternal nausea, vomiting and drowsiness, although different opioid drugs were associated with different adverse effects. There was no clear

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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

Parenteral opioids provide some relief from pain in labour but are associated with adverse effects. Maternal satisfaction with opioid analgesia was largely unreported but appeared moderate at best. This review needs to be examined alongside related Cochrane reviews examining pain management in labour. 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

The use of opioid intramuscular and intravenous pain relieving drugs in labour

Pain during labour is normal and its management is influenced by an interaction between a woman's mental and emotional state and the physiological changes that occur during labour. The use of pain-relieving drugs during labour is now part of standard care in many countries throughout the world. In recent years, many women in Western countries have chosen to have epidural analgesia to relieve pain. However, some women prefer not to have an epidural, or in some settings an epidural is not available. In many maternity units intramuscular injections of opioid drugs are widely used for pain relief in labour and options for intravenous infusions may also be available. The opioid drugs used include pethidine (also known as meperidine or demerol), diamorphine, nalbuphine, butorphanol, meptazinol, pentazocine, fentanyl and tramadol, and are relatively inexpensive. It is not clear how effective these drugs are, which opioid is best, and how unpleasant side effects (such as vomiting or sleepiness) or harm to women or their babies can be avoided.

We included 57 randomised controlled trials involving more than 7000 women that compared an opioid with placebo, another opioid or transcutaneous electrical nerve stimulation (TENS). Overall, our findings indicated 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, and different types of opioids were associated with different side effects. There was no clear evidence of adverse effects of opioids on the newborn. Maternal satisfaction with opioid analgesia was largely unreported but appeared moderate. We did not have sufficient evidence to assess which opioid drug women were most satisfied with, or which provided the best pain relief with the least side effects for mothers and babies.

In this review the 57 studies reported on 29 different comparisons, and for many outcomes only one study contributed data. We did not examine the effectiveness and safety of intramuscular or intravenous (parenteral) opioids compared with other pharmacological methods of pain relief in labour (such as epidural analgesia) and this review needs to be examined alongside related Cochrane reviews. As parenteral opioid drugs are so widely used it is important that more research is carried out so that women can make informed choices about these forms of pain relief.

BACKGROUND

This review is one in a series of Cochrane reviews examining pain management in labour. These reviews contribute to an overview of systematic reviews of pain management for women in labour ([Jones 2011b](#)) and share a generic protocol ([Jones 2011a](#)).

Description of the condition

Pain during labour is normal, 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 woman in labour and those providing care.

Characteristics of labour pain

Pain during labour is intermittent, accompanying uterine contractions ([Findley 1999](#)). Characteristically the pain intensifies as the contraction increases, reaching a peak when the contraction is at its strongest, then diminishing as the uterus relaxes. 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 painful, 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 (Findley 1999).

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 (Hodnett 2002). Two other key determinants that may influence the pain level that a woman experiences are feeling in control of her behaviour, and the care she receives. 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. Having more control will foster a woman's sense of self-belief and confidence in her capacity to labour and give birth, which will also affect her pain perception (Lowe 1993; Lowe 1996). From the clinical point of view, the management of pain during labour involves much more than simply the provision of a pharmacological intervention. Related Cochrane reviews have demonstrated the value of continuous support, midwifery models and non-pharmacological approaches to managing pain in labour (Barragán 2011; Cluett 2009; Dowswell 2009; Hatem 2008; Hodnett 2007; Hunter 2007).

A caregiver's perception of a woman's labour pain may be different from what the woman is actually experiencing (Callister 1995). A large UK survey that collected maternal and midwifery assessments of pain relief found that midwives rated pethidine more positively than the women who received it (Chamberlain 1993). Practitioners' attitudes to maternal pain vary (Leap 2004), wherein 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. 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).

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 (Findley 1999; Reynolds 2000). The extent of usage of parenteral opioids during labour is unclear; however, most obstetric units in developed 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 more recently remifentanyl (Evron 2007). Worldwide, pethidine is the most commonly used opioid (Bricker 2002). 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, estimates for opioid use showed that 34% of women overall used pethidine or another opioid during labour, with variation between NHS Hospital Trusts between 5% and 66% (Healthcare Commission 2007). A survey of 4800 women reported that 32.9% used pethidine or another opioid, and 10.5% of these women also had an epidural (Redshaw 2007). The use of an opioid varied by parity, with more nulliparae reporting use (with or without an epidural) compared with multiparous women. Use of pethidine in the UK has declined from 42% in 1995 to 33% in 2006, yet the proportion of women who received an epidural has changed little over this time period: 27% in 1995 and 28% in 2006 (Redshaw 2007). In the USA, 39% to 56% of women received an opioid during labour (Hawkins 1999). 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 2009).

Effects on the baby

Opioids readily cross the placenta by passive diffusion. 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). Pethidine has been shown to significantly affect fetal heart rate variability, accelerations and decelerations during labour (Sekhavat 2009; 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 (Nissen 1995; Ransjo-Arvidson 2001; Righard 1990).

Why it is important to do this review

This review evaluates effects of parenteral opioids for analgesia in labour. The use of intramuscular injection of opioid analgesia in labour became a traditional part of midwifery practice without evidence from randomised controlled trials for its analgesic effectiveness, impact on labour outcomes or acceptability to women. It is thought its perceived analgesic efficacy may be due, at least in part, to its sedative effects rather than a true reduction in perceived pain (NICE 2007). 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.

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. We did not include quasi-randomised trials. 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 have excluded studies focusing specifically and exclusively on women in high-risk groups, or women in pre-mature 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, nalbuphine, butorphanol, diamorphine, buprenorphine, meptazinol, pentazocine, tramadol, alfentanil, sufentanil, remifentanil and fentanyl.

The following comparisons were eligible for the review.

- An opioid versus placebo using the same route of administration.
- An opioid versus another opioid using the same route of administration.
- An opioid plus an add-on drug versus another opioid plus the same add-on drug using the same route of administration.
- 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 review is one in a series of Cochrane reviews examining pain management in labour. These reviews contribute to an overview of systematic reviews of interventions for pain management in labour (Jones 2011b), and share a generic protocol (Jones 2011a). To avoid duplication, the different methods of pain management have been listed in a specific order, from one to 15. Individual reviews focusing on particular interventions include comparisons with only the intervention above it on the list. Methods of pain management identified in the future will be added to the end of the list. The current list is as follows.

1. Placebo/no treatment
2. Hypnosis

3. Biofeedback (Barragán 2011)
4. Intracutaneous or subcutaneous sterile water injection (Derry 2011)
5. Immersion in water (Cluett 2009)
6. Aromatherapy (Smith 2011b)
7. Relaxation techniques (yoga, music, audio)
8. Acupuncture or acupressure (Smith 2011a)
9. Manual methods (massage, reflexology)
10. Transcutaneous electrical nerve stimulation (TENS) (Dowswell 2009)
11. Inhaled analgesia
12. Opioids (this review)
13. Non-opioid drugs (Othman 2011)
14. Local anaesthetic nerve blocks (Novikova 2011)
15. Epidural (including combined spinal epidural) (Anim-Somuah 2005; Simmons 2007)

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: epidural.
3. Maternal sleepiness during labour.
4. Nausea and vomiting in labour.
5. Caesarean section.
6. Assisted vaginal birth.
7. Postpartum haemorrhage (as defined by the trial authors).
8. Breastfeeding at discharge.
9. Breastfeeding in the postnatal period (four to six weeks).
10. Sense of control in labour (as defined by trialists).
11. Satisfaction with childbirth experience (as defined by trialists).
12. 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

Electronic searches

We contacted the Trials Search Co-ordinator to search the Cochrane Pregnancy and Childbirth Group's Trials Register (30 April 2011).

The Cochrane Pregnancy and Childbirth Group's Trials Register is maintained by the Trials Search Co-ordinator and contains trials identified from:

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

Details of the search strategies for CENTRAL, MEDLINE and EMBASE, the list of handsearched journals and conference proceedings, and the list of journals reviewed via the current awareness service can be found in the 'Specialized Register' section within the editorial information about the [Cochrane Pregnancy and Childbirth Group](#).

Trials identified through the searching activities described above are each assigned to a review topic (or topics). The Trials Search Co-ordinator searches the register for each review using the topic list rather than keywords.

Searching other resources

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

Data collection and analysis

Selection of studies

Four review authors (R Ullman, T Dowswell, L Smith, E Burns) independently assessed for inclusion all the studies identified as a result of the search strategy. Two authors assessed each report and we resolved any disagreement through discussion or, if required, we consulted a third author.

Data extraction and management

We designed a form to collect data. For each report, two review authors independently collected the data using the agreed form (all review authors were involved in data collection). We resolved discrepancies through discussion or, if required, we consulted a third author. We entered data into Review Manager software (RevMan 2011) and checked them for accuracy.

When information in trial reports was unclear, we attempted to contact 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 included study using the criteria described in the *Cochrane Handbook for Systematic Reviews of Interventions* (Higgins 2011) and outlined below. We resolved any disagreement by discussion, or by involving a third assessor.

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

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

We will assessed the method as:

- 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); or
- unclear risk of bias.

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

We described for each included study 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:

- 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)

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

We assessed the methods as:

- 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)

We described for each included study 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:

- 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)

We described for each included study, and for each outcome or class of outcomes, the completeness of data including attrition and exclusions from the analysis. We stated whether attrition and exclusions were reported, 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:

- 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)

We described for each included study how we investigated the possibility of selective outcome reporting bias and what we found. We assessed the methods as:

- low risk of bias (where it is 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 have been reported; one or more reported primary outcomes were not prespecified; outcomes of interest are reported incompletely and so cannot be used; study fails 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)

We describe for each included study any important concerns we have about other possible sources of bias, for example was there a potential source of bias related to the specific study design? Was the trial stopped early due to some data-dependent process? Was there extreme baseline imbalance? Has the study been claimed to be fraudulent?

We assessed whether each study was free of other problems that could put it at risk of bias:

- low risk of other bias;
- high risk of other bias;
- unclear whether there is risk of other 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 *Handbook* (Higgins 2011). With reference to (1) to (6) above, we assessed the likely magnitude and direction of the bias and whether we considered it likely to impact on the findings. We aimed to explore the impact of the level of bias through undertaking sensitivity analyses - see [Sensitivity analysis](#).

Measures of treatment effect

We carried out statistical analysis using Review Manager software (RevMan 2011). We used fixed-effect meta-analysis for combining data where trials examined the same intervention, and where we judged the trials' populations and methods to be sufficiently similar. Where we suspected clinical or statistical heterogeneity between studies, sufficient to suggest that treatment effects might differ between trials, we carried out random-effects meta-analysis.

Dichotomous data

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

Continuous data

For continuous data, we have used the mean difference if outcomes were measured in the same way (e.g. using the same pain scale) between trials. We used the standardised mean difference to combine trials that measured the same outcome, but used different scales.

Unit of analysis issues

Cluster-randomised trials

We intended to include cluster-randomised trials in the analyses along with individually randomised trials using the methods described in the *Handbook* (Higgins 2011). Their sample sizes would be adjusted using an estimate of the intracluster correlation coefficient (ICC) derived from the trial (if possible), or from another source. If we used ICCs from other sources, we would report this and conduct sensitivity analyses to investigate the effect of variation in the ICC. If we had identified both cluster-randomised trials and individually randomised trials, we planned to synthesise the relevant information. We would consider it reasonable to combine the results from both if there was little heterogeneity between the study designs and the interaction between the effect of intervention and the choice of randomisation unit was considered to be unlikely.

Crossover trials

We did not include crossover trials.

Dealing with missing data

For included studies, we noted levels of attrition. We planned to explore the impact of including studies with high levels of missing data (more than 10% for outcomes where data were collected in labour) in the overall assessment of treatment effect by using sensitivity analyses.

Where data were not reported for some outcomes or groups, we attempted to contact the study authors for further information.

We analysed data on all participants with available data in the group to which they were allocated, regardless of whether or not they received the allocated intervention. If in the original reports participants were not analysed in the group to which they were randomised, and there was sufficient information in the trial report, we attempted to restore them to the correct group.

Assessment of heterogeneity

We examined heterogeneity between trials using the T^2 and I^2 statistics. If we identified heterogeneity among the trials, we planned to explore it by prespecified subgroup analysis provided

data were available to do this, and by performing sensitivity analysis. Where we thought that an average treatment effect was clinically meaningful, we used a random-effects model for meta-analysis in the presence of moderate or high levels of heterogeneity (I^2 greater than 30%), and for these outcomes we have reported I^2 , T^2 , the P value for the Chi^2 test for heterogeneity.

Assessment of reporting biases

Where we suspected reporting bias (*see* 'Selective reporting bias' above), we attempted to contact study authors asking them to provide missing outcome data. We were not able to explore possible publication bias by using funnel plots, as too few studies were included in each comparison.

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 2011](#)).

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. For fixed-effect and random-effects meta-analyses we planned to assess differences between subgroups by inspection of the subgroups' confidence intervals: non-overlapping confidence intervals indicating a statistically significant difference in treatment effect between the subgroups.

Sensitivity analysis

We planned to carry out sensitivity analyses to explore the effect of trial quality for important outcomes in the review. Where there was risk of bias associated with a particular aspect of study quality (e.g. inadequate allocation concealment), we have explored this by sensitivity analyses.

RESULTS

Description of studies

See: [Characteristics of included studies](#); [Characteristics of excluded studies](#).

Results of the search

Using the search strategy, in an earlier version of this review, we identified 165 papers representing 138 studies. For this updated version we identified a further five studies ([Castro 2004](#); [El-Kerdawy 2010](#); [Solek-Pastuszka 2009](#); [Tawfik 1982](#); [Thakur 2004](#)) and an additional published report for a study which was ongoing when the earlier review was completed ([Douma 2010](#)). Following the updated search we excluded three of these studies ([Castro 2004](#); [El-Kerdawy 2010](#); [Solek-Pastuszka 2009](#)) and included three ([Douma 2010](#); [Tawfik 1982](#); [Thakur 2004](#)). In this update we have included 57 studies and excluded 86.

Included studies

We included 57 studies involving more than 7000 women (*see Characteristics of included studies*).

Most of the studies included in the review examined an opioid drug administered intramuscularly (IM) and compared either an opioid with placebo, 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 (PCA). None of the included studies examined subcutaneous administration of opioids. Some of the studies compared opioids with other non-pharmacological interventions such as TENS (three studies). Trials with more than two arms may be included in more than one comparison.

IM comparisons

1. IM pethidine versus IM placebo (three studies) ([Kamyabi 2003](#); [Sliom 1970](#); [Tsui 2004](#)).
2. 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.)
3. IM meptazinol versus IM pethidine PCA administration (one study) ([Li 1988](#)).
4. IM diamorphine versus IM pethidine (both groups had prochlorperazine) ([Fairlie 1999](#)).
5. IM tramadol versus IM pethidine (seven studies) ([Bitsch 1980](#); [Fieni 2000](#); [Husslein 1987](#); [Keskin 2003](#); [Khooshideh 2009](#); [Prasertsawat 1986](#); [Viegas 1993](#)).
6. In an additional study comparing tramadol with pethidine, both groups also had triflupromazine ([Kainz 1992](#)).
7. IM dihydrocodeine versus IM pethidine ([Sliom 1970](#)).
8. IM pentazocine versus IM pethidine (six studies) ([Borglin 1971](#); [Duncan 1969](#); [Levy 1971](#); [Moore 1970](#); [Mowat 1970](#); [Refstad 1980](#)).
9. IM Pentazocine + promazine versus IM pethidine + promazine ([Refstad 1980](#)).

10. IM nalbuphine versus IM pethidine (four studies) (Lardizabal 1999; Lisboa 1997; Mitterschiffthaler 1991; Wilson 1986).
 11. IM phenazocine versus IM pethidine (Grant 1970).
 12. IM morphine versus pethidine (one study) (Prasertsawat 1986).
 13. IM butorphanol versus IM pethidine (Maduska 1978).
 14. IM tramadol versus no treatment (one study) (Li 1994).
 15. One study compared a spasmolytic drug (Avacan®) with IM pentazocine (Hamann 1972).
 16. IM pentazocine versus IM Pethilorphan® (O'Dwyer 1971).
- We were unable to include data from the following comparisons because of a lack of information in the reports of the studies. IM buprenorphine versus IM pethidine (Tharamas 1999). A four-arm trial by Wahab 1988 compared nalbuphine, butorphanol, pentazocine and a placebo.

IV comparisons

17. IV fentanyl versus IV pethidine (one study) (Rayburn 1989).
 18. IV nalbuphine versus IV pethidine (one study) (Giannina 1995).
 19. IV phenazocine versus IV pethidine (one study) (Olson 1964).
 20. IV butorphanol versus IV pethidine (three studies) (Hodgkinson 1979; Nelson 2005; Quilligan 1980).
 21. IV morphine versus IV pethidine (two studies) (Campbell 1961; Olofsson 1996).
 22. IV alphaprodine (nisentil) versus IV pethidine (one study) (Gillam 1958).
 23. IV fentanyl versus butorphanol (one study) (Atkinson 1994).
- IV pethidine versus no treatment (one study) (Neumark 1978). (We were unable to use data from this study for this comparison in the review. See Characteristics of included studies tables.)

IV/PCA comparisons

24. PCA pentazocine versus PCA pethidine (one study) (Erskine 1985).
25. PCA remifentanyl versus PCA pethidine (three studies) (Blair 2005; Douma 2010; Volikas 2001).
26. PCA nalbuphine versus PCA pethidine (one study) (Frank 1987).
27. PCA fentanyl versus PCA alfentanil (one study) (Morley-Forster 2000).
28. PCA fentanyl versus PCA pethidine (one study) (Douma 2010).

Opioids versus TENS

29. 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).

Excluded studies

We have excluded 86 studies (see Characteristics of excluded studies).

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

- In 16 studies the focus was on epidural analgesia (Camann 1992; Evron 2007; Evron 2008; El-Kerdawy 2010; Gambling 1998; Ginosar 2003; Grandjean 1979; McGrath 1992; Morris 1994; Nafisi 2006; Polley 2000; Rabie 2006; Solek-Pastuszka 2009; Volmanen 2008; Wiener 1979; Wong 2005). The use of epidural analgesia for pain management in labour is covered in related Cochrane reviews (Anim-Somuah 2005; Simmons 2007).

- 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).

- Eighteen 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; 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).

- In three studies it was not clear that participants were in labour (Chang 1976; Krins 1969; Tomlin 1965).

- In the study by Bare 1962 women did not receive an opioid.

- 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.

- 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.

- 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).

- 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).

- 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).
- In five 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; Isenor 1993; McInnes 2004; Rayburn 1989; Rayburn 1991).
- In two 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).

- In the studies by Calderon 2006, Evron 2005, Li 1995, Nikkola 2000; Shahriari 2007 and Thurlow 2002, 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.
- 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).

Risk of bias in included studies

See Figure 1; Figure 2.

Figure 1. Risk of bias graph: review authors' judgements about each risk of bias item presented as percentages across all included studies.

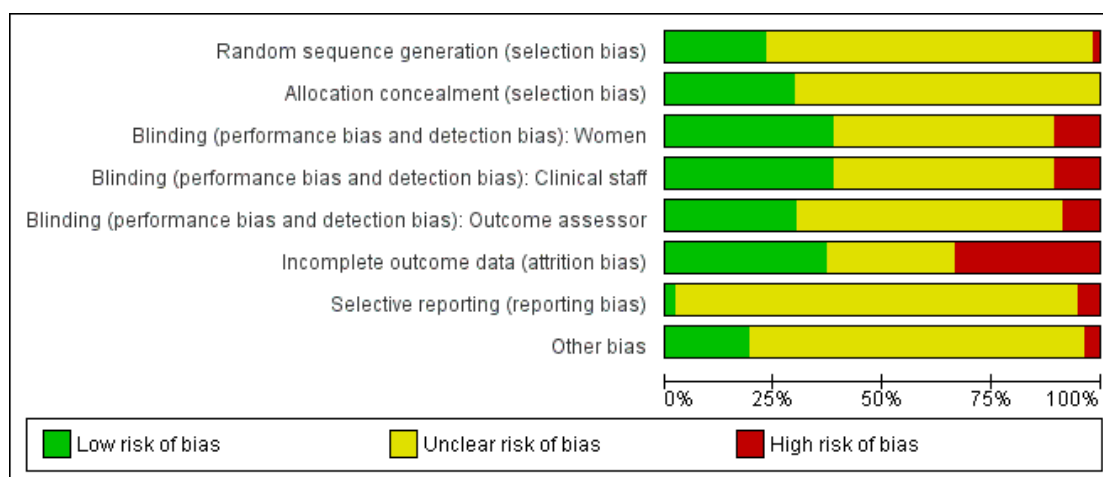


Figure 2. Risk of bias summary: review authors' judgements about each risk of bias item for each included study.



Allocation

Sequence generation

In eight studies, authors stated that a computer-generated random sequence was used (Atkinson 1994; Douma 2010; Fieni 2000; Giannina 1995; Khooshideh 2009; Lardizabal 1999; Nelson 2005; Tsui 2004); in two that an external randomisation service was used (Morley-Forster 2000; Rayburn 1989a); and in four studies that random number tables were consulted (Erskine 1985; Hamann 1972; Kainz 1992; Tharamas 1999). The majority of included studies did not give clear information 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. Four studies described using numbered opaque sealed envelopes to conceal allocation (Giannina 1995; Khooshideh 2009; Tsui 2004; Volikas 2001). Seventeen 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; Borglin 1971; Campbell 1961; Douma 2010; Fairlie 1999; Gillam 1958; Grant 1970; Lardizabal 1999; Levy 1971; Maduska 1978; Moore 1970; Morley-Forster 2000; Morrison 1987; Olofsson 1996; Olson 1964; Sheikh 1986; Wilson 1986). 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.

In six studies blinding was impractical as women were given different types of treatment (e.g. IM drug versus no treatment; IM drug versus TENS) (Li 1994; Neumark 1978; Rayburn 1989a; Refstad 1980; Tawfik 1982; Thakur 2004), and in a further nine studies methods were not described or were not clear (Bitsch 1980; Erskine 1985; Fieni 2000; Giannina 1995; Husslein 1987; Keskin 2003; Lisboa 1997; Mitterschiffthaler 1991; Wahab 1988).

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. In some studies loss to follow-up or missing data were greater than 10% (Bitsch 1980; Fairlie 1999; Hamann 1972; Levy 1971; Moore 1970; Mowat 1970; Olson 1964; Wilson 1986), or greater than 20% (De Boer 1987; Frank 1987; Giannina 1995; Gillam 1958; Nicholas 1982; O'Dwyer 1971; Refstad 1980).

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.

In some studies women were explicitly excluded from the analysis because of factors that may have related to study medication; in Hamann 1972 13% were excluded after randomisation because they had a long labour or a caesarean section, and in Moore 1970 women were excluded because they had had additional pain relief. Wilson 1986 excluded 10% of the sample because women reported that they had had inadequate 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.

Selective reporting

We did not formally assess outcome reporting bias, as we had access only to published study reports and without study protocols it is difficult to assess whether all outcomes have been accounted for. 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. 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.

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

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 study quality as for most outcomes only one or two studies contributed data, and excluding lower-quality studies from the analyses was unlikely to shed any further light on findings.

Intramuscular opioids for pain relief in labour

1. IM pethidine versus placebo

Three studies with 254 women were included in this comparison ([Kamyabi 2003](#); [Sliom 1970](#); [Tsui 2004](#)), although for most outcomes only a single study contributed data.

Primary outcomes

One study involving 50 women ([Tsui 2004](#)) showed no significant difference in maternal satisfaction 30 minutes after administration of study drug (risk ratio (RR) 7.00, 95% confidence interval (CI) 0.38 to 128); only three of 25 women receiving pethidine and none of the women receiving placebo were 'satisfied' or 'very satisfied' with analgesia ([Analysis 1.1](#)).

One study involving 116 women ([Sliom 1970](#)) reported significantly more women in the pethidine group with "fair" or "good" pain relief (RR 1.75, 95% CI 1.24 to 2.47) ([Analysis 1.2](#)).

Secondary outcomes

Maternal

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 significantly greater for pethidine 100 mg compared with placebo (RR 25, 95% CI 1.56 to 400) though the CI for this estimate is very wide ([Analysis 1.3](#)). In this study, although the majority of women in both groups required additional analgesia, this applied to fewer women with pethidine 100 mg compared with placebo (RR 0.71, 95% CI 0.54 to 0.94) ([Analysis 1.4](#)).

There was no evidence of differences between groups in the number of women requiring an epidural (RR 0.50, 95% CI 0.14 to 1.78) ([Analysis 1.5](#)), in the incidence of nausea and vomiting (RR 1.47, 95% CI 0.65 to 3.31) ([Analysis 1.6](#)), assisted vaginal birth (RR 0.86, 95% CI 0.34 to 2.19) ([Analysis 1.8](#)), or caesarean section (RR 0.83, 95% CI 0.29 to 2.38) ([Analysis 1.9](#)). Significantly 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) ([Analysis 1.7](#)).

In one study, 12/25 women in the placebo group had pethidine at 30 minutes as rescue analgesia confounding interpretation of reported outcomes after 30 minutes ([Tsui 2004](#)).

Neonatal

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), (heterogeneity: $I^2 = 61%$, $\text{Tau}^2 = 0.46$, Chi^2 test for heterogeneity $P = 0.11$) ([Analysis 1.10](#)). No babies had Apgar scores less than or equal to seven at five minutes in the one study that reported this outcome ([Analysis 1.10](#)). The incidence of newborn resuscitation and admission to neonatal intensive care unit (NICU) was low; no significant differences between groups was detected ([Analysis 1.11](#); [Analysis 1.12](#)).

One study reported 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).

2. 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).

Primary outcomes

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) (Analysis 2.1). 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.

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: $I^2 = 43%$, $\text{Tau}^2 = 0.08$, Chi^2 test for heterogeneity $P = 0.18$) (Analysis 2.2).

Secondary outcomes

Maternal

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) (Analysis 2.3). 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 in the one study (Osler 1987), and a second dose of study drug in the other (Wheble 1988).

The use of epidural analgesia was similar between meptazinol and pethidine (RR 0.96, 95% CI 0.71 to 1.29) in four studies (Nicholas 1982; Osler 1987; Sheikh 1986; Wheble 1988) involving 788 women (Analysis 2.4). 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 2.7). Overall, 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, 2.00) (heterogeneity: $I^2 = 75%$, $T^2 = 0.84$, Chi^2 test for heterogeneity $P = 0.02$), (Analysis 2.8).

Three studies each reported nausea, vomiting and sleepiness (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); however, significantly more women reported vomiting (RR 1.25, 95% CI 1.06 to 1.47) with meptazinol compared with pethidine. Fewer women in the meptazinol group reported sleepiness (average RR 0.55, 95% CI 0.28 to 1.07), although there was moderate heterogeneity for this outcome (heterogeneity: $I^2 = 44%$, $T^2 = 0.18$, Chi^2 test for heterogeneity $P = 0.17$) and the difference between groups did not reach statistical significance (Analysis 2.6).

Neonatal

Four studies involving 662 women reported number of babies with Apgar scores less than or equal to seven at one minute (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 0.76, 95% CI 0.50 to 1.13) or five minutes (RR 0.49, 95% CI 0.05 to 5.37) 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) (Analysis 2.10). 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), admission to NICU (RR 0.88, 95% CI 0.48 to 1.63) or newborn resuscitation (Analysis 2.11; Analysis 2.12; Analysis 2.13). 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. Breastfeeding problems were reported by a small number of women in one study (Sheikh 1986); there was no evidence of a difference between groups (RR 0.76, 95% CI 0.17 to 3.30).

Meptazinol versus pethidine with add-on drugs

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.

Primary and secondary outcomes

Maternal outcomes were not measured.

Neonatal

Both studies reported the number of babies with Apgar scores less than or equal to seven at one minute. There was no evidence of a difference between meptazinol compared with pethidine (RR 0.89, 95% CI, 0.47 to 1.67). In the study by [De Boer 1987](#), Apgar at five and 10 minutes were reported as 'similar' in both groups and there was no evidence of difference in the number of babies with fetal heart rate changes (decelerations). In the study by [Jackson 1983](#), no babies in either group had Apgar scores less than or equal to seven at 10 minutes. In one study ([Jackson 1983](#)), three babies in the meptazinol group and two in the pethidine group required resuscitation.

3. 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 and secondary outcomes

All women in both groups were satisfied with the mode of administration ([Analysis 3.2](#)).

Pain scores measured one day postpartum were lower with meptazinol compared with pethidine; however, there was no evidence of a significant difference (mean difference (MD) -17.60, 95% CI -49.93 to 14.73) ([Analysis 3.1](#)). Epidural rates and nausea and drowsiness scores evaluated one day postpartum were similar between groups ([Analysis 3.3](#); [Analysis 3.4](#); [Analysis 3.5](#)).

Neonatal

Naloxone was administered to one baby in each group ([Analysis 3.6](#)).

4. IM diamorphine + prochlorperazine versus IM pethidine + prochlorperazine

One study involving 133 women compared IM diamorphine 5 mg to 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

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) ([Analysis 4.1](#)).

Secondary outcomes

Maternal

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 significant 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) ([Analysis 4.2](#)). There was no evidence for a difference between groups in the number of women requiring additional analgesia (RR 1.35, 95% CI 0.53 to 3.4) ([Analysis 4.3](#)), an epidural (RR 1.22, 95% CI 0.72 to 2.07) ([Analysis 4.4](#)), assisted vaginal birth (RR 0.96, 95% CI 0.46 to 2.02) ([Analysis 4.7](#)), or caesarean section (RR 0.52, 95% CI 0.10 to 2.76) ([Analysis 4.8](#)).

The number of women vomiting was significantly lower with diamorphine compared with pethidine (RR 0.39, 95% CI 0.17 to 0.86) ([Analysis 4.5](#)), but 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 4.6](#)).

Neonatal

Significantly 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) ([Analysis 4.9](#)). However, there was no evidence of a 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) ([Analysis 4.10](#)). There were no significant differences between groups for the number of babies needing resuscitation (RR 1.21, 95% CI 0.73 to 2.02) ([Analysis 4.11](#)), or admission to NICU (RR 0.58, 95% CI 0.21 to 1.64) ([Analysis 4.12](#)).

5. 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, 75 or 100 mg.

Primary and secondary outcomes

Maternal

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

Pain intensity was defined in disparate ways in the studies; however, significantly more women had poor pain relief with tramadol compared with pethidine (RR 1.56, 95% CI 1.10 to 2.21) (Analysis 5.1).

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) (Analysis 5.2).

There was no evidence for a difference in incidence of nausea and/or vomiting with tramadol compared with placebo (average RR 0.97, 95% CI 0.34 to 2.76) (Analysis 5.3). There was a substantial level of heterogeneity detected for this outcome ($I^2 = 72%$, $T^2 = 1.09$, Chi² test for heterogeneity $P = 0.003$) therefore we used a random-effects model for the analysis. More women in the pethidine group reported sleepiness and the difference between groups reached statistical significance although, again, heterogeneity was high and we used a random-effects model (average RR 0.57, 95% CI 0.33 to 0.97), (heterogeneity $I^2 = 72%$, $T^2 = 0.24$, Chi² test for heterogeneity $P = 0.007$) (Analysis 5.4).

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 5.7; Analysis 5.8).

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 results were not statistically significant for either outcome (RR 2.26, 95% CI 0.64 to 7.89) (Analysis 5.9; Analysis 5.10).

6. 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 analgesic effect was not measured.

The authors reported that the analgesic effect was equally good in each study arm. 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).

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) (Analysis 6.1). Sleepiness was more frequently reported by women who received tramadol, though no statistically significant

difference between groups was detected (RR 2.86, 95% CI 0.68 to 12.12) (Analysis 6.2).

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

7. IM dihydrocodeine versus IM pethidine

One study involving 106 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

There was no evidence of a 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) (Analysis 7.1).

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) (Analysis 7.2), or sleepiness (RR 0.67, 95% CI 0.43 to 1.04) (Analysis 7.3).

Significantly 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) (Analysis 7.4). Apgar score at five minutes was reported as mean scores rather than number of babies in each group: there was no significant difference between groups reported (data not shown).

8. IM pentazocine versus pethidine

Six studies with 877 women are included in this comparison (Borglin 1971; Duncan 1969; Levy 1971; Moore 1970; Mowat 1970; Refstad 1980).

Primary outcomes

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 statistically significant difference between groups in either study, or when results were pooled (Analysis 8.1).

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 statistically significant difference between groups (Analysis 8.2).

Secondary outcomes

The use of additional analgesic drugs was reported by two studies (Mowat 1970; Refstad 1980). There was no statistically significant difference between groups in either study (Analysis 8.3).

One or more studies reported nausea, vomiting, sleepiness or assisted vaginal birth; there was no significant evidence of a difference between groups for any of these outcomes (Analysis 8.4; Analysis 8.5; Analysis 8.6).

Two studies reported the incidence of low Apgar scores at one and five minutes (Borglin 1971; Levy 1971) with no statistically significant difference between groups (Analysis 8.7).

9. IM pentazocine + promazine versus pethidine + promazine

One study with 85 women contributed data to this comparison (Refstad 1980).

Primary and secondary outcomes

This study reported on only two of the review's outcomes: low Apgar score at one and five minutes and naloxone administration. There was no statistically significant difference between groups for either outcome (Analysis 9.1; Analysis 9.2).

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

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 the difference between groups was statistically significant (RR 0.73, 95% CI 0.55 to 0.96) (Analysis 10.1). One study reported the number of women that were free of pain (Mitterschiffthaler 1991); the difference between groups was not statistically significant, with few women in either group having no pain (Analysis 10.2). Two studies reported pain intensity: one at 30 minutes (Lardizabal 1999) and the other at 60 minutes (Wilson 1986). There was no statistically significant difference between groups in either study (Analysis 10.3; Analysis 10.4).

Secondary outcomes

Maternal

Two studies reported the use of additional analgesia (Lardizabal 1999; Wilson 1986) and there was no statistically significant difference between groups in either study (Analysis 10.5; Analysis 10.6). One study reported nausea and vomiting as separate outcomes (Lardizabal 1999), and another reported nausea and vomiting as a single outcome (Wilson 1986). Statistically significantly fewer women who received nalbuphine reported nausea alone (RR 0.62, 95% CI 0.42 to 0.91, $P = 0.02$), or vomiting (RR 0.41, 95% CI 0.22 to 0.76) 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). There was no evidence of significant differences between groups for maternal sleepiness, assisted or caesarean births in studies reporting these outcomes (Analysis 10.8; Analysis 10.9; Analysis 10.10).

Neonatal

Two studies reported neonatal outcomes (Lardizabal 1999; Wilson 1986). There was no statistically significant difference between groups for low Apgar scores at one, five and 10 minutes, naloxone administration or admission to NICU (Analysis 10.11; Analysis 10.12; Analysis 10.13). 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).

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 uptake and vomiting. There was no statistically significant difference between groups for epidural (Analysis 11.1), but fewer women who received phenazocine vomited (RR 0.39, 95% CI 0.20 to 0.78) compared with those who received pethidine.

12. IM morphine versus pethidine

We included one study with 135 women in this comparison (Prasertsawat 1986).

Primary and secondary outcomes

There was no statistically significant difference between groups in the number of women describing their pain relief as poor (RR 1.22, 95% CI 0.56 to 2.66), additional analgesia (Analysis 12.2), nausea and vomiting (Analysis 12.3), or maternal sleepiness (Analysis 12.4). There was also no statistically significant difference between groups for number of babies born with an Apgar score less than or equal to seven at birth (Analysis 13.1), or requiring resuscitation (Analysis 12.6).

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 significant evidence of differences between groups for additional analgesia (Analysis 13.1), nausea (Analysis 13.2), or vomiting (Analysis 13.3). Likewise, there was no significant difference between groups for neonatal resuscitation (Analysis 13.4) or naloxone administration (Analysis 13.5).

14. IM tramadol versus no treatment

One study with 60 women compared IM tramadol with no treatment (Li 1994).

Primary and secondary outcomes

This study reported only two outcomes: satisfaction with analgesia and mean blood loss at birth. Only five out of 30 of the women receiving tramadol described it as satisfactory, but the difference between groups was not significant (Analysis 14.1). There was no difference between groups for mean blood loss at birth (Analysis 14.2).

15. 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 statistically significant differences between groups for the uptake of nitrous oxide (Analysis 15.1). More women in the Avacan® group received a pudendal-paracervical block (RR 2.02, 95% CI 1.16 to 3.53). There was no evidence of a difference between groups for the number of women having a caesarean section, or babies born with an Apgar score less than or equal to seven at birth (Analysis 15.3; Analysis 15.4). This study did not report on any other secondary outcomes.

16. IM pentazocine versus IM Pethilorfan®

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

Primary and secondary outcomes

There was no statistically significant difference between study groups in the number of women saying that they did not obtain any relief from medication at one hour (RR 1.22, 95% CI 0.77 to 1.95) (Analysis 16.1).

No statistically or clinically significant differences were reported for any of the secondary outcomes recorded (additional analgesia

required, assisted vaginal birth, Apgar score less than eight at one minute, Apgar score less than eight at five minutes) (Analysis 16.2; Analysis 16.3; Analysis 16.4; Analysis 16.5).

Intravenous opioids for pain relief in labour

17. IV fentanyl versus IV pethidine

We included one study with 105 women in this comparison (Rayburn 1989a).

Primary and secondary outcomes

The mean maternal pain score was significantly lower one hour after drug administration for women allocated to the IV fentanyl compared with those in the IV pethidine group; however, women in both groups reported mean pain scores of approximately six on a 10 mm scale (MD -0.20, 95% CI -0.34 to -0.06).

Maternal sedation was significantly 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). There were no statistically significant differences for all other reported outcomes including side effects, interventions in labour and outcomes for babies (Analysis 17.3; Analysis 17.4; Analysis 17.6; Analysis 17.7; Analysis 17.9; Analysis 17.11). The study, however, 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.

18. 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 low Apgar score at one minute), neither of which showed any significant difference between the two groups (Analysis 18.1; Analysis 18.2).

19. IV phenazocine versus IV pethidine

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

Primary and secondary outcomes

There was no statistically significant difference between groups for women's satisfaction with pain relief (comparing the number of women with "fair" or "poor" pain relief) (RR 0.72, 95% CI 0.48 to 1.10). No other primary outcomes were reported.

Only one identified secondary outcome reported estimable data: nausea with vomiting. There was no statistically significant difference between the two groups for this outcome (Analysis 19.2).

20. 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).

Primary outcomes

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 significantly higher for those in the group receiving butorphanol (MD 0.67, 95% CI 0.25 to 1.09). 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). The clinical significance of a difference of this magnitude (i.e. 0.6 on a 10-point scale) is more difficult to determine.

The other two studies comparing IV butorphanol with IV pethidine did not report any outcomes relating to women's pain during labour.

Secondary outcomes

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). Other secondary outcomes reported by one or more of the three studies within this comparison (second dose of analgesia required, epidural analgesia, assisted vaginal birth, caesarean section, Apgar score less than or equal to seven at one and five minutes) showed no statistically significant differences between groups (Analysis 20.3; Analysis 20.4; Analysis 20.6; Analysis 20.7; Analysis 20.8).

21. 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 women's 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), 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 significantly more likely to request a second dose of analgesia compared with women allocated to receive IV pethidine (RR 3.41, 95% CI 1.90 to 6.12). 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 statistically significant differences were found for each of the three secondary outcomes reported (nausea, vomiting and caesarean section), although the incidence of nausea was lower in the morphine group (6/10 pethidine versus 1/10 morphine; RR 0.17, 95% CI 0.02 to 1.14) (Analysis 21.3; Analysis 21.4).

22. 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 statistically significant (RR 0.71, 95% CI 0.33 to 1.52).

The incidence of babies requiring resuscitation and/or ventilatory support was two times 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). Although this difference is not statistically significant, 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.

23. 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 women's pain relief.

Women allocated to receive IV fentanyl were statistically significantly more likely to request additional doses of the study analgesia compared with women allocated to receive IV butorphanol (RR 1.39, 95% CI 1.05 to 1.85). The study author claims the study doses of drug were equivalent (IV fentanyl 50 to 100 mcg every one to two hours; IV butorphanol 1 to 2 mg every one to two hours). 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). Other women's outcomes reported (drowsiness, caesarean section) showed no statistically significant difference between study groups (Analysis 23.3; Analysis 23.4).

Whilst there were no statistically significant differences observed between groups for any of the neonatal outcomes reported (Apgar score less than seven at five minutes, naloxone administration, need for ventilatory support, neuro-behavioural score at two to four hours and neuro-behavioural score at 24 to 36 hours) babies born to women allocated to the fentanyl group were more likely to need ventilatory support (5/50 versus 0/50; RR 11.00, 95% CI 0.62 to 193.80) and naloxone administration (14/50 versus 8/50; RR 1.75, 95% CI 0.81 to 3.80) (Analysis 23.5; Analysis 23.6; Analysis 23.6; Analysis 23.7; Analysis 23.8; Analysis 23.9).

Intravenous patient controlled opioids for pain relief in labour

24. PCA pentazocine versus PCA pethidine

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

Primary and secondary outcomes

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 failed to reach statistical significance (SMD -0.76, 95% CI -1.62 to 0.09), a difference of 1.6 cm on a 10 cm pain scale might be considered clinically significant. Similar numbers of women in the two treatment groups rated their pain relief as good one day after the birth (Analysis 24.2).

None of the secondary outcomes studied showed a significant difference between the two study groups (epidural use, sedation, caesarean section, Apgar score less than seven at five minutes, breastfeeding at discharge) (Analysis 24.3; Analysis 24.5; Analysis 24.6; Analysis 24.7; Analysis 24.8), with low numbers of events recorded for a number of these outcomes. Nausea and vomiting was reported more frequently by women allocated to the pethidine group

compared with the pentazocine group (5/15 versus 0/14; RR 0.10, 95% CI 0.01 to 1.61) but the difference between groups was not significant.

25. PCA remifentanyl versus PCA pethidine

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

Primary

No primary outcomes were reported upon in these studies.

Secondary outcomes

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 significant difference in mean pain scores at one hour between the remifentanyl and pethidine groups (average MD -8.59, 95% CI -27.61 to 10.44), Analysis 25.1. There was substantial heterogeneity for this outcome and so a random-effects model has been used (heterogeneity $I^2 = 62%$, $T^2 = 136.73$, Chi² test for heterogeneity $P = 0.10$) (Analysis 25.1). 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), Analysis 25.2.

Two studies reported number of women crossing over to epidural as an outcome (Douma 2010; Volikas 2001), with fewer women in the remifentanyl group requiring an epidural (RR 0.42, 95% CI 0.20 to 0.89) (Analysis 25.3).

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, unrousable). Mean hourly scores at inclusion and then at one, two and three hours after analgesia were reported. There was no evidence of a significant difference in mean sedation scores at one hour between the remifentanyl and pethidine groups (MD 0.40, 95% CI 0.14 to 0.66, (Analysis 25.4).

There was no significant difference found between groups for any of the other secondary outcomes reported (nausea and vomiting, assisted vaginal birth, caesarean section, Apgar score less than seven at five minutes, naloxone administration, admission to NICU) (Analysis 25.5; Analysis 25.6; Analysis 25.7; Analysis 25.8; Analysis 25.9; Analysis 25.10). 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.

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 remifentanyl groups had slightly higher mean satisfaction scores (MD 1.10, 95% CI 0.46 to 1.74) (Analysis 25.11).

Newborn neuro-behavioural scores were reported in one study (Douma 2010). The Neurologic and Adaptive Capacity Score (NACS) was recorded at 15 minutes and two hours after delivery. There was no significant difference found between groups for mean scores at 15 minutes or two hours after delivery (Analysis 25.12; Analysis 25.13).

26. PCA nalbuphine versus PCA pethidine

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

Primary and secondary outcomes

Pain score recorded in labour was lower in women allocated to the PCA nalbuphine group compared with women in the PCA pethidine group (SMD -0.51, 95% CI -1.02 to 0.00) (Analysis 26.3). Satisfaction with pain relief recorded one day postnatally was greater for women allocated to receive nalbuphine compared to those allocated to receive pethidine, although this difference was not statistically significant (RR 1.29, 95% CI 0.88 to 1.89) (Analysis 26.1). Similar numbers in the two groups said that they would use the same pain relief method again in a future labour (Analysis 26.2).

No statistically significant differences were found between groups for the three secondary outcomes reported (additional analgesia, nausea and vomiting, Apgar score less than seven at five minutes) (Analysis 26.4; Analysis 26.5; Analysis 26.6).

27. PCA fentanyl versus PCA alfentanil

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

Primary and secondary outcomes

Women in the PCA fentanyl group reported lower pain scores on average than those in the alfentanil group, although the observed mean difference of 1.3 cm was not statistically significant (MD -12.80, 95% CI -32.12 to 6.52). In contrast, women allocated to receive fentanyl were 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).

No statistically significant differences were found for any of the other secondary outcomes reported (nausea, caesarean section, naloxone administration) (Analysis 27.3; Analysis 27.4; Analysis 27.5).

28. 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 upon in this study (Douma 2010).

Secondary outcomes

One study (Douma 2010) involving 107 women reported women's pain score during 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 evidence of a significant difference in mean pain scores at one hour between the fentanyl and pethidine groups (MD -0.65, 95% CI -1.56 to 0.26, Analysis 28.1); however, fewer women in the fentanyl group required epidural (RR 0.44, 95% CI 0.21 to 0.92) (Analysis 28.2). Maternal sleepiness was reported in one study (Douma 2010). This outcome was assessed using an observer sedation score (from 1, awake to 5, unrousable) recorded hourly. There was no evidence of a significant difference in mean sedation scores at one hour between the fentanyl and pethidine groups (MD -0.06, 95% CI -0.25 to 0.13) (Analysis 28.3).

There was no significant difference found between groups for any of the other secondary outcomes reported (nausea and vomiting, assisted vaginal birth, caesarean section) (Analysis 28.4; Analysis 28.5; Analysis 28.6).

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. NACS were recorded at 15 minutes and two hours after delivery. There was no significant difference found between groups for mean scores at either time point (Analysis 28.7; Analysis 28.8).

Opioids versus TENS for pain relief in labour

29. Opioids versus TENS

Three trials involving 305 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) and the third IM tramadol (100 mg) versus TENS to the back (Thakur 2004).

Primary and secondary outcomes

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 significant 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, two studies) (Analysis 29.1).

Three studies (Neumark 1978; Tawfik 1982; Thakur 2004) involving 305 women 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 significant difference in maternal pain scores between the opioid and TENS groups (average RR 1.15, 95% CI 0.81 to 1.61, two studies). There was substantial heterogeneity for this outcome and so a random-effects model has been used (heterogeneity $I^2 = 64%$, $T^2 = 0.04$, Chi² test for heterogeneity $P = 0.10$) (Analysis 29.2).

Two studies (Tawfik 1982; Thakur 2004) involving 290 women reported on maternal side effects of drowsiness and nausea/vomiting. Women in the opioid group were more likely to report drowsiness (RR 8.96, 95% CI 1.13 to 71.07) (Analysis 29.3) and nausea/vomiting (RR 14.06, 95% CI 1.96 to 100.61) (Analysis 29.4) compared with those in the TENS group, although the 95% CIs were very wide for both of these outcomes.

One study reported on caesarean section and assisted vaginal birth rates (Thakur 2004). There were no caesarean sections reported in either the opioid or TENS groups. There was no evidence of a significant difference in the number of assisted vaginal births between groups (RR 5.00, 95% CI 0.24 to 102.85) (Analysis 29.6).

One study reported on fetal distress (Thakur 2004) and found no evidence of a significant difference between groups (RR 5.00, 95% CI 0.24 to 102.85) (Analysis 29.7).

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).

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 effect the conclusions of the review or offer any other helpful insights.

DISCUSSION

Summary of main results

We set out to answer the question of whether parenteral opioids provide effective pain relief in labour without causing unpleasant adverse effects or harm to women and babies. We don't have a simple answer to this question. The review includes 29 different comparisons, where an opioid was compared with placebo, with another opioid, where different modes of administration were used, or with transcutaneous electrical nerve stimulation (TENS). Furthermore, 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.

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 preeclampsia or pre-existing conditions or with a compromised fetus.

Summary of results

- Parenteral opioids provided some pain relief during labour.
- Up to two-thirds of women who received opioids reported moderate or severe pain following administration of analgesia and/or poor or moderate pain relief.
- Opioid drugs were associated with nausea, vomiting and drowsiness, although different types of opioids were associated with different adverse effects.
- For most outcomes there was no significant evidence of differences between treatment groups.
- There was insufficient evidence to assess the safety of opioids in labour.

Intramuscular administration

- For pethidine versus placebo, there was better pain relief with pethidine, with sleepiness as the main adverse effect. There

was no evidence of significant differences in adverse effects on the woman or on the neonate.

- For meptazinol versus pethidine, there was no evidence of a difference in analgesic effect whether assessed either early or late during labour, although significantly more women had vomiting with meptazinol. There was no evidence of a difference in outcomes for the neonate.

- For diamorphine versus pethidine, an antiemetic was given as co-therapy to both groups. There was no evidence of difference in analgesic or adverse effects, with the exception of vomiting which occurred more frequently in women given pethidine. Whilst significantly more babies had Apgar less than seven at one minute with pethidine, by five minutes there was no difference between groups, and no evidence of differences in other neonatal outcomes.

- For tramadol versus pethidine, the analgesic effect was better with pethidine than tramadol, and there was no evidence of a difference in adverse effects on mother or baby.

- For dihydrocodeine versus pethidine, only one study contributed data and there was no evidence of a difference in analgesic effect or adverse effects. Significantly 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.

- Other intramuscular comparisons, most of which were tested in only one study, provided few statistically significant 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 difference in maternal or neonatal outcomes between groups.

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

Intravenous administration

- For most comparisons very few studies contributed data, and for most outcomes there was no evidence of significant differences between groups. Several intravenous 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, sedation 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 further analgesia, a reduced need for neonatal ventilatory support, and fewer babies required naloxone (one study).

Opioids versus transcutaneous electrical nerve stimulation (TENS)

- For most outcomes there was no evidence of significant differences between groups (maternal satisfaction with analgesia; maternal pain scores; caesarean section; assisted vaginal birth rates; fetal distress). The only significant 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 2011b), relaxation techniques (Smith in progress), acupuncture (Smith 2011a), TENS (Dowswell 2009), epidural analgesia (Anim-Somuah 2005) and a range of other methods of pain management.

Studies included in the review were carried out over a long time period (1958 to 2009) during which 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. 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. Having said this, in many parts of the world epidural analgesia is not available to all women, and throughout the world 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 not simple 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 with other types of analgesia or as a co-therapy. At the same time, in many of the studies we have 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 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 and perceived. 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 57 studies, there were relatively few statistically significant 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 significant findings we have reported 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 did not achieve statistical significance. 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 visual analogue scale means in this context.

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 intravenous or intramuscular 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).

Quality of the evidence

Overall we found the evidence to be of poor quality regarding the analgesic effect of opioids, satisfaction with analgesia, adverse effects and harm to women and babies.

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.

While we attempted to be as inclusive as possible in the search strategy, the literature identified was predominantly written in English and published in North American and European journals. We are also aware that publication bias is a possibility, as the review includes several small studies which reported a number of statistically significant results. Although we did attempt to assess reporting bias, constraints of time meant that this assessment relied on information available in the published trial report and thus, reporting bias was not usually apparent.

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 2007) 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 intravenous and intramuscular opioids and of their limitations; NICE 2007 guidelines suggest that intramuscular and intravenous 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

There is little high-quality evidence to inform practice; however, for healthy women with an uncomplicated pregnancy who are giving birth at 37 to 42 weeks we have reached the following conclusions.

Parenteral opioids provide moderate pain relief in labour, but cause sedation, nausea and vomiting in the woman and effects on the newborn are unclear.

There is insufficient evidence from the review to support the choice of one opioid over another.

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.

We recommend that a large pragmatic randomised controlled trial (RCT) 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 include additional analgesia and anti-emetics, labour augmentation by means of artificial rupture of membranes or intravenous infusion of oxytocin, use of electronic fetal monitoring and mode of birth. Outcomes for women and their babies in the short and longer term are also required.

Maternal outcomes that would be important to guide practice are actual pain relief and maternal satisfaction with analgesia, 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.

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 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.

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.

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This updated review forms part of a series of reviews focusing on pain management in labour that will be included in a Cochrane overview of reviews (Jones 2011b); contributing reviews share a generic protocol (Jones 2011a). 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.

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* 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 3-4 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 50-100 mcg every 1-2 hrs to a max of 5 doses Control: IV butorphanol 1-2 mg every 1-2 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 min; infant neurological exam 2-4 and 24-36 hrs after birth	
Notes		
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 (performance bias and detection bias) Women	Low risk	Identical syringes.
Blinding (performance bias and detection bias) Clinical staff	Low risk	Described as double blind.
Blinding (performance bias and detection bias) Outcome assessor	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 one hour 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	Germany: hospital setting. 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 5-10 min 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.

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 (performance bias and detection bias) Women	Unclear risk	Not reported.

Bitsch 1980 (Continued)

Blinding (performance bias and detection bias) Clinical staff	Unclear risk	Not reported.
Blinding (performance bias and detection bias) Outcome assessor	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 remifentanyl 40 mcg with lock-out of 2 minutes Control: PCA pethidine 15 mg with lock-out of 10 minutes. Nitrous oxide was available to all women and women were free to choose an epidural at any stage
Outcomes	Maternal sedation score (1-5 fully awake to unrousable); VAS 0-10 for pain and satisfaction with pain relief; nausea; anxiety; Apgar scores at 1 and 5 min; 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

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	"women were randomly allocated."
Allocation concealment (selection bias)	Unclear risk	Not clear when randomisation occurred or how it was carried out

Blair 2005 (Continued)

Blinding (performance bias and detection bias) Women	Low risk	Described as double-blind study.
Blinding (performance bias and detection bias) Clinical staff	Low risk	Double-blind.
Blinding (performance bias and detection bias) Outcome assessor	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 20-40 mg (N = 91). Control: IM pethidine 50-100 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

Risk of bias

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.

Borglin 1971 (Continued)

Blinding (performance bias and detection bias) Women	Unclear risk	Reported as double blind, but no description of how achieved. Identical volume but appearance not described
Blinding (performance bias and detection bias) Clinical staff	Unclear risk	Reported as double blind, but no description of how achieved. Identical volume but appearance not described
Blinding (performance bias and detection bias) Outcome assessor	Unclear risk	Not reported.
Incomplete outcome data (attrition bias) All outcomes	Low risk	All participants analysed, but missing data for some outcomes
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 3-4 cm dilatation for primiparous, and 4-5 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
Outcomes	Length of labour, amount of analgesia required, obstetric complications and neonatal condition (Apgar score at 1 minute). 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

Campbell 1961 (Continued)

	medication was deemed suitable	
Notes	All women included delivered under regional anaesthesia.	
Risk of bias		
Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	"in a random manner."
Allocation concealment (selection bias)	Low risk	Coded vials containing study drugs were provided by pharmacy
Blinding (performance bias and detection bias) Women	Low risk	Described as blinded.
Blinding (performance bias and detection bias) Clinical staff	Low risk	"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 (performance bias and detection bias) Outcome assessor	Low risk	"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 was 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: UK hospital. 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

De Boer 1987 (Continued)

	pregnancy, non-vertex presentation, preterm or postmature labour, previous caesarean section, birth weight 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 min PN
Notes	If additional analgesia required opioid repeated > 3 hrly. Actual dose received by women 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 (performance bias and detection bias) Women	Unclear risk	States double blind but not described.
Blinding (performance bias and detection bias) Clinical staff	Unclear risk	States double blind but not described.
Blinding (performance bias and detection bias) Outcome assessor	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)
Other bias	Low risk	No baseline imbalances.

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 ($BMI \geq 40 \text{ kg m}^{-2}$), opioid allergy, substance abuse history, and high-risk patients (pre-eclampsia, severe asthma, insulin-dependent diabetes mellitus, hepatic insufficiency, or renal failure)
Interventions	1. Remifentanyl, patient controlled IV, 40 µg loading dose, remifentanyl 40 µg per bolus with a lockout of 2 min 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 min and max dose limit of 200 mg 3. Fentanyl, patient controlled IV, 50 µg loading dose and 20 µg bolus with lockout of 5 min and a max dose limit of 240 µg h ⁻¹ .
Outcomes	Outcomes: pain scores (VAS) every hour; sedation score (1 awake, 2 sleepy, 3 eyes closed, 4 eyes closed but rousable, 5 unrousable); overall satisfaction on 10-point scale 2 hours after delivery; side effects - nausea, vomiting, itching; Apgar scores at 1, 5 mins; cord blood gas analysis; NACS scores at 15 min and 2 hr after delivery; oxytocin use; instrumental delivery; CS; spontaneous delivery
Notes	"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."

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	"Established using a computer generated random sequence in numbered envelopes."
Allocation concealment (selection bias)	Low risk	"Study medication was prepared and blinded by hospital pharmacy."
Blinding (performance bias and detection bias) Women	Unclear risk	Not reported.
Blinding (performance bias and detection bias) Clinical staff	Low risk	"Observants and medical personnel attending to the parturient were unaware of the drug assignment."
Blinding (performance bias and detection bias) Outcome assessor	Low risk	"with exception of baseline data, all observations and measurements were made by blinded observers."

Douma 2010 (Continued)

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 hour after randomisation Says "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: UK hospital. 200 women. 66% primips, 34% multips, > 35 weeks' gestation. Singleton, uncomplicated pregnancy Exclusions: toxemia, chronic medical disease, isoimmunization, obstetric complication
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 minutes 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 minute 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

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 (performance bias and detection bias) Women	Unclear risk	States 'double blind' but does not report how achieved.

Duncan 1969 (Continued)

Blinding (performance bias and detection bias) Clinical staff	Unclear risk	States 'double blind' but does not report how achieved.
Blinding (performance bias and detection bias) Outcome assessor	Unclear risk	Not reported.
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.
Other bias	Unclear risk	Balanced at baseline for age, parity, height, weight, blood pressure, attendance at antenatal classes and infant weight

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 minute lock out, 0.3 mg per kg Control: pentazocine, IV PCA 10 minute 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 and 5 min; infant weight; neuro-behavioural examination on 1st and 5th day
Notes	The study also included a non-randomised control group; we have not included this group in the analysis

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Random number table.

Erskine 1985 (Continued)

Allocation concealment (selection bias)	Unclear risk	Not described.
Blinding (performance bias and detection bias) Women	Unclear risk	Not specified.
Blinding (performance bias and detection bias) Clinical staff	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 (performance bias and detection bias) Outcome assessor	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 was 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	UK setting: hospital. 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)
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 and 5 min, 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

Fairlie 1999 (Continued)

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 (performance bias and detection bias) Women	Low risk	States double blind, drug containers identical in appearance
Blinding (performance bias and detection bias) Clinical staff	Low risk	States double blind, drug containers identical in appearance
Blinding (performance bias and detection bias) Outcome assessor	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.

Fiini 2000

Methods	RCT 2-arm parallel group design.
Participants	Italy: hospital care setting. 40 women. Full-term pregnancy, $cx \geq 4$ 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 hrly up to 5 hrs, VAS 1-3 Secondary outcomes: maternal: observations (pulse, BP, respiratory rate, arterial oxygen saturation). Neonatal: Apgar at 1 and 5 min. Umbilical 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

Fienni 2000 (Continued)

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 (performance bias and detection bias) Women	Unclear risk	Not reported.
Blinding (performance bias and detection bias) Clinical staff	Unclear risk	Not reported.
Blinding (performance bias and detection bias) Outcome assessor	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 hour; lockout time 10 minutes (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 minutes (total max dose = 210 mg) Entonox [®] was available to women in both groups but was withheld for 30 min for analgesia assessment. Analgesia was stopped in the 2nd stage if there were side effects or if the woman requested an alternative method

Frank 1987 (Continued)

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 - 10 hrs after birth; FHR	
Notes		
Risk of bias		
Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	"randomly allocated."
Allocation concealment (selection bias)	Unclear risk	Described as double blind but allocation concealment was not described
Blinding (performance bias and detection bias) Women	Low risk	Very little information. Described as double blind.
Blinding (performance bias and detection bias) Clinical staff	Low risk	Very little information. Described as double blind.
Blinding (performance bias and detection bias) Outcome assessor	Unclear risk	Unclear.
Incomplete outcome data (attrition bias) All outcomes	Unclear risk	There was 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)
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 - 41 weeks), 4 cm or less cervical dilatation, at least 3 contractions in 10 minutes, 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 nalbuphine 10 mg. Control: IV pethidine 50 mg. Both groups had continuous fetal monitoring for 1 hour following medication	
Outcomes	FHR (accelerations, high and low variation); Apgar scores < 8 at 1 and 5 min; mode of birth; cord pH < 7.15	
Notes		
<i>Risk of bias</i>		
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.
Blinding (performance bias and detection bias) Women	Unclear risk	Not specified.
Blinding (performance bias and detection bias) Clinical staff	Unclear risk	Not specified.
Blinding (performance bias and detection bias) Outcome assessor	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 40mg 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		
<i>Risk of bias</i>		
Bias	Authors’ judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	No information.
Allocation concealment (selection bias)	Low risk	Coded drug containers.
Blinding (performance bias and detection bias) Women	Low risk	Drugs were prepared by pharmacy in coded containers and the codes were not revealed until after birth
Blinding (performance bias and detection bias) Clinical staff	Low risk	Drugs were prepared by pharmacy in coded containers and the codes were not revealed until after birth
Blinding (performance bias and detection bias) Outcome assessor	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.

Gillam 1958 (Continued)

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
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Grant 1970

Methods	RCT 2-arm parallel group design.
Participants	UK: hospital setting. 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 hours of birth Secondary outcomes: maternal: amnesia, restlessness, anxiety, vomiting. Neonatal: Apgar at 1 and 5 min
Notes	Epidural available if further analgesia required.

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 (performance bias and detection bias) Women	Low risk	States double blind, coded ampoules but no further description given
Blinding (performance bias and detection bias) Clinical staff	Low risk	States double blind, coded ampoules but no further description given
Blinding (performance bias and detection bias) Outcome assessor	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

Grant 1970 (Continued)

Selective reporting (reporting bias)	High 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)
Notes	Data extraction was done from translation notes.

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 (performance bias and detection bias) Women	Low risk	Described as double-blind.
Blinding (performance bias and detection bias) Clinical staff	Low risk	Described as double-blind.
Blinding (performance bias and detection bias) Outcome assessor	Unclear risk	Unclear.

Hamann 1972 (Continued)

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)	
Outcomes	Pain intensity (graphs with hourly readings); pain relief (4-point scale); neuro-behavioural assessment 1 day after birth (Scanlon scale)	
Notes		
<i>Risk of bias</i>		
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 (performance bias and detection bias) Women	Low risk	Described as double blind but little detail of methods of allocation concealment or blinding
Blinding (performance bias and detection bias) Clinical staff	Low risk	Described as double blind but little detail of methods of allocation concealment or blinding

Hodgkinson 1979 (Continued)

Blinding (performance bias and detection bias) Outcome assessor	Low 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	Austria: hospital setting. 40 women with no pregnancy complications, in spontaneous and induced labour, cx 3 - 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 min after injection using VAS 0-100, 0 = pain free to 100 strongest pain experienced Secondary: side effects, augmentation and type of birth.
Notes	Not stated in one dose only.

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 (performance bias and detection bias) Women	Unclear risk	Blinding not described.
Blinding (performance bias and detection bias) Clinical staff	Unclear risk	Blinding not described.
Blinding (performance bias and detection bias) Outcome assessor	Unclear risk	Blinding not described.

Husslein 1987 (Continued)

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: UK hospital. 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 and 3 min.
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

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 (performance bias and detection bias) Women	Unclear risk	States double blind but method not described.
Blinding (performance bias and detection bias) Clinical staff	Unclear risk	States double blind but method not described.
Blinding (performance bias and detection bias) Outcome assessor	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.

Jackson 1983 (Continued)

Other bias	Unclear risk	Balanced for parity, weight and size of baby at baseline.
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Kainz 1992

Methods	RCT 3-arm parallel group design.
Participants	Setting: Germany, hospital. 66 women. 38-41 weeks' gestation, free of complications, in active labour and requiring analgesia, excluded if analgesia received within 4 hours 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 (0-10 cm) 30, 60, 120 and 180 minutes, vomiting, drowsiness, blood pressure, heart rate, cardiotocogram
Notes	Tramadol 100 mg only group (A) not included in our analyses. German language, translation obtained

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	"zufallszahlentafel" coincidence number table.
Allocation concealment (selection bias)	Unclear risk	Not reported.
Blinding (performance bias and detection bias) Women	Unclear risk	Stated as double blind but methods not described.
Blinding (performance bias and detection bias) Clinical staff	Unclear risk	Stated as double blind but methods not described.
Blinding (performance bias and detection bias) Outcome assessor	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 hour of study drug administration
Selective reporting (reporting bias)	Unclear risk	Unclear.

Kainz 1992 (Continued)

Other bias	Unclear risk	Unclear.
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Kamyabi 2003

Methods	RCT 2-arm parallel group design.
Participants	Setting: hospital in Iran. 88 primiparous women in spontaneous labour, gestation \geq 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 - 60 min post injection) and neonatal Apgar score at 1 and 5 min
Notes	Timing of maternal pain assessment 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 (performance bias and detection bias) Women	Low risk	Study agents were of identical volume and appearance.
Blinding (performance bias and detection bias) Clinical staff	Low risk	Study agents were of identical volume and appearance.
Blinding (performance bias and detection bias) Outcome assessor	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.

Kamyabi 2003 (Continued)

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
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Keskin 2003

Methods	RCT 2-arm parallel group design.
Participants	Turkey: hospital setting. 59 primiparous women with uncomplicated pregnancy at term gestation, in labour with cervix 3-5 cm dilated and reporting a pain score 4 - 5 according to Wong-Baker 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 minutes 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 and 5 min)
Notes	

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 (performance bias and detection bias) Women	Unclear risk	Not reported.
Blinding (performance bias and detection bias) Clinical staff	Unclear risk	Not reported.
Blinding (performance bias and detection bias) Outcome assessor	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 intention-to-treat analysis

Keskin 2003 (Continued)

Selective reporting (reporting bias)	Unclear risk	Unclear.
Other bias	Unclear risk	Unclear.

Khooshideh 2009

Methods	RCT 2-arm parallel group design.
Participants	Setting: Iran, hospital. 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 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 hours but pethidine withheld if cx dilated > 8 cm and tramadol given instead
Outcomes	Maternal outcomes: maternal pain intensity VAS (0-10 cm) 10, 30 and 1 hourly intervals until birth, maternal satisfaction 24 hours postpartum 5-point scale (excellent, very good, good, fair, poor), drowsiness, nausea, vomiting. Neonatal outcomes: Apgar score at 1 and 5 minutes, naloxone administration, respiratory depression
Notes	

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 (performance bias and detection bias) Women	Unclear risk	Not reported.
Blinding (performance bias and detection bias) Clinical staff	Unclear risk	Drugs administered by clinician blind to group allocation, but does not state how this was achieved
Blinding (performance bias and detection bias) Outcome assessor	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.

Khooshideh 2009 (Continued)

Selective reporting (reporting bias)	Unclear risk	Unclear.
Other bias	Unclear risk	Baseline characteristics similar.

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 4-6 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 and 120 min 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.

Risk of bias

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 (performance bias and detection bias) Women	Low risk	Identical ampoules.
Blinding (performance bias and detection bias) Clinical staff	Low risk	Identical ampoules.
Blinding (performance bias and detection bias) Outcome assessor	Unclear risk	Not reported.
Incomplete outcome data (attrition bias) All outcomes	Low risk	Few losses to follow-up.

Lardizabal 1999 (Continued)

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 and 5 min
Notes	If additional analgesia was required, a second injection could be administered at the discretion of medic. Not stated if IOL onset included

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 (performance bias and detection bias) Women	Low risk	Identical vials with code number.
Blinding (performance bias and detection bias) Clinical staff	Low risk	Identical vials with code number.
Blinding (performance bias and detection bias) Outcome assessor	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

Levy 1971 (Continued)

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

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 (performance bias and detection bias) Women	Unclear risk	Described as a double-blind comparison but methods not described
Blinding (performance bias and detection bias) Clinical staff	Unclear risk	Described as a double-blind comparison but methods not described
Blinding (performance bias and detection bias) Outcome assessor	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.

Li 1988 (Continued)

Other bias	Unclear risk	No baseline imbalance apparent.
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Li 1994

Methods	RCT. 2-arm parallel groups.
Participants	Setting: Beijing hospital, China. 60 women in early labour (cervical dilatation 2-3 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.

Risk of bias

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 (performance bias and detection bias) Women	High risk	Women in the control arm received no treatment.
Blinding (performance bias and detection bias) Clinical staff	High risk	Women in the control arm received no treatment.
Blinding (performance bias and detection bias) Outcome assessor	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	Brazil: hospital. 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.

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	High risk	Described as "randomly selected" but not explained how.
Allocation concealment (selection bias)	Unclear risk	Not mentioned.
Blinding (performance bias and detection bias) Women	Unclear risk	Not mentioned.
Blinding (performance bias and detection bias) Clinical staff	Unclear risk	Not mentioned.
Blinding (performance bias and detection bias) Outcome assessor	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.

Maduska 1978

Methods	RCT 2-arm parallel group design.
Participants	Setting: US hospital. 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 min 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 min, 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-Caucasian and all were delivered with local or regional anaesthesia

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
Blinding (performance bias and detection bias) Women	Low risk	States double blind, drugs in identical vials.
Blinding (performance bias and detection bias) Clinical staff	Low risk	States double blind, drugs in identical vials.
Blinding (performance bias and detection bias) Outcome assessor	Unclear risk	Not reported.
Incomplete outcome data (attrition bias) All outcomes	Low risk	All women analysed.
Selective reporting (reporting bias)	Unclear risk	Unclear.

Maduska 1978 (Continued)

Other bias	Unclear risk	Balanced at baseline for type of labour, weight, age, type of birth and anaesthetic agent
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Mitterschiffthaler 1991

Methods	RCT 2-arm parallel group design.
Participants	Setting: Germany. 40 women. Term pregnancy, cx dilated 2-3 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 (0-20 cm) 30, 60, 90 and 120 minutes, opinion of pain relief 12 hours 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 minutes, 'side effects', blood pressure, heart rate, CTG. Neonatal outcomes: Apgar score at 10 minutes, respiratory depression
Notes	German language - translation obtained.

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 (performance bias and detection bias) Women	High risk	Not reported.
Blinding (performance bias and detection bias) Clinical staff	High risk	Not reported.
Blinding (performance bias and detection bias) Outcome assessor	Unclear risk	Not reported.
Incomplete outcome data (attrition bias) All outcomes	High risk	4/40 women excluded due to insufficient pain relief.

Mitterschiffthaler 1991 (Continued)

Selective reporting (reporting bias)	Unclear risk	Unclear.
Other bias	Unclear risk	Unclear.

Moore 1970

Methods	RCT 2-arm parallel group design.
Participants	Setting: UK hospital. 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 100mg or 50 mg (N = 133).
Outcomes	Primary: pain intensity assessed at 30, 60 and 90 min post injection, described as severe, moderate or slight. Asked at 12 - 24 hr postnatal if drug had helped Secondary: neonatal Apgar score at 1 and 5 min, maternal side effects of nausea or vomiting
Notes	If additional analgesia required, a maximum of 3 further doses of study drug could be administered at 2-3 hrly intervals. Women could also use nitrous oxide and some had a paracervical block > 35 weeks' gestation therefore preterm babies may be included

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 (performance bias and detection bias) Women	Unclear risk	States double blind. Coded ampoules but not stated if identical in appearance
Blinding (performance bias and detection bias) Clinical staff	Unclear risk	States double blind. Coded ampoules but not stated if identical in appearance
Blinding (performance bias and detection bias) Outcome assessor	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.

Moore 1970 (Continued)

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 fetal heart tracing (Women recruited to the study had medical contraindications to epidural although it was no specified what these were.)
Interventions	Experimental: fentanyl, PCA 10 micro g 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 min
Outcomes	Pain (rated on a 100 mm VAS, recorded at baseline and every 30 minutes thereafter); sedation (nurse rated hourly); side effects; satisfaction with pain relief (good, adequate, inadequate); Apgar scores at 5 and 10 minutes; cord blood gases; naloxone dose; neonatal neuro-behavioural score at 4 and 24 hrs
Notes	

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Randomisation schedule prepared by pharmacy.
Allocation concealment (selection bias)	Low risk	Plain, numbered vials prepared by pharmacy.
Blinding (performance bias and detection bias) Women	Low risk	Plain vials prepared by pharmacy.
Blinding (performance bias and detection bias) Clinical staff	Low risk	Plain vials prepared by pharmacy.

Morley-Forster 2000 (Continued)

Blinding (performance bias and detection bias) Outcome assessor	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 was 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: UK hospital. 1,100 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 minutes VAS (0-100 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 and 5 min, resuscitation, naloxone administration, fetal distress, type of feeding	
Notes		

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 (performance bias and detection bias) Women	Low risk	States double blind and used coded drug containers.

Morrison 1987 (Continued)

Blinding (performance bias and detection bias) Clinical staff	Low risk	States double blind and used coded drug containers.
Blinding (performance bias and detection bias) Outcome assessor	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: UK hospital. 94 women. > 35 weeks' gestation, age \geq 18 years, excluded if diabetic, history of renal or hepatic impairment or taking monoamine oxidase inhibitors, in active labour and requiring analgesia Parity: \leq 3.
Interventions	Experimental: IM pentazocine 60 \leq mg (N = 46). Control: IM pethidine 15 \leq 0 mg (N = 48). Up to 3 injections > 3 hours 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 and 5 min
Notes	Data for some outcomes available after first dose.

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 (performance bias and detection bias) Women	Unclear risk	States double blind but how achieved not reported.

Mowat 1970 (Continued)

Blinding (performance bias and detection bias) Clinical staff	Unclear risk	States double blind but how achieved not reported.
Blinding (performance bias and detection bias) Outcome assessor	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: South Africa - hospital. 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 and 5 min, paediatrician assessment at 24 hours
Notes	

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 (performance bias and detection bias) Women	Unclear risk	States double blind but does not describe how blinding achieved

Nel 1981 (Continued)

Blinding (performance bias and detection bias) Clinical staff	Unclear risk	States double blind but does not describe how blinding achieved
Blinding (performance bias and detection bias) Outcome assessor	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 and 5 minutes
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

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	"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

Nelson 2005 (Continued)

Blinding (performance bias and detection bias) Women	Low risk	Described as double blind.
Blinding (performance bias and detection bias) Clinical staff	Low risk	The "drug was prepared by an anaesthesiologist not involved with the treatment of the patient or obtaining study measures"
Blinding (performance bias and detection bias) Outcome assessor	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 "their randomization was re-entered for another 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: "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-minute 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

Neumark 1978 (Continued)

Notes	<p>Paper in German. Translation notes used for data extraction.</p> <p>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</p> <p>Results - categories for pain relief (good, insufficient, none) do not correspond with pain scale - 6 perceptions reported in the translation</p>	
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.
Blinding (performance bias and detection bias) Women	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 (performance bias and detection bias) Clinical staff	Unclear risk	Not clear.
Blinding (performance bias and detection bias) Outcome assessor	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: UK hospital. 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 38-50 kg, 100 mg if 51-69 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 min (rated none, poor, satisfactory, good, very good or complete), type of birth, epidural, sleepiness, nausea and vomiting. Neonatal outcomes: Apgar at 1 and 5 min, apnoea, resuscitation, and lethargy, muscle tone, irritability success of feeding within first 24-hour period
Notes	Does not report number randomised to each group.

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 (performance bias and detection bias) Women	Unclear risk	States double blind but does not describe methods used.
Blinding (performance bias and detection bias) Clinical staff	Unclear risk	States double blind but does not describe methods used.
Blinding (performance bias and detection bias) Outcome assessor	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 intention-to-treat analysis.
Selective reporting (reporting bias)	Unclear risk	Unclear.

Nicholas 1982 (Continued)

Other bias	Unclear risk	Unclear.
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O'Dwyer 1971

Methods	RCT 2-arm parallel group design.
Participants	Setting: UK hospital. 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 and 5 min, naloxone administration
Notes	Does not state actual number randomised to each group.

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 (performance bias and detection bias) Women	Unclear risk	States double blind but does not describe how this was achieved
Blinding (performance bias and detection bias) Clinical staff	Unclear risk	States double blind but does not describe how this was achieved
Blinding (performance bias and detection bias) Outcome assessor	Unclear risk	States double blind but does not describe how this was achieved
Incomplete outcome data (attrition bias) All outcomes	High risk	31/98 excluded from primary outcome as delivered within 1 hour of administration of study drug, and 16 babies excluded from Apgar assessment as study drug administered more than 4 hours before birth

O'Dwyer 1971 (Continued)

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	Stockholm Sweden, hospital setting. 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.
Outcomes	Sedation rates; CS, nausea and vomiting.
Notes	

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	"assigned at random."
Allocation concealment (selection bias)	Low risk	Coded ampoules provided by pharmacy.
Blinding (performance bias and detection bias) Women	Low risk	Described as double blind; pharmacy provided identical coded ampoules
Blinding (performance bias and detection bias) Clinical staff	Low risk	Described as double blind; pharmacy provided identical coded ampoules
Blinding (performance bias and detection bias) Outcome assessor	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.

Olofsson 1996 (Continued)

Other bias	Unclear risk	Small sample and no clear information that groups were comparable at baseline. Range of cervical dilations at recruitment between 4 and 9 cm
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Olson 1964

Methods	RCT, 2-arm parallel group design.
Participants	Setting: Washington, USA. 194 women in established labour. Analgesia was given at approximately 4-5 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 trichloroethylene"
Outcomes	Pain relief (recorded by women on the first postpartum day); nausea and vomiting; adverse effects; progress in labour; Apgar scores at 1 and 5 mins
Notes	

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 (performance bias and detection bias) Women	Low risk	Drugs in identical vials.
Blinding (performance bias and detection bias) Clinical staff	Low risk	Pharmacy prepared identical coded drugs.
Blinding (performance bias and detection bias) Outcome assessor	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%

Olson 1964 (Continued)

		for nurse recorded evaluations in labour)
Selective reporting (reporting bias)	Low risk	None apparent.
Other bias	Low risk	None apparent.

Osler 1987

Methods	RCT 2-arm parallel group design.
Participants	Setting: Denmark - hospital. 199 women. Spontaneous or induced labour onset, in active labour and requiring analgesia Parity: 78% nullips, 22% multips.
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 hours between doses
Outcomes	Maternal outcomes: maternal assessment of pain relief 5, 15, 30, 60, 90, 120 min (rated complete, good, satisfactory, unsatisfactory), type of birth, additional analgesia required, epidural, adverse effects. Neonatal outcomes: Apgar at 1 and 5 min, neonatal distress, admission to SCBU
Notes	

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 (performance bias and detection bias) Women	Unclear risk	Described as double blind but no methods described.
Blinding (performance bias and detection bias) Clinical staff	Unclear risk	Described as double blind but no methods described.
Blinding (performance bias and detection bias) Outcome assessor	Unclear risk	Described as double blind but no methods described.
Incomplete outcome data (attrition bias) All outcomes	Low risk	All women analysed.

Osler 1987 (Continued)

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: Thailand - hospital. 135 women. 37 to 42 weeks' gestation, $cx \geq 3$ 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 min, 1, 2, 3, and 4 hrs (rated good, satisfactory, no response), drowsiness, nausea, vomiting. Neonatal outcomes: Apgar at 1 and 5 min, neonatal resuscitation
Notes	

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 (performance bias and detection bias) Women	Unclear risk	States blind but does not describe the method.
Blinding (performance bias and detection bias) Clinical staff	Unclear risk	States blind but does not describe the method.
Blinding (performance bias and detection bias) Outcome assessor	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.

Prasertsawat 1986 (Continued)

Other bias	Low risk	Age and maternal weight balanced at baseline.
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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 1-2 mg (44 women had an initial dose of 1 mg and 6 an initial dose of 2 mg, after one hr or more a 2nd dose was given if requested) Control: (50 women) IV pethidine 40-80 mg (45 women had an initial dose of 40 mg and 5 an initial dose of 80 mg, a 2nd dose was given after 1hr 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 and 5 minutes
Notes	

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 (performance bias and detection bias) Women	Unclear risk	Described as double blind study but no details provided.
Blinding (performance bias and detection bias) Clinical staff	Unclear risk	Unclear.
Blinding (performance bias and detection bias) Outcome assessor	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.

Quilligan 1980 (Continued)

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
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Rayburn 1989a

Methods	RCT. 2-arm parallel groups.
Participants	Setting: Nebraska university hospital, USA. 105 women in early active labour (3-4 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 50-100 mcg per hr. Control: (56 women) IV pethidine 25-50 mg per hr.
Outcomes	Pain (measured on 10-point VAS recorded by labour ward nurses); nausea and vomiting; sedation; itching; fetal heart rate changes
Notes	Women were recruited only between 8 am and 3 pm on weekdays.

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 (performance bias and detection bias) Women	High risk	Decribed as not blinded.
Blinding (performance bias and detection bias) Clinical staff	High risk	Staff not blind to group allocation.
Blinding (performance bias and detection bias) Outcome assessor	High risk	Staff not blind to group allocation.
Incomplete outcome data (attrition bias) All outcomes	Low risk	All women randomised seem to be included in the results.

Rayburn 1989a (Continued)

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: Norway - hospital. 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 hr 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 and 5 min, naloxone administration, fetal heart rate changes
Notes	

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 (performance bias and detection bias) Women	High risk	No blinding.
Blinding (performance bias and detection bias) Clinical staff	High risk	No blinding.
Blinding (performance bias and detection bias) Outcome assessor	High risk	No blinding.

Refstad 1980 (Continued)

Incomplete outcome data (attrition bias) All outcomes	High risk	25/85 women excluded from analysis as delivered within 1 hour 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

Sheikh 1986

Methods	RCT, 2-arm parallel group design.	
Participants	Setting: UK - hospital. 205 women. Healthy women 38-41 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 min 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 and 5 min, resuscitation. Within 72 hrs postpartum feeding problems, irritability and muscle tone	
Notes		

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 ampoules kept at a site remote from trial.
Blinding (performance bias and detection bias) Women	Low risk	Described as double blind, used coded ampoules and states that identity of drug unknown
Blinding (performance bias and detection bias) Clinical staff	Low risk	Described as double blind, used coded ampoules and states that identity of drug unknown

Sheikh 1986 (Continued)

Blinding (performance bias and detection bias) Outcome assessor	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 minutes 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

Slom 1970

Methods	RCT, 3-arm parallel group design.
Participants	Setting: SA - hospital. 196 women. Healthy women at term, uncomplicated labour, in active labour expected to deliver in next 4 hours and requiring analgesia. Excluded if likely to deliver within 30 min and had received analgesia within previous 6 hours 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 hour (rated good, fair, poor), sedation (rated drowsy, alert but calm, restless), nausea, vomiting. Neonatal outcomes: Modified Apgar at 1 and 5 min (minus colour)
Notes	Women excluded after randomisation if delivered more than 4 hours after injection of study drug

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 (performance bias and detection bias) Women	Unclear risk	States double blind. Not reported how blinding was achieved.

Sliom 1970 (Continued)

Blinding (performance bias and detection bias) Clinical staff	Unclear risk	States double blind. Not reported how blinding was achieved.
Blinding (performance bias and detection bias) Outcome assessor	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 minutes or > 4 hours 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 4-5 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	

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	"Randomly divided between 2 groups."

Tawfik 1982 (Continued)

Allocation concealment (selection bias)	Unclear risk	No information provided.
Blinding (performance bias and detection bias) Women	High risk	Not reported - but not feasible with nature of interventions
Blinding (performance bias and detection bias) Clinical staff	High risk	Not reported - but not feasible with nature of interventions
Blinding (performance bias and detection bias) Outcome assessor	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 (37-42 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 intramuscular 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; side effects for mothers
Notes	

Thakur 2004 (Continued)

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 (performance bias and detection bias) Women	High risk	No blinding reported - but not possible due to nature of intervention
Blinding (performance bias and detection bias) Clinical staff	High risk	No blinding reported.
Blinding (performance bias and detection bias) Outcome assessor	High risk	No blinding reported.
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 (37-42 weeks) spontaneous labour, in active labour, vertex presentation Exclusions: age < 16 or > 35, weight < 50 or > 75 kg, infant birthweight estimated < 2500 or > 4000 g, medical or surgical complication or unable to understand VAS
Interventions	Intervention group: IM buprenorphine 300 mcg. Comparison group: IM pethidine 75 mg.
Outcomes	Analgesic effect at 1, 2, 3, 4 hrs, side effects (nausea, drowsiness, use of antidote)
Notes	Data extraction from translation notes.

Tharamas 1999 (Continued)

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 (performance bias and detection bias) Women	Low risk	Treatment described as blinded.
Blinding (performance bias and detection bias) Clinical staff	Low risk	Treatment described as blinded.
Blinding (performance bias and detection bias) Outcome assessor	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: Hong Kong - hospital. 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 min nitrous-oxide or epidural for women in pethidine group and pethidine for women in placebo group
Outcomes	Maternal outcomes: pain intensity at 15 and 30 min VAS (0-100), maternal assessment of sedation at 15 and 30 min VAS (0-100), type of birth, additional analgesia required, vomiting, maternal satisfaction at 30 min 5-point scale (1 = totally dissatisfied to 5 = very satisfied). Neonatal outcomes: Apgar at 1 and 5 min, resuscitation and admission

Tsui 2004 (Continued)

	to SCBU	
Notes	Study terminated after 50 women recruited as interim analysis demonstrated benefit for pethidine. Stratified by parity	
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 (performance bias and detection bias) Women	Unclear risk	States double blind and women blind to contents of syringe.
Blinding (performance bias and detection bias) Clinical staff	Unclear risk	States double blind and staff blind to contents of syringe.
Blinding (performance bias and detection bias) Outcome assessor	Unclear risk	States double blind and assessor blind to contents of syringe
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: Singapore - hospital. 90 women. Women aged 18 to 35 years in active labour and requiring analgesia, cx 3-5 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.

Viegas 1993 (Continued)

Outcomes	Maternal outcomes: pain relief at 10, 20, 30, 45 and 1 hour 4-point scale (0 = none, 1 = insufficient, 2 = sufficient, 3 = complete pain relief), type of birth, drowsiness, nausea, vomiting. Neonatal outcomes: Apgar at 1 and 5 min, resuscitation and admission to SCBU	
Notes		
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 (performance bias and detection bias) Women	Low risk	States double blind, identical syringes prepared separately from clinical observer
Blinding (performance bias and detection bias) Clinical staff	Low risk	States double blind, identical syringes prepared separately from clinical observer
Blinding (performance bias and detection bias) Outcome assessor	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 36-40 weeks' gestation requesting pethidine for pain relief in labour, ASA I or II. Women with a contraindication to pethidine or remifentanyl or requesting epidural were excluded
Interventions	Experimental: IV PCA remifentanyl, 0.5 mcg bolus per kg (based on antenatal booking weight) with 2 min lock-out, no hourly max Control: IV PCA pethidine, 10 mg bolus, 5 min lock-out, 100 mg hourly max All women were given 10 mg metoclopramide IV over 8 hrs.

Volikas 2001 (Continued)

Outcomes	Maternal: pain on 10 cm VAS recorded hourly; nausea recorded on a 10 cm VAS; itching; BP pulse and resps Neonate: 1 and 5 min Apgar scores.	
Notes		
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	"by selecting the next in a series of sealed envelopes prepared by pharmacy."
Blinding (performance bias and detection bias) Women	Low risk	Women were described as blind.
Blinding (performance bias and detection bias) Clinical staff	Unclear risk	"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 (performance bias and detection bias) Outcome assessor	Unclear risk	See above.
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
Selective reporting (reporting bias)	Unclear risk	Unclear.
Other bias	Low risk	None apparent.

Wahab 1988

Methods	RCT. 4-arm parallel groups.
Participants	Setting: hospital in Cairo, Egypt. 80 multiparous women at term (39-41 weeks), 19-27 years (parity 2-6), in the first stage of labour following uncomplicated pregnancies, spontaneous labour Women with respiratory or cardiac disease were excluded.

Wahab 1988 (Continued)

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 and 5 min. 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

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 (performance bias and detection bias) Women	Unclear risk	Not clear. Placebo controlled, but not clear if women or staff were aware of group assignment
Blinding (performance bias and detection bias) Clinical staff	Unclear risk	Unclear.
Blinding (performance bias and detection bias) Outcome assessor	Unclear risk	Unclear.
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

Wheble 1988

Methods	RCT, 2-arm parallel group design.
Participants	Setting: UK - hospital. 47 women. Women in active labour and requiring analgesia, 37-42 weeks' gestation, singleton pregnancies with no known disorders, spontaneous or induced labour onset

Wheble 1988 (Continued)

	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, metoclorpromide as required for nausea and vomiting	
Outcomes	Maternal outcomes: type of birth, additional analgesia, epidural. Neonatal outcomes: Apgar at 1 and 5 min, fetal heart rate changes	
Notes	Open non-randomised control arm.	
<i>Risk of bias</i>		
Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Not reported.
Allocation concealment (selection bias)	Unclear risk	Not reported.
Blinding (performance bias and detection bias) Women	Unclear risk	Described as double blind but methods not described.
Blinding (performance bias and detection bias) Clinical staff	Unclear risk	Described as double blind but methods not described.
Blinding (performance bias and detection bias) Outcome assessor	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, socio-economic group, gestation, cervical dilation, parity and smoking

Wilson 1986

Methods	RCT, 2-arm parallel group design.	
Participants	Setting: UK - hospital. 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 min (rated very severe, severe, moderate, slight) and with VAS (0-100), type of birth, sleepiness, nausea and vomiting. Neonatal outcomes: Apgar at 1 and 5 min, naloxone administration, Scanlon score (neuro-behavioural score) at 2-4 and 24 hrs	
Notes		
<i>Risk of bias</i>		
Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Not reported.
Allocation concealment (selection bias)	Unclear risk	Not reported.
Blinding (performance bias and detection bias) Women	Unclear risk	States double blind and study drugs were dispensed in coded ampoules
Blinding (performance bias and detection bias) Clinical staff	Unclear risk	States double blind and study drugs were dispensed in coded ampoules
Blinding (performance bias and detection bias) Outcome assessor	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

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
 IM: intramuscular
 IOL: induction of labour
 ITT: intention to treat
 IV: intravenous
 min: minutes
 multips: multiparous women
 MW: midwife
 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
 TENS: transcutaneous electrical nerve stimulation
 VAS: visual analogue scale

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

Study	Reason for exclusion
Aiken 1971	This study compares the use of diazepam versus a placebo. Both groups had pethidine
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 (remifentanyl) 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
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
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
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, amileridine IM, pethidine + perphenazine IM and amileridine + perphenazine IM. We are not aware that amileridine is used any longer in obstetric practice
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
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 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

(Continued)

El-Kerdawy 2010	This study compared opioids with epidural analgesia. Epidural analgesia in labour is covered in a related Cochrane review
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 remifentanyl (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 remifentanyl, the remaining 3 received epidural analgesia. Epidurals are covered in a separate Cochrane 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
Grandjean 1979	Study examining IV versus epidural analgesia.
Greer 1988	The study evaluated the effects of the interventions on platelet function in the newborn
Hodgkinson 1978	In this study both randomised groups received pethidine. 1 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
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
Krins 1969	Study participants were not women in labour
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

(Continued)

MacVicar 1960	Not an RCT; consecutive allocation to groups. Study examining the sedative effects of drugs and their effects on memory
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
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.
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
Ransom 1966	This study had 2 groups: pethidine 125 mg IM and oxymorphone 1.25 mg IM

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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 (methylpentanol) 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 methylpentanol 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 didn't. 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 ten 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
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 remifentanyl 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
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
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

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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
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
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
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
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 ongoing studies *[ordered by study ID]*

DATA AND ANALYSES

Comparison 1. Pethidine 100 mg IM versus placebo

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Maternal satisfaction at 30 minutes (number of women satisfied or very satisfied)	1	50	Risk Ratio (M-H, Fixed, 95% CI)	7.0 [0.38, 128.87]
2 Maternal pain relief good or fair (1 hour)	1	116	Risk Ratio (M-H, Fixed, 95% CI)	1.75 [1.24, 2.47]
3 Pain relief at 30 minutes (reduction in VAS of at least 40 mm)	1	50	Risk Ratio (M-H, Fixed, 95% CI)	25.0 [1.56, 400.54]
4 Additional analgesia	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	1	50	Risk Ratio (M-H, Fixed, 95% CI)	0.83 [0.29, 2.38]
10 Low Apgar score (≤ 7) at 1 and 5 minutes	2		Risk Ratio (M-H, Random, 95% CI)	Subtotals only
10.1 Low scores at 1 minute	2	166	Risk Ratio (M-H, Random, 95% CI)	1.64 [0.52, 5.18]
10.2 Low scores at 5 minutes	1	50	Risk Ratio (M-H, Random, 95% CI)	0.0 [0.0, 0.0]
11 Neonatal resuscitation	1	50	Risk Ratio (M-H, Fixed, 95% CI)	1.67 [0.45, 6.24]
12 Admission to NICU	1	50	Risk Ratio (M-H, Fixed, 95% CI)	1.0 [0.07, 15.12]

Comparison 2. Meptazinol versus pethidine

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 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 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 Nausea and vomiting	3		Risk Ratio (M-H, Fixed, 95% CI)	Subtotals only
5.1 Nausea	3	1590	Risk Ratio (M-H, Fixed, 95% CI)	1.11 [0.95, 1.28]
5.2 Vomiting	3	1589	Risk Ratio (M-H, Fixed, 95% CI)	1.25 [1.06, 1.47]
6 Maternal sleepiness	3	1590	Risk Ratio (M-H, Random, 95% CI)	0.55 [0.28, 1.07]
7 Assisted vaginal delivery	3	1266	Risk Ratio (M-H, Fixed, 95% CI)	1.00 [0.81, 1.22]
8 Caesarean section	3	1266	Risk Ratio (M-H, Random, 95% CI)	0.56 [0.16, 2.00]
9 Fetal heart rate changes (decelerations)	1	34	Risk Ratio (M-H, Fixed, 95% CI)	1.23 [0.92, 1.64]

10 Low Apgar score (≤ 7) at 1 and 5 minutes	4		Risk Ratio (M-H, Fixed, 95% CI)	Subtotals only
10.1 Low scores at 1 minute	4	662	Risk Ratio (M-H, Fixed, 95% CI)	0.76 [0.50, 1.13]
10.2 Low scores at 5 minutes	3	616	Risk Ratio (M-H, Fixed, 95% CI)	0.50 [0.05, 5.37]
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 \geq 36 weeks' gestation	1	975	Risk Ratio (M-H, Fixed, 95% CI)	0.89 [0.77, 1.02]
12 Neonatal resuscitation	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 \geq 36 weeks' gestation	2	1333	Risk Ratio (M-H, Fixed, 95% CI)	1.00 [0.95, 1.05]
13 Admission to NICU	1	199	Risk Ratio (M-H, Fixed, 95% CI)	0.88 [0.48, 1.63]
14 Breastfeeding problems	1	197	Risk Ratio (M-H, Fixed, 95% CI)	0.76 [0.17, 3.30]
15 Apgar less than or equal to 7 at 1 minute	2	129	Risk Ratio (M-H, Fixed, 95% CI)	0.89 [0.47, 1.67]
16 Neonatal resuscitation	1	100	Risk Ratio (M-H, Fixed, 95% CI)	1.5 [0.26, 8.60]

Comparison 3. PCA (IM) meptazinol versus PCA (IM) pethidine

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Pain score (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)	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 Nausea score in labour (rated 1 day after delivery)	1	10	Mean Difference (IV, Fixed, 95% CI)	-8.0 [-48.70, 32.70]
5 Drowsiness score in labour (rated 1 day after delivery)	1	10	Mean Difference (IV, Fixed, 95% CI)	5.60 [-28.19, 39.39]
6 Naloxone administered	1	10	Risk Ratio (M-H, Fixed, 95% CI)	1.0 [0.08, 11.93]

Comparison 4. Diamorphine + prochloperazine versus pethidine + prochloperazine

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Global assessment of pain relief at 24 hours	1	133	Risk Ratio (M-H, Fixed, 95% CI)	0.88 [0.67, 1.16]
2 Pain intensity at 1 hour (moderate or severe)	1	133	Risk Ratio (M-H, Fixed, 95% CI)	0.85 [0.72, 1.01]
3 Additional 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 Vomiting	1	133	Risk Ratio (M-H, Fixed, 95% CI)	0.39 [0.17, 0.86]
6 Maternal sleepiness	1	133	Risk Ratio (M-H, Fixed, 95% CI)	0.93 [0.52, 1.66]
7 Assisted vaginal delivery	1	133	Risk Ratio (M-H, Fixed, 95% CI)	0.96 [0.46, 2.02]
8 Caesarean section	1	133	Risk Ratio (M-H, Fixed, 95% CI)	0.52 [0.10, 2.76]

9 Apgar < 7 at 1 minute	1	133	Risk Ratio (M-H, Fixed, 95% CI)	0.41 [0.18, 0.91]
10 Apgar < 7 at 5 minutes	1	133	Risk Ratio (M-H, Fixed, 95% CI)	0.35 [0.04, 3.27]
11 Neonatal resuscitation	1	133	Risk Ratio (M-H, Fixed, 95% CI)	1.21 [0.73, 2.02]
12 Admission to NICU	1	133	Risk Ratio (M-H, Fixed, 95% CI)	0.58 [0.21, 1.64]

Comparison 5. Tramadol versus pethidine

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 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 Nausea and vomiting	6	454	Risk Ratio (M-H, Random, 95% CI)	0.97 [0.34, 2.76]
4 Maternal sleepiness	5	409	Risk Ratio (M-H, Random, 95% CI)	0.57 [0.33, 0.97]
5 Assisted vaginal delivery	3	260	Risk Ratio (M-H, Fixed, 95% CI)	0.56 [0.12, 2.56]
6 Caesarean section	3	260	Risk Ratio (M-H, Fixed, 95% CI)	0.71 [0.23, 2.18]
7 Low Apgar scores (≤ 7) at 1 and 5 minutes	2		Risk Ratio (M-H, Fixed, 95% CI)	Subtotals only
7.1 Low scores at 1 minute	2	250	Risk Ratio (M-H, Fixed, 95% CI)	0.0 [0.0, 0.0]
7.2 Low scores at 5 minutes	1	160	Risk Ratio (M-H, Fixed, 95% CI)	0.0 [0.0, 0.0]
8 Neonatal resuscitation	1	90	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 6. Tramadol + triflupromazine versus pethidine + triflupromazine

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	40	Risk Ratio (M-H, Fixed, 95% CI)	0.82 [0.13, 5.25]
1.2 Vomiting	1	40	Risk Ratio (M-H, Fixed, 95% CI)	0.40 [0.02, 9.35]
2 Maternal sleepiness	1	40	Risk Ratio (M-H, Fixed, 95% CI)	2.86 [0.68, 12.12]

Comparison 7. Dihydrocodeine 50 mg IM versus pethidine 100 mg IM

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Maternal pain relief poor (1 hour)	1	138	Risk Ratio (M-H, Fixed, 95% CI)	1.09 [0.64, 1.86]
2 Nausea and vomiting	1	138	Risk Ratio (M-H, Fixed, 95% CI)	0.87 [0.40, 1.88]
3 Maternal sleepiness	1	138	Risk Ratio (M-H, Fixed, 95% CI)	0.67 [0.43, 1.04]

4 Apgar ≤ 7 at 1 minute	1	138	Risk Ratio (M-H, Fixed, 95% CI)	0.57 [0.39, 0.84]
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Comparison 8. Pentazocine IM versus pethidine IM

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Pain relief (good or very good) at delivery	2	253	Risk Ratio (M-H, Fixed, 95% CI)	1.08 [0.92, 1.27]
2 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 Nausea and vomiting	3		Risk Ratio (M-H, Fixed, 95% CI)	Subtotals only
4.1 Nausea	3	391	Risk Ratio (M-H, Fixed, 95% CI)	0.46 [0.24, 0.90]
4.2 Vomiting	1	73	Risk Ratio (M-H, Fixed, 95% CI)	0.92 [0.27, 3.14]
5 Assisted vaginal delivery	2		Risk Ratio (M-H, Fixed, 95% CI)	Subtotals only
5.1 No add-on drugs	1	94	Risk Ratio (M-H, Fixed, 95% CI)	5.22 [0.63, 42.97]
5.2 With promazine	1	85	Risk Ratio (M-H, Fixed, 95% CI)	0.78 [0.23, 2.71]
6 Maternal sleepiness	3	391	Risk Ratio (M-H, Fixed, 95% CI)	1.00 [0.89, 1.12]
7 Low Apgar score (≤ 7) at 1 and 5 minutes	2		Risk Ratio (M-H, Random, 95% CI)	Subtotals only
7.1 Low score at 1 minute	2	242	Risk Ratio (M-H, Random, 95% CI)	1.39 [0.06, 32.97]
7.2 Low score at 5 minutes	1	62	Risk Ratio (M-H, Random, 95% CI)	0.23 [0.01, 4.54]

Comparison 9. Pentazocine + promazine versus pethidine + promazine

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Low Apgar score (≤ 7) at 1 and 5 minutes (with promazine)	1		Risk Ratio (M-H, Fixed, 95% CI)	Subtotals only
1.1 Low score at 1 minute	1	66	Risk Ratio (M-H, Fixed, 95% CI)	1.13 [0.07, 17.30]
1.2 Low score at 5 minutes	1	66	Risk Ratio (M-H, Fixed, 95% CI)	0.38 [0.02, 8.88]
2 Naloxone administration (neonatal)	1	85	Risk Ratio (M-H, Fixed, 95% CI)	0.49 [0.09, 2.53]
2.1 With promazine	1	85	Risk Ratio (M-H, Fixed, 95% CI)	0.49 [0.09, 2.53]

Comparison 10. Nalbuphine versus pethidine

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Maternal satisfaction with analgesia at 24 hours; numbers dissatisfied	1	72	Risk Ratio (M-H, Fixed, 95% CI)	0.73 [0.55, 0.96]
2 Pain free	1	40	Risk Ratio (M-H, Fixed, 95% CI)	6.0 [0.79, 45.42]
3 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 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 Nausea and vomiting	2		Risk Ratio (M-H, Fixed, 95% CI)	Subtotals only
7.1 Nausea	1	301	Risk Ratio (M-H, Fixed, 95% CI)	0.62 [0.42, 0.91]
7.2 Vomiting	1	301	Risk Ratio (M-H, Fixed, 95% CI)	0.41 [0.22, 0.76]
7.3 Nausea and vomiting	1	72	Risk Ratio (M-H, Fixed, 95% CI)	0.41 [0.18, 0.94]
8 Maternal sleepiness	1	72	Risk Ratio (M-H, Fixed, 95% CI)	3.78 [0.86, 16.60]
9 Assisted vaginal delivery	2	382	Risk Ratio (M-H, Random, 95% CI)	0.98 [0.25, 3.85]
10 Caesarean section	1	310	Risk Ratio (M-H, Fixed, 95% CI)	0.45 [0.12, 1.69]
11 Low Apgar score (≤ 7) at 1 and 5 minutes	2		Risk Ratio (M-H, Random, 95% CI)	Subtotals only
11.1 Low score at 1 minute	2	382	Risk Ratio (M-H, Random, 95% CI)	1.18 [0.72, 1.95]
11.2 Low score at 5 minutes	1	72	Risk Ratio (M-H, Random, 95% CI)	0.47 [0.04, 4.99]
12 Naloxone administration (neonatal)	1	72	Risk Ratio (M-H, Fixed, 95% CI)	6.63 [0.35, 123.93]
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. 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. Morphine versus pethidine

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Pain relief described as poor	1	90	Risk Ratio (M-H, Fixed, 95% CI)	1.22 [0.56, 2.66]
2 Additional analgesia required	1	90	Risk Ratio (M-H, Fixed, 95% CI)	1.14 [0.45, 2.89]
3 Nausea and vomiting	1	90	Risk Ratio (M-H, Fixed, 95% CI)	1.0 [0.21, 4.69]
4 Maternal sleepiness	1	90	Risk Ratio (M-H, Fixed, 95% CI)	0.6 [0.29, 1.23]
5 Apgar < 7 at 1 minute	1	90	Risk Ratio (M-H, Fixed, 95% CI)	0.0 [0.0, 0.0]
6 Neonatal resuscitation	1	90	Risk Ratio (M-H, Fixed, 95% CI)	0.0 [0.0, 0.0]

Comparison 13. 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 tramadol versus no treatment

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Analgesic effect described as satisfactory (not clear when measured)	1	60	Risk Ratio (M-H, Fixed, 95% CI)	11.0 [0.64, 190.53]
2 Mean blood loss at delivery (ml)	1	60	Mean Difference (IV, Fixed, 95% CI)	25.70 [-9.83, 61.23]

Comparison 15. IM Avacan® versus IM pentazocine

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Further analgesia required (nitrous oxide)	1	160	Risk Ratio (M-H, Fixed, 95% CI)	0.92 [0.53, 1.63]
2 Further 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 16. IM pentazocine versus IM pethilorfan

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 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 delivery	1	98	Risk Ratio (M-H, Fixed, 95% CI)	1.04 [0.07, 16.19]
4 Apgar < 8 at 1 minute	1	82	Risk Ratio (M-H, Fixed, 95% CI)	5.71 [0.72, 45.39]
5 Apgar < 8 at 5 minutes	1	82	Risk Ratio (M-H, Fixed, 95% CI)	0.0 [0.0, 0.0]

Comparison 17. IV fentanyl versus IV pethidine

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Pain score (1 hour after drug administration)	1	105	Mean Difference (IV, Fixed, 95% CI)	-0.20 [-0.34, -0.06]
2 Mean doses of analgesia	1	105	Mean Difference (IV, Fixed, 95% CI)	0.40 [0.14, 0.66]
3 Nausea and/or vomiting	1	105	Risk Ratio (M-H, Fixed, 95% CI)	0.51 [0.17, 1.55]
4 Anti-emetic required	1	105	Risk Ratio (M-H, Fixed, 95% CI)	0.09 [0.01, 1.52]
5 Maternal sedation	1	105	Risk Ratio (M-H, Fixed, 95% CI)	0.05 [0.00, 0.82]
6 Caesarean section	1	105	Risk Ratio (M-H, Fixed, 95% CI)	1.14 [0.24, 5.40]
7 Apgar score < 7 at 1 and 5 minutes	1		Risk Ratio (M-H, Fixed, 95% CI)	Subtotals only
7.1 Low score at 1 minute	1	105	Risk Ratio (M-H, Fixed, 95% CI)	0.63 [0.23, 1.77]
7.2 Low score at 5 minutes	1	105	Risk Ratio (M-H, Fixed, 95% CI)	0.38 [0.02, 9.12]
8 Naloxone administered	1	105	Risk Ratio (M-H, Fixed, 95% CI)	0.16 [0.02, 1.28]
9 Babies requiring resuscitation/ventilatory support	1	105	Risk Ratio (M-H, Fixed, 95% CI)	1.03 [0.46, 2.32]
10 Neurobehavioural score (1 - 2 hours after delivery)	1	105	Mean Difference (IV, Fixed, 95% CI)	1.30 [0.15, 2.45]

11 Neurobehavioural score (2 hours - 24 hours)	1	105	Mean Difference (IV, Fixed, 95% CI)	0.90 [-0.42, 2.22]
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Comparison 18. 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 and 5 minutes	1		Risk Ratio (M-H, Fixed, 95% CI)	Subtotals only
2.1 Low score at 1 minute	1	28	Risk Ratio (M-H, Fixed, 95% CI)	3.0 [0.13, 67.91]
2.2 Low score at 5 minutes	1	28	Risk Ratio (M-H, Fixed, 95% CI)	0.0 [0.0, 0.0]

Comparison 19. IV phenazocine versus IV pethidine

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Satisfaction with pain relief (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 20. IV butorphanol versus IV pethidine

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Pain relief score	1	80	Mean Difference (IV, Fixed, 95% CI)	0.67 [0.25, 1.09]
2 Pain score (1 hour after drug administration)	1	80	Mean Difference (IV, Fixed, 95% CI)	-0.60 [-1.02, -0.18]
3 Further analgesia (2nd dose) 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 Assisted vaginal delivery	1	200	Risk Ratio (M-H, Fixed, 95% CI)	1.3 [0.60, 2.83]
7 Caesarean section	1	200	Risk Ratio (M-H, Fixed, 95% CI)	0.8 [0.22, 2.89]
8 Apgar score < 7 at 1 and 5 minutes	2		Risk Ratio (M-H, Fixed, 95% CI)	Subtotals only
8.1 Low score at 1 minute	2	230	Risk Ratio (M-H, Fixed, 95% CI)	0.5 [0.15, 1.61]
8.2 Low score at 5 minutes	2	230	Risk Ratio (M-H, Fixed, 95% CI)	1.0 [0.06, 15.77]

Comparison 21. IV morphine versus IV pethidine

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Women satisfied with analgesia (assessed 3 days postpartum)	1	141	Risk Ratio (M-H, Fixed, 95% CI)	0.87 [0.78, 0.98]
2 Further dose of study 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 22. 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 Babies requiring resuscitation/ventilatory support	1	395	Risk Ratio (M-H, Fixed, 95% CI)	1.99 [0.85, 4.63]

Comparison 23. IV fentanyl versus IV butorphanol

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Additional analgesia required (women requesting two or more doses)	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 Maternal drowsiness (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 Apgar score < 7 at 5 minutes	1	100	Risk Ratio (M-H, Fixed, 95% CI)	1.2 [0.39, 3.68]
6 Babies requiring ventilatory support	1	100	Risk Ratio (M-H, Fixed, 95% CI)	11.0 [0.62, 193.80]
7 Naloxone required	1	100	Risk Ratio (M-H, Fixed, 95% CI)	1.75 [0.81, 3.80]
8 Neurobehavioural score at 2-4 hours	1	100	Mean Difference (IV, Fixed, 95% CI)	0.0 [-1.61, 1.61]
9 Neurobehavioural score at 24-36 hours	1	100	Mean Difference (IV, Fixed, 95% CI)	-0.50 [-1.62, 0.62]

Comparison 24. PCA pentazocine versus PCA pethidine

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Pain score in labour	1	23	Std. Mean Difference (IV, Fixed, 95% CI)	-0.76 [-1.62, 0.09]
2 Pain relief 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 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 Apgar score < 7 at 5 minutes	1	29	Risk Ratio (M-H, Fixed, 95% CI)	0.0 [0.0, 0.0]
8 Breastfeeding at discharge	1	23	Risk Ratio (M-H, Fixed, 95% CI)	1.0 [0.85, 1.17]

Comparison 25. PCA remifentanyl versus PCA pethidine

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Pain score in labour	2	122	Mean Difference (IV, Random, 95% CI)	-8.59 [-27.61, 10.44]
2 Women receiving other analgesia (Entonox)	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 Assisted vaginal birth	2	97	Risk Ratio (M-H, Fixed, 95% CI)	0.96 [0.46, 2.00]
7 Caesarean section	2	97	Risk Ratio (M-H, Fixed, 95% CI)	1.81 [0.60, 5.46]
8 Apgar score < 7 at 5 minutes	1	17	Risk Ratio (M-H, Fixed, 95% CI)	0.13 [0.01, 2.16]
9 Naloxone administered	2	56	Risk Ratio (M-H, Fixed, 95% CI)	0.3 [0.01, 6.47]
10 Admission to NICU	1	17	Risk Ratio (M-H, Fixed, 95% CI)	0.3 [0.01, 6.47]
11 Satisfaction with childbirth experience	1	68	Mean Difference (IV, Fixed, 95% CI)	1.10 [0.46, 1.74]
12 Neurobehavioural score (15 minutes post delivery)	1	56	Mean Difference (IV, Fixed, 95% CI)	0.20 [-0.93, 1.33]
13 Neurobehavioural score (2 hours post delivery)	1	56	Mean Difference (IV, Fixed, 95% CI)	0.60 [-0.66, 1.86]

Comparison 26. PCA nalbuphine versus PCA pethidine

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Pain relief in labour measured in the postnatal period (rated good or excellent)	1	60	Risk Ratio (M-H, Fixed, 95% CI)	1.29 [0.88, 1.89]
2 Would use the same pain relief again	1	59	Risk Ratio (M-H, Fixed, 95% CI)	1.06 [0.79, 1.43]
3 Pain score in labour	1	60	Std. Mean Difference (IV, Fixed, 95% CI)	-0.51 [-1.02, 0.00]
4 Women receiving other analgesia (Entonox)	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 27. PCA fentanyl versus PCA alfentanil

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Pain relief described as adequate (recorded after delivery)	1	23	Risk Ratio (M-H, Fixed, 95% CI)	1.56 [0.93, 2.60]
2 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 28. PCA fentanyl versus PCA pethidine

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Pain score 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 Assisted vaginal birth	1	81	Risk Ratio (M-H, Fixed, 95% CI)	0.57 [0.22, 1.49]
6 Caesarean section	1	81	Risk Ratio (M-H, Fixed, 95% CI)	0.25 [0.03, 2.34]
7 Neurobehavioural score (15 minutes post delivery)	1	63	Mean Difference (IV, Fixed, 95% CI)	-0.90 [-2.31, 0.51]
8 Neurobehavioural score (2 hours post delivery)	1	64	Mean Difference (IV, Fixed, 95% CI)	-0.5 [-1.95, 0.95]

Comparison 29. Opioids versus TENS

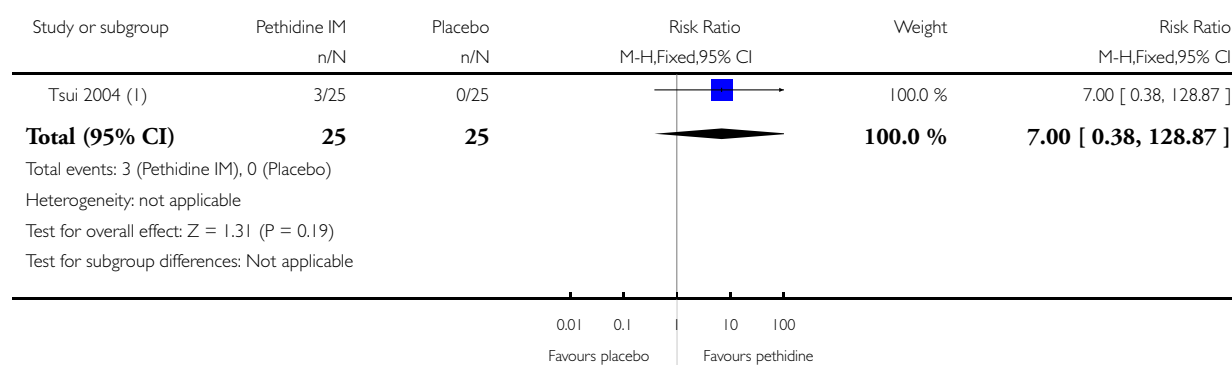
Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Maternal satisfaction with analgesia measured post delivery (rated as good)	2	104	Risk Ratio (M-H, Fixed, 95% CI)	1.23 [0.79, 1.92]
2 Maternal pain score measured during labour	2	290	Risk Ratio (M-H, Random, 95% CI)	1.15 [0.81, 1.61]
3 Drowsiness	2	290	Risk Ratio (M-H, Fixed, 95% CI)	8.96 [1.13, 71.07]
4 Nausea and vomiting	2	290	Risk Ratio (M-H, Fixed, 95% CI)	14.06 [1.96, 100.61]
5 Caesarean section	1	200	Risk Ratio (M-H, Fixed, 95% CI)	0.0 [0.0, 0.0]
6 Assisted vaginal birth	1	200	Risk Ratio (M-H, Fixed, 95% CI)	5.0 [0.24, 102.85]
7 Fetal distress	1	200	Risk Ratio (M-H, Fixed, 95% CI)	5.0 [0.24, 102.85]

Analysis 1.1. Comparison 1 Pethidine 100 mg IM versus placebo, Outcome 1 Maternal satisfaction at 30 minutes (number of women satisfied or very satisfied).

Review: Parenteral opioids for maternal pain management in labour

Comparison: 1 Pethidine 100 mg IM versus placebo

Outcome: 1 Maternal satisfaction at 30 minutes (number of women satisfied or very satisfied)



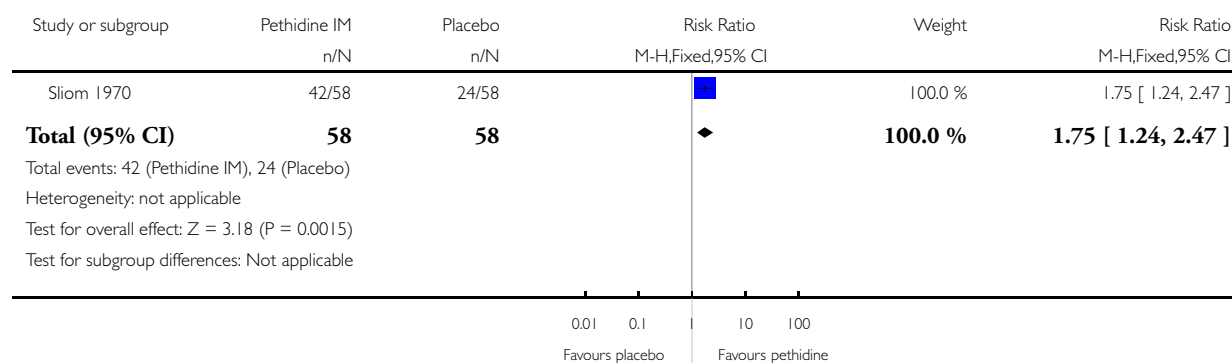
(1) Maternal satisfaction rated as 4 or 5 on rating scale 0-5 where 0 = very dissatisfied to 5= very satisfied

Analysis 1.2. Comparison 1 Pethidine 100 mg IM versus placebo, Outcome 2 Maternal pain relief good or fair (1 hour).

Review: Parenteral opioids for maternal pain management in labour

Comparison: 1 Pethidine 100 mg IM versus placebo

Outcome: 2 Maternal pain relief good or fair (1 hour)

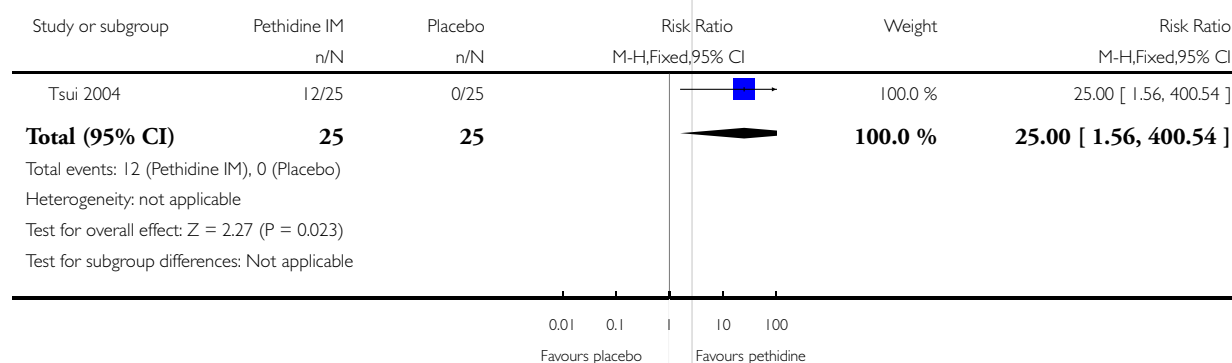


Analysis 1.3. Comparison 1 Pethidine 100 mg IM versus placebo, Outcome 3 Pain relief at 30 minutes (reduction in VAS of at least 40 mm).

Review: Parenteral opioids for maternal pain management in labour

Comparison: 1 Pethidine 100 mg IM versus placebo

Outcome: 3 Pain relief at 30 minutes (reduction in VAS of at least 40 mm)

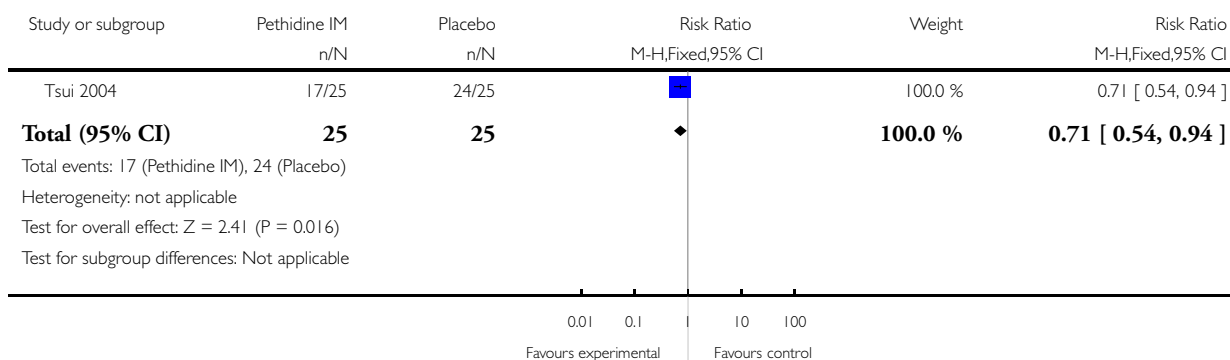


Analysis 1.4. Comparison 1 Pethidine 100 mg IM versus placebo, Outcome 4 Additional analgesia.

Review: Parenteral opioids for maternal pain management in labour

Comparison: 1 Pethidine 100 mg IM versus placebo

Outcome: 4 Additional analgesia

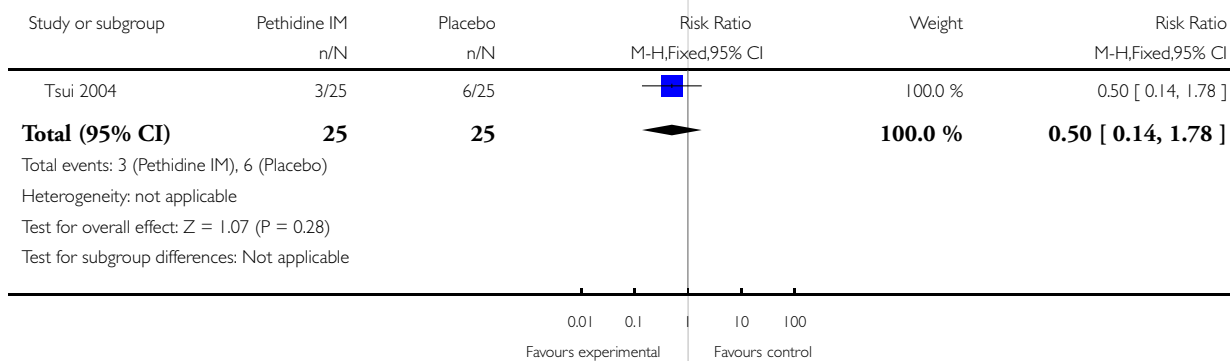


Analysis 1.5. Comparison 1 Pethidine 100 mg IM versus placebo, Outcome 5 Epidural.

Review: Parenteral opioids for maternal pain management in labour

Comparison: 1 Pethidine 100 mg IM versus placebo

Outcome: 5 Epidural

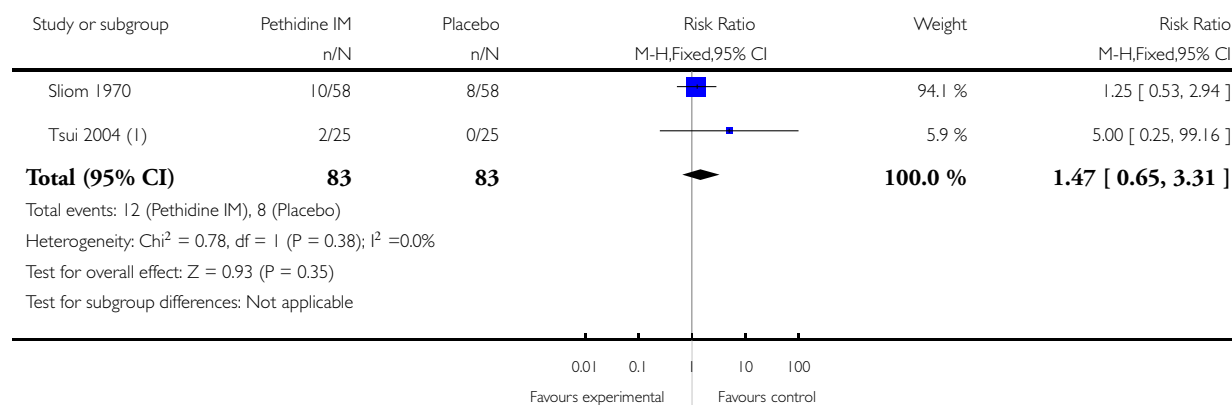


Analysis 1.6. Comparison 1 Pethidine 100 mg IM versus placebo, Outcome 6 Nausea and vomiting.

Review: Parenteral opioids for maternal pain management in labour

Comparison: 1 Pethidine 100 mg IM versus placebo

Outcome: 6 Nausea and vomiting



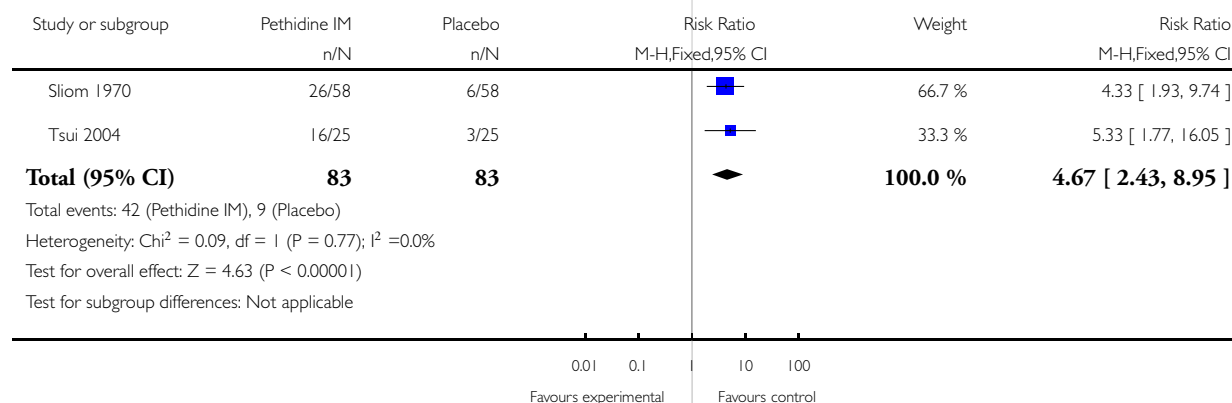
(1) Figures for vomiting only

Analysis 1.7. Comparison 1 Pethidine 100 mg IM versus placebo, Outcome 7 Maternal sleepiness.

Review: Parenteral opioids for maternal pain management in labour

Comparison: 1 Pethidine 100 mg IM versus placebo

Outcome: 7 Maternal sleepiness

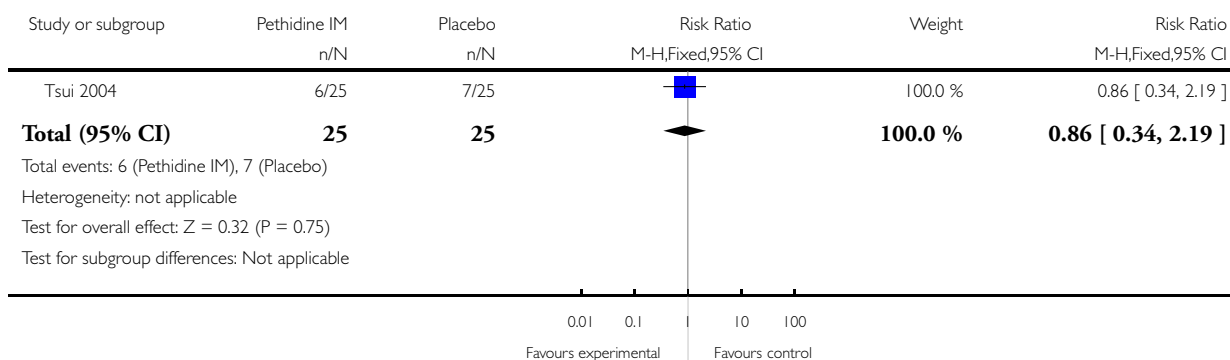


Analysis 1.8. Comparison 1 Pethidine 100 mg IM versus placebo, Outcome 8 Assisted vaginal delivery.

Review: Parenteral opioids for maternal pain management in labour

Comparison: 1 Pethidine 100 mg IM versus placebo

Outcome: 8 Assisted vaginal delivery

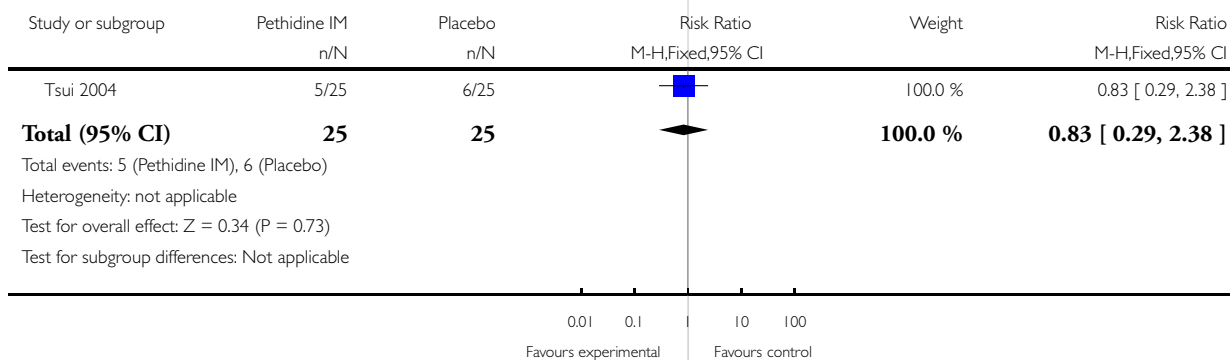


Analysis 1.9. Comparison 1 Pethidine 100 mg IM versus placebo, Outcome 9 Caesarean section.

Review: Parenteral opioids for maternal pain management in labour

Comparison: 1 Pethidine 100 mg IM versus placebo

Outcome: 9 Caesarean section

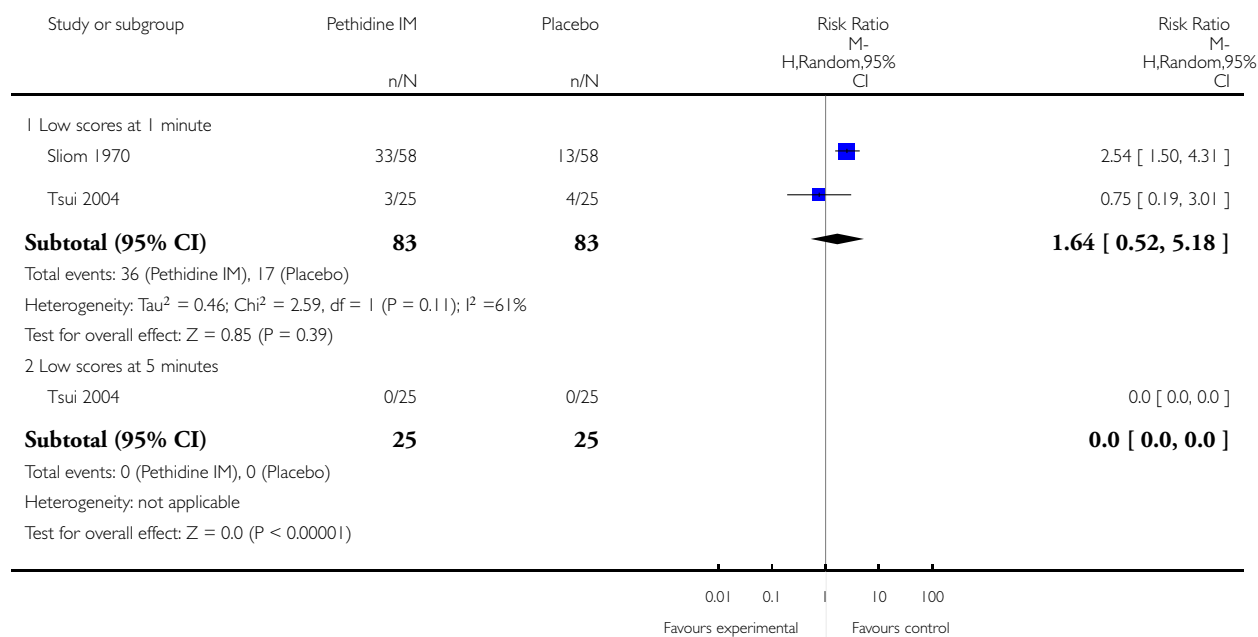


Analysis 1.10. Comparison 1 Pethidine 100 mg IM versus placebo, Outcome 10 Low Apgar score (≤ 7) at 1 and 5 minutes.

Review: Parenteral opioids for maternal pain management in labour

Comparison: 1 Pethidine 100 mg IM versus placebo

Outcome: 10 Low Apgar score (≤ 7) at 1 and 5 minutes

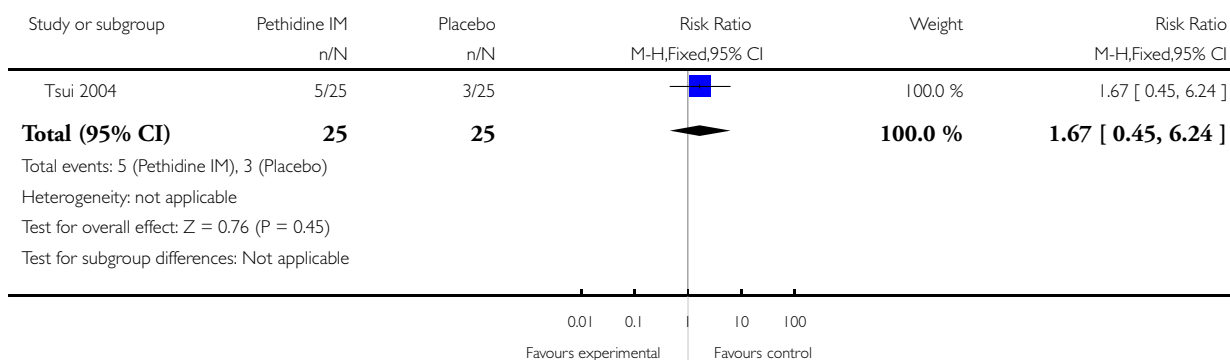


Analysis 1.11. Comparison 1 Pethidine 100 mg IM versus placebo, Outcome 11 Neonatal resuscitation.

Review: Parenteral opioids for maternal pain management in labour

Comparison: 1 Pethidine 100 mg IM versus placebo

Outcome: 11 Neonatal resuscitation

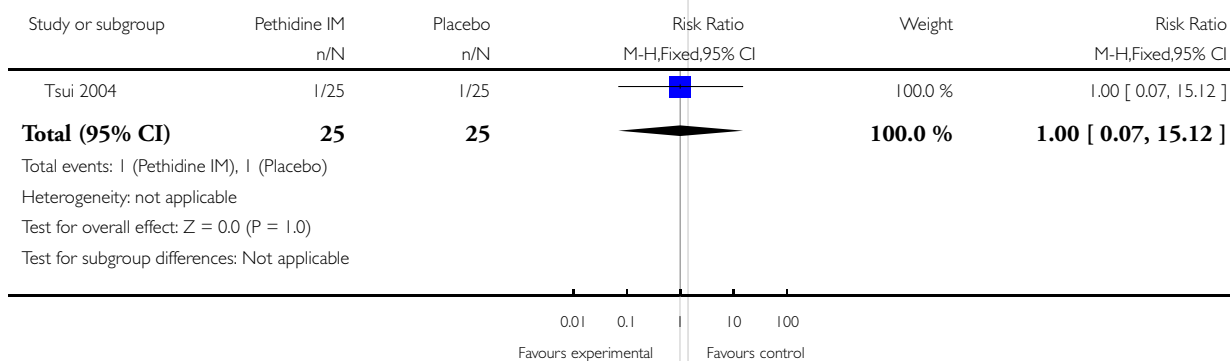


Analysis 1.12. Comparison 1 Pethidine 100 mg IM versus placebo, Outcome 12 Admission to NICU.

Review: Parenteral opioids for maternal pain management in labour

Comparison: 1 Pethidine 100 mg IM versus placebo

Outcome: 12 Admission to NICU

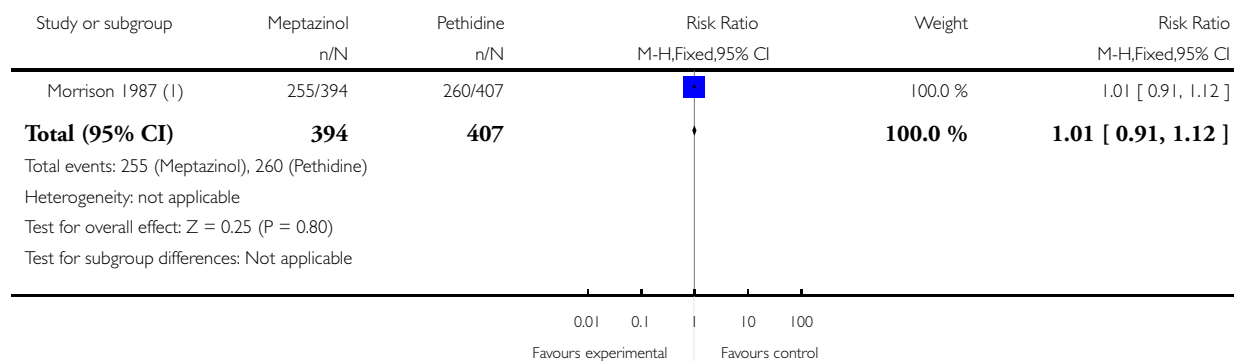


Analysis 2.1. Comparison 2 Meptazinol versus pethidine, Outcome 1 Maternal pain relief poor or none (3-5 PN).

Review: Parenteral opioids for maternal pain management in labour

Comparison: 2 Meptazinol versus pethidine

Outcome: 1 Maternal pain relief poor or none (3-5 PN)



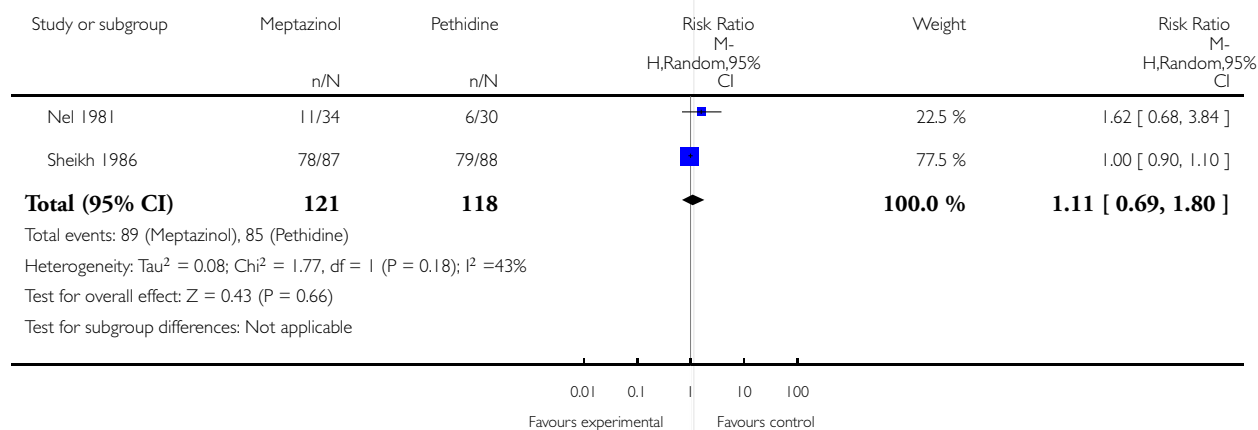
(1) Post partum assessment of analgesia 3-5 postpartum

Analysis 2.2. Comparison 2 Meptazinol versus pethidine, Outcome 2 Pain intensity 4 or 5 on 5-point scale (1 hour).

Review: Parenteral opioids for maternal pain management in labour

Comparison: 2 Meptazinol versus pethidine

Outcome: 2 Pain intensity 4 or 5 on 5-point scale (1 hour)

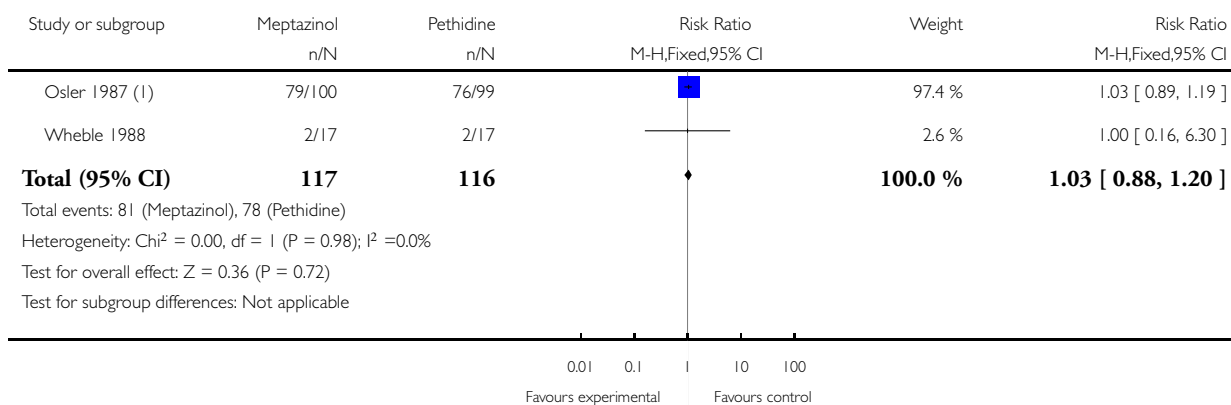


Analysis 2.3. Comparison 2 Meptazinol versus pethidine, Outcome 3 Additional analgesia required.

Review: Parenteral opioids for maternal pain management in labour

Comparison: 2 Meptazinol versus pethidine

Outcome: 3 Additional analgesia required



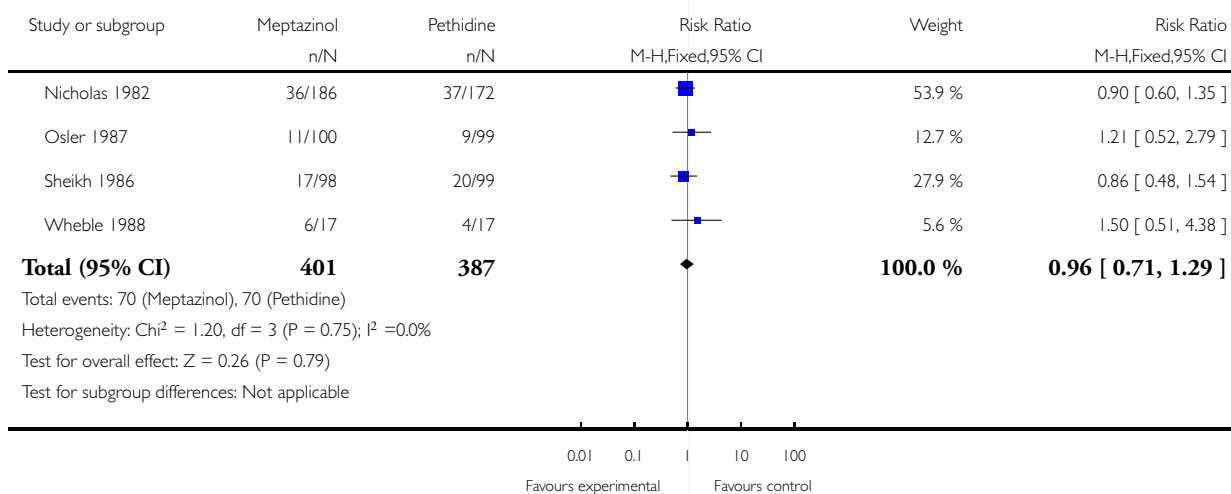
(1) For Osler 1987 additional analgesia relates to a pudendal, whereas for Wheble it relates to a second dose of study drug.

Analysis 2.4. Comparison 2 Meptazinol versus pethidine, Outcome 4 Epidural.

Review: Parenteral opioids for maternal pain management in labour

Comparison: 2 Meptazinol versus pethidine

Outcome: 4 Epidural

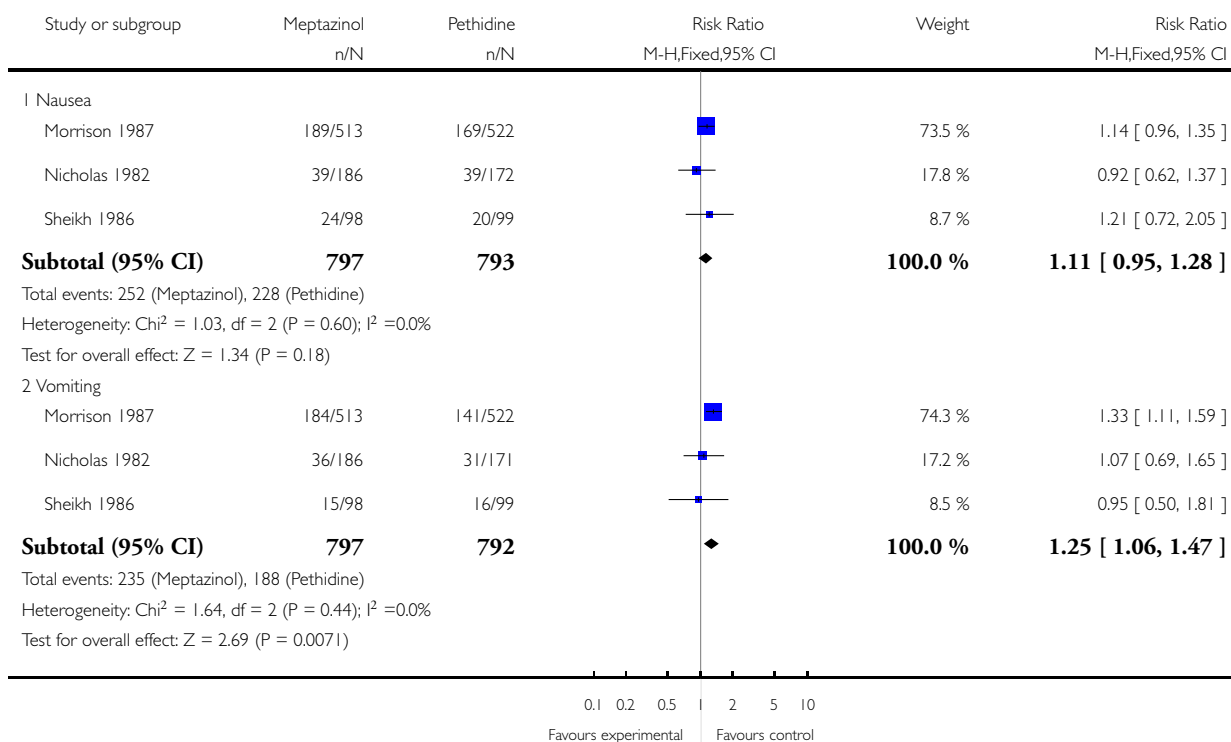


Analysis 2.5. Comparison 2 Meptazinol versus pethidine, Outcome 5 Nausea and vomiting.

Review: Parenteral opioids for maternal pain management in labour

Comparison: 2 Meptazinol versus pethidine

Outcome: 5 Nausea and vomiting

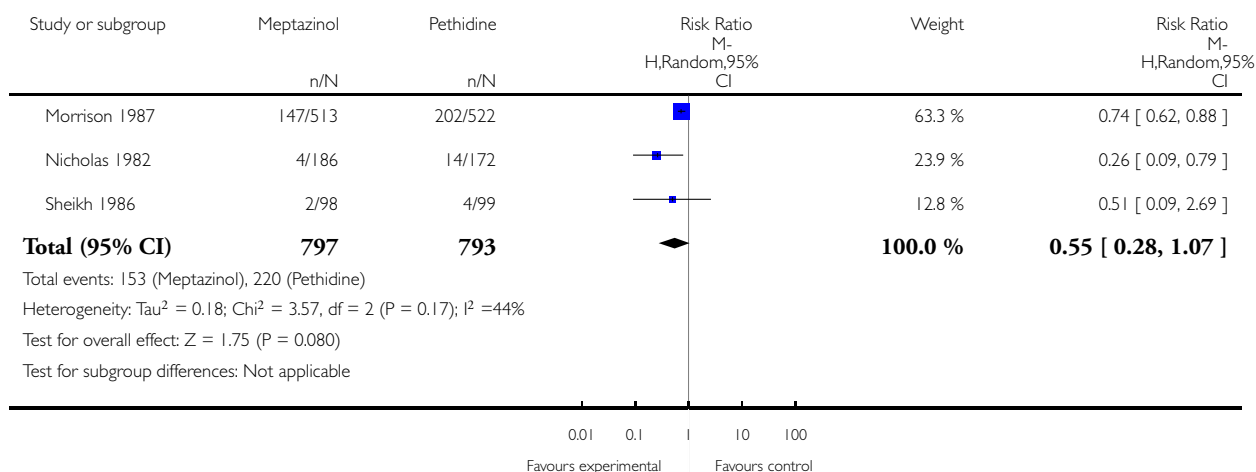


Analysis 2.6. Comparison 2 Meptazinol versus pethidine, Outcome 6 Maternal sleepiness.

Review: Parenteral opioids for maternal pain management in labour

Comparison: 2 Meptazinol versus pethidine

Outcome: 6 Maternal sleepiness

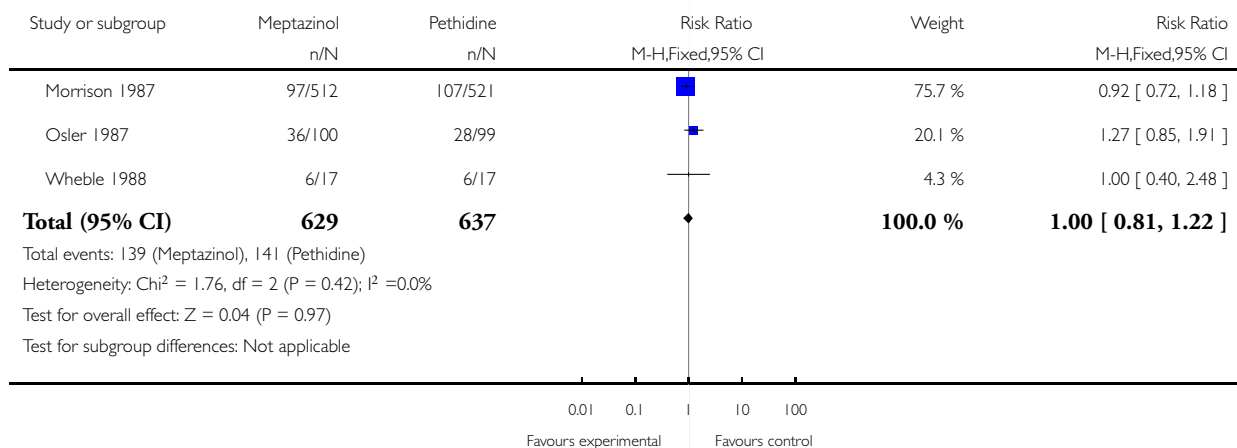


Analysis 2.7. Comparison 2 Meptazinol versus pethidine, Outcome 7 Assisted vaginal delivery.

Review: Parenteral opioids for maternal pain management in labour

Comparison: 2 Meptazinol versus pethidine

Outcome: 7 Assisted vaginal delivery

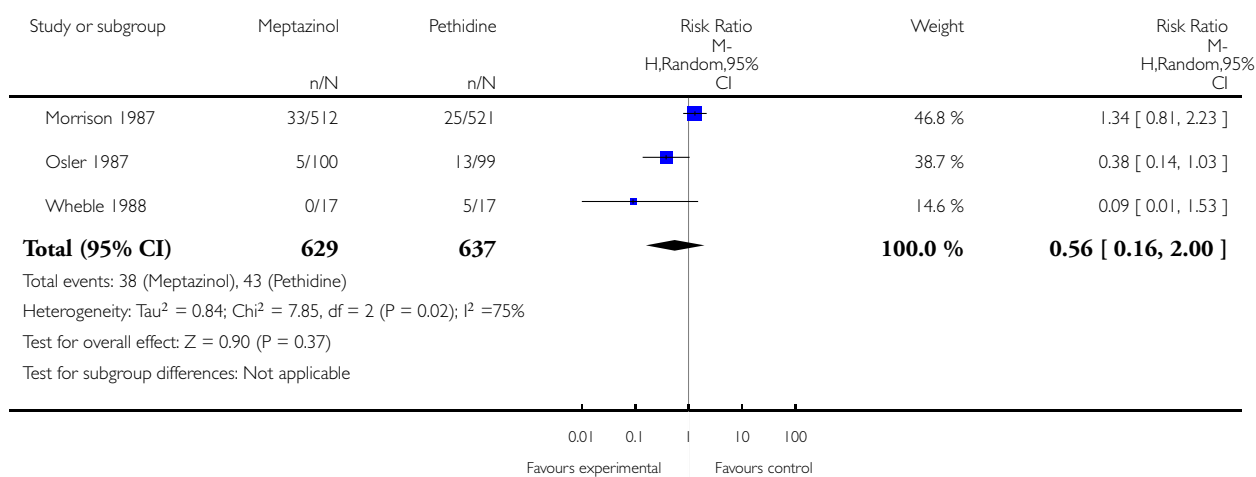


Analysis 2.8. Comparison 2 Meptazinol versus pethidine, Outcome 8 Caesarean section.

Review: Parenteral opioids for maternal pain management in labour

Comparison: 2 Meptazinol versus pethidine

Outcome: 8 Caesarean section

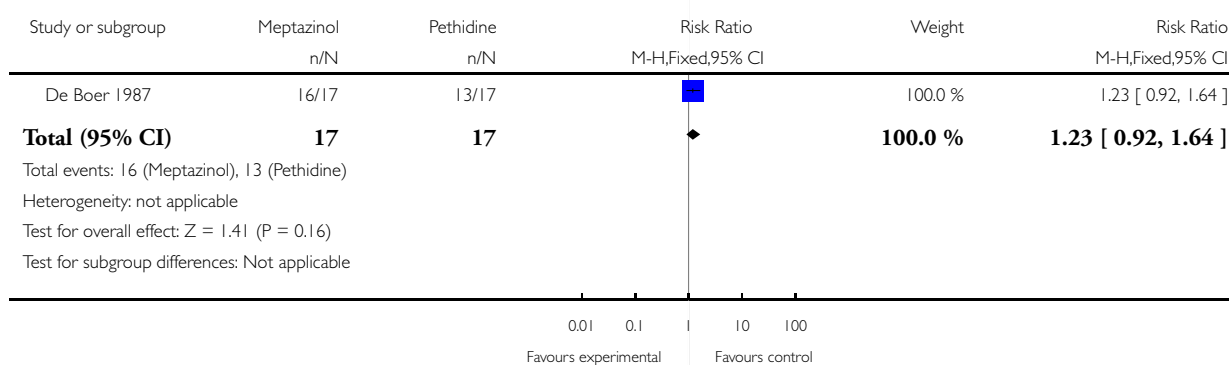


Analysis 2.9. Comparison 2 Meptazinol versus pethidine, Outcome 9 Fetal heart rate changes (decelerations).

Review: Parenteral opioids for maternal pain management in labour

Comparison: 2 Meptazinol versus pethidine

Outcome: 9 Fetal heart rate changes (decelerations)

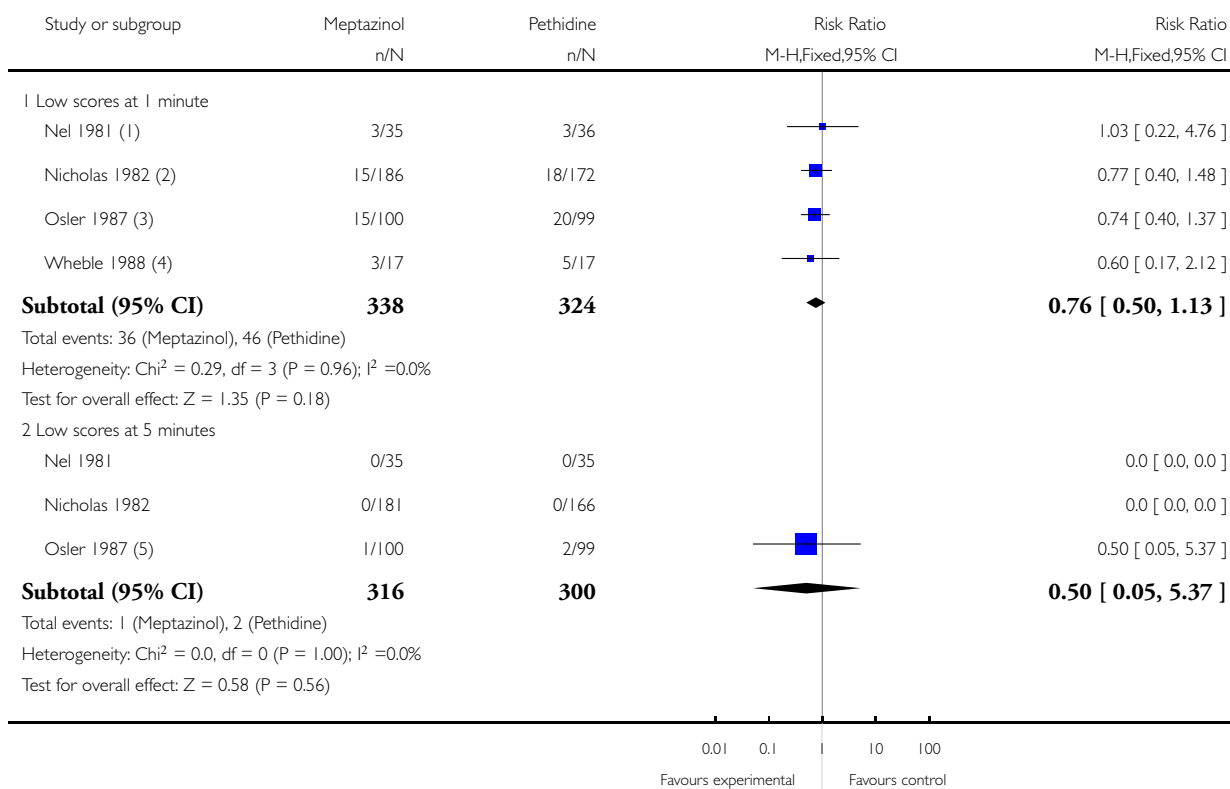


Analysis 2.10. Comparison 2 Meptazinol versus pethidine, Outcome 10 Low Apgar score (≤ 7) at 1 and 5 minutes.

Review: Parenteral opioids for maternal pain management in labour

Comparison: 2 Meptazinol versus pethidine

Outcome: 10 Low Apgar score (≤ 7) at 1 and 5 minutes



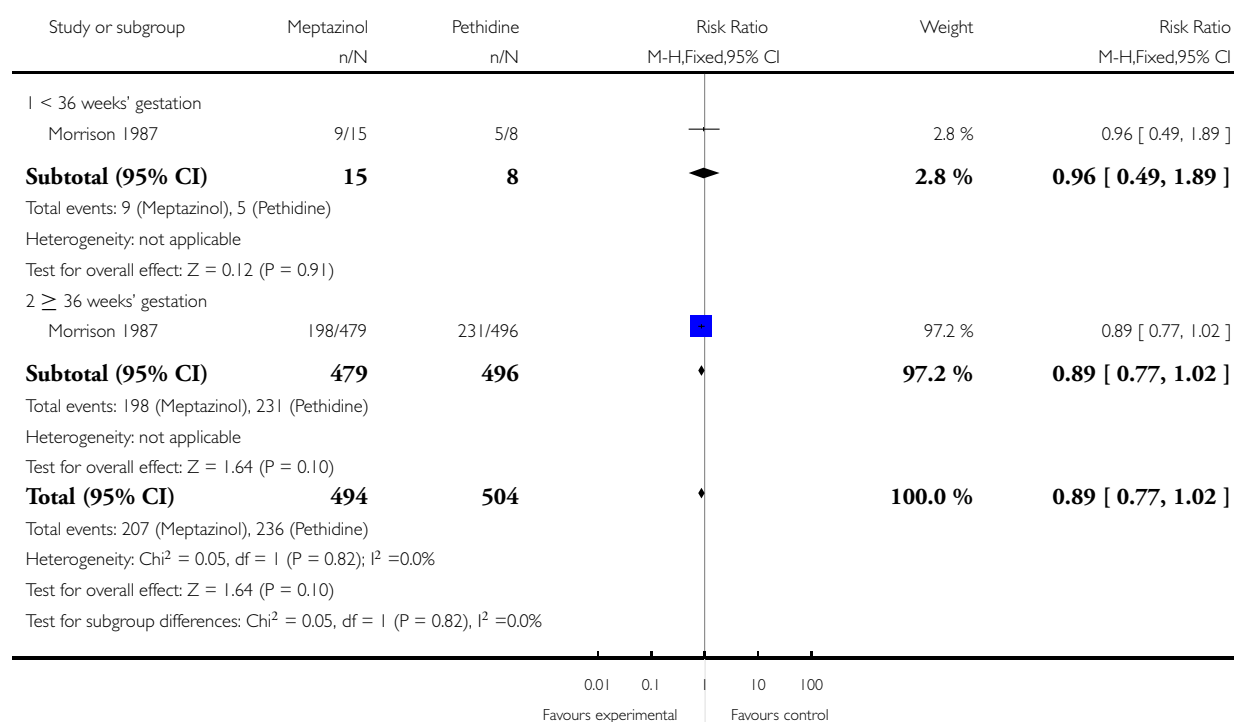
- (1) Nel = Apgar < 7
 (2) Nicholas = Apgar < 7
 (3) Osler <= 7
 (4) Wheble Apgar < 7
 (5) Osler Apgar =< 7

Analysis 2.11. Comparison 2 Meptazinol versus pethidine, Outcome 11 Naloxone administration.

Review: Parenteral opioids for maternal pain management in labour

Comparison: 2 Meptazinol versus pethidine

Outcome: 11 Naloxone administration

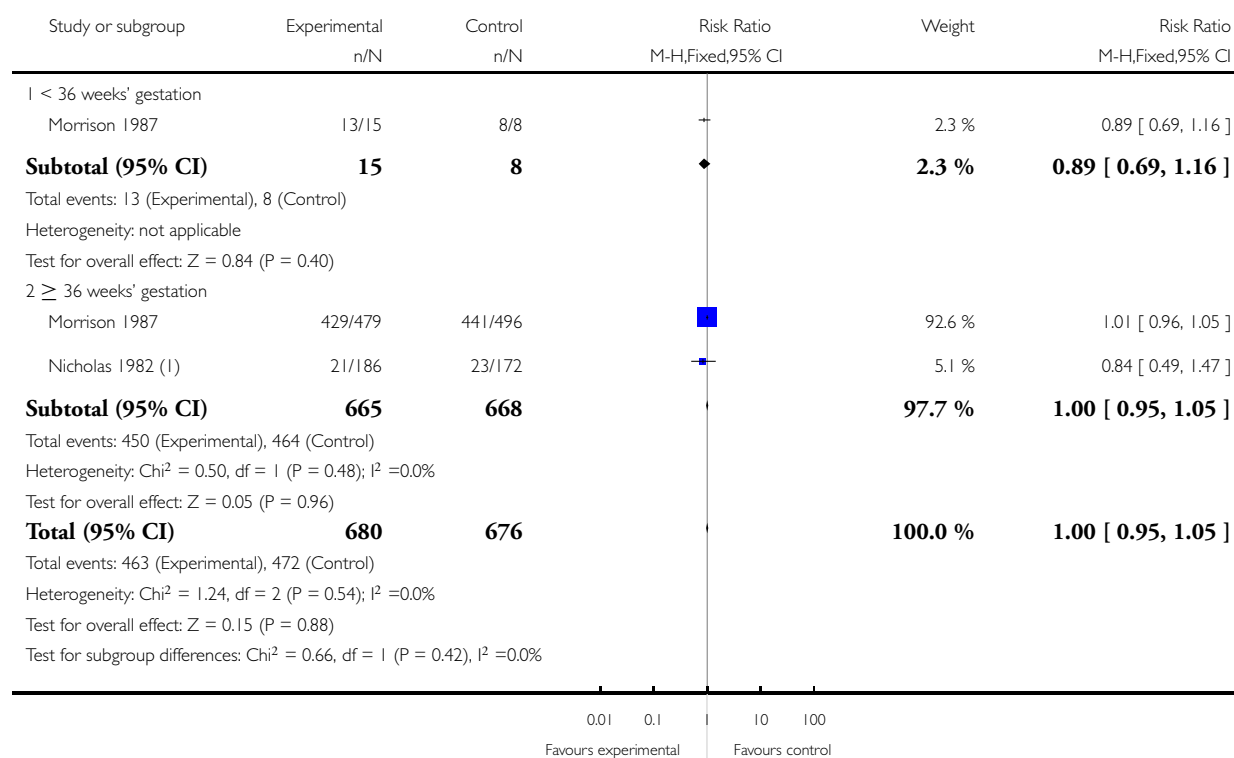


Analysis 2.12. Comparison 2 Meptazinol versus pethidine, Outcome 12 Neonatal resuscitation.

Review: Parenteral opioids for maternal pain management in labour

Comparison: 2 Meptazinol versus pethidine

Outcome: 12 Neonatal resuscitation



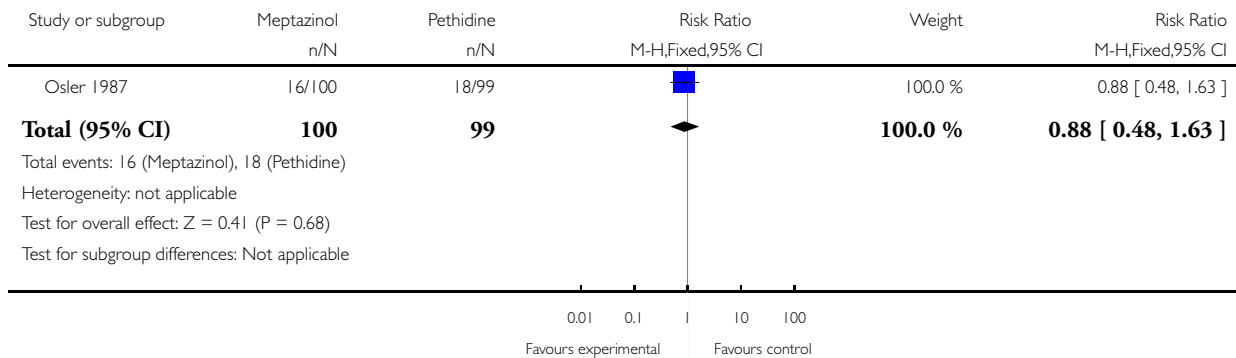
(1) Nicholas = apnoea interpreted as requirement for resuscitation

Analysis 2.13. Comparison 2 Meptazinol versus pethidine, Outcome 13 Admission to NICU.

Review: Parenteral opioids for maternal pain management in labour

Comparison: 2 Meptazinol versus pethidine

Outcome: 13 Admission to NICU

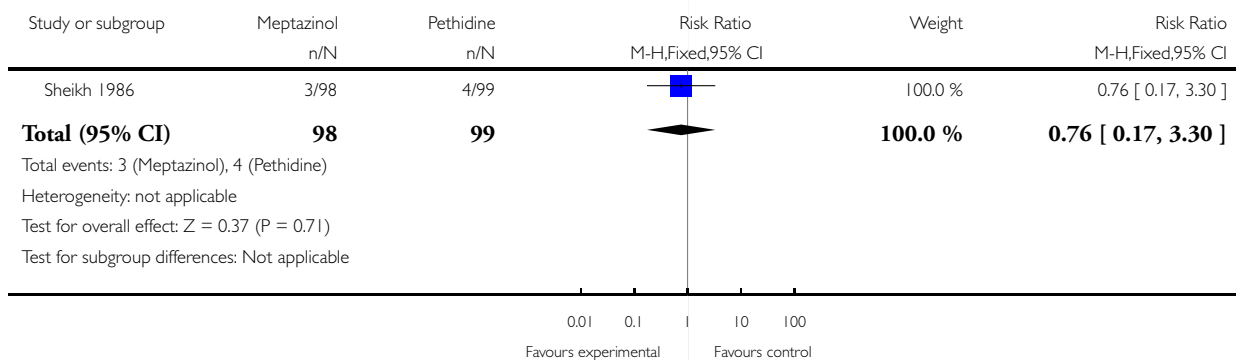


Analysis 2.14. Comparison 2 Meptazinol versus pethidine, Outcome 14 Breastfeeding problems.

Review: Parenteral opioids for maternal pain management in labour

Comparison: 2 Meptazinol versus pethidine

Outcome: 14 Breastfeeding problems

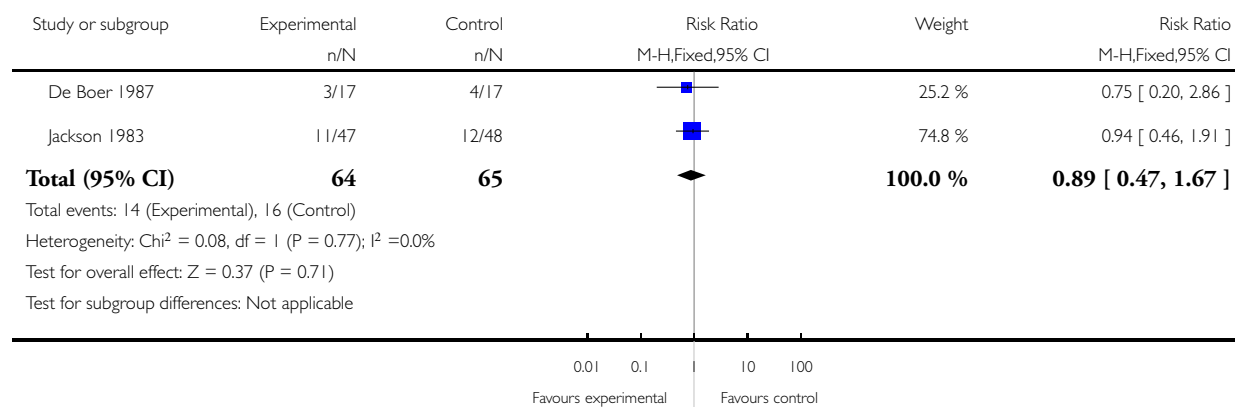


Analysis 2.15. Comparison 2 Meptazinol versus pethidine, Outcome 15 Apgar less than or equal to 7 at 1 minute.

Review: Parenteral opioids for maternal pain management in labour

Comparison: 2 Meptazinol versus pethidine

Outcome: 15 Apgar less than or equal to 7 at 1 minute

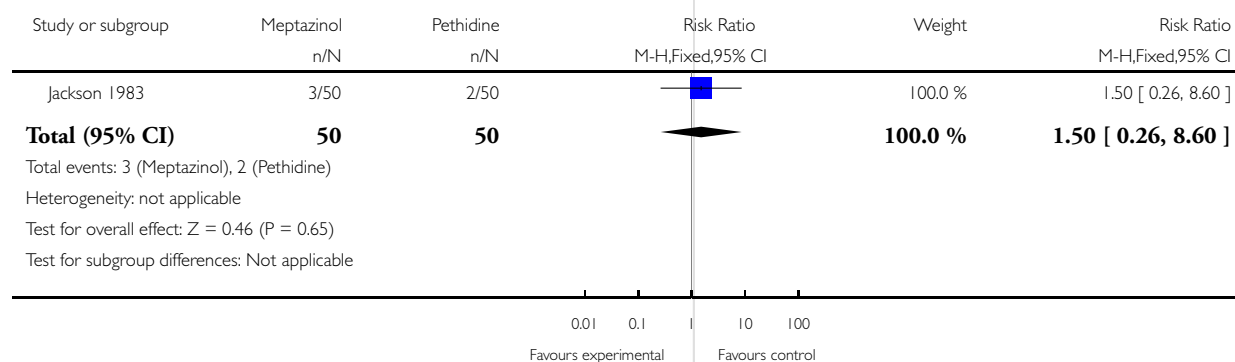


Analysis 2.16. Comparison 2 Meptazinol versus pethidine, Outcome 16 Neonatal resuscitation.

Review: Parenteral opioids for maternal pain management in labour

Comparison: 2 Meptazinol versus pethidine

Outcome: 16 Neonatal resuscitation

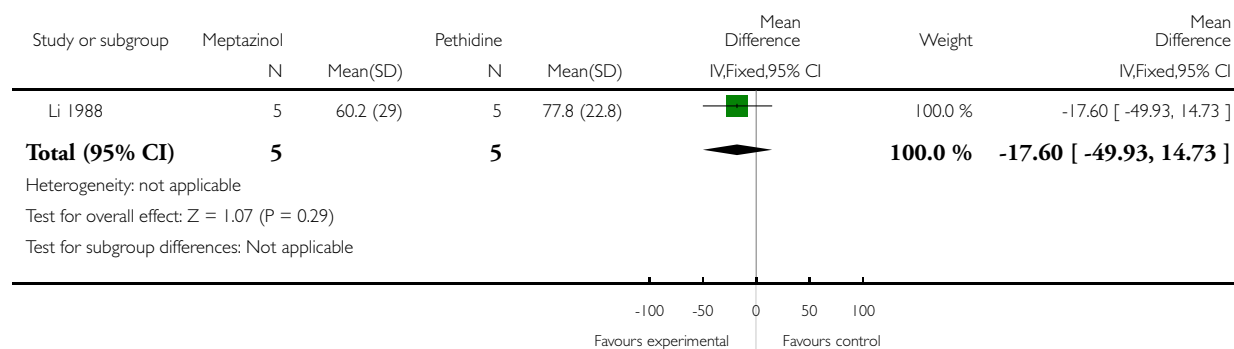


Analysis 3.1. Comparison 3 PCA (IM) meptazinol versus PCA (IM) pethidine, Outcome 1 Pain score (measured 1 day after delivery).

Review: Parenteral opioids for maternal pain management in labour

Comparison: 3 PCA (IM) meptazinol versus PCA (IM) pethidine

Outcome: 1 Pain score (measured 1 day after delivery)

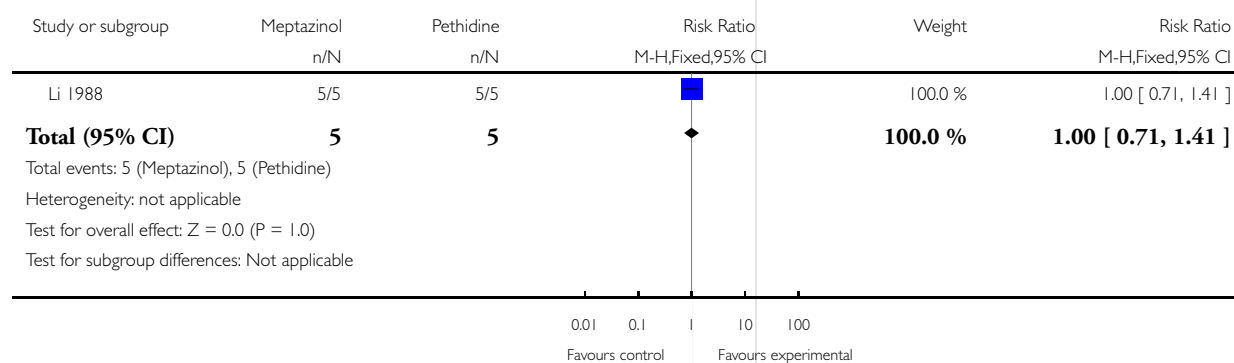


Analysis 3.2. Comparison 3 PCA (IM) meptazinol versus PCA (IM) pethidine, Outcome 2 Satisfied with mode of administration (PCA IM).

Review: Parenteral opioids for maternal pain management in labour

Comparison: 3 PCA (IM) meptazinol versus PCA (IM) pethidine

Outcome: 2 Satisfied with mode of administration (PCA IM)

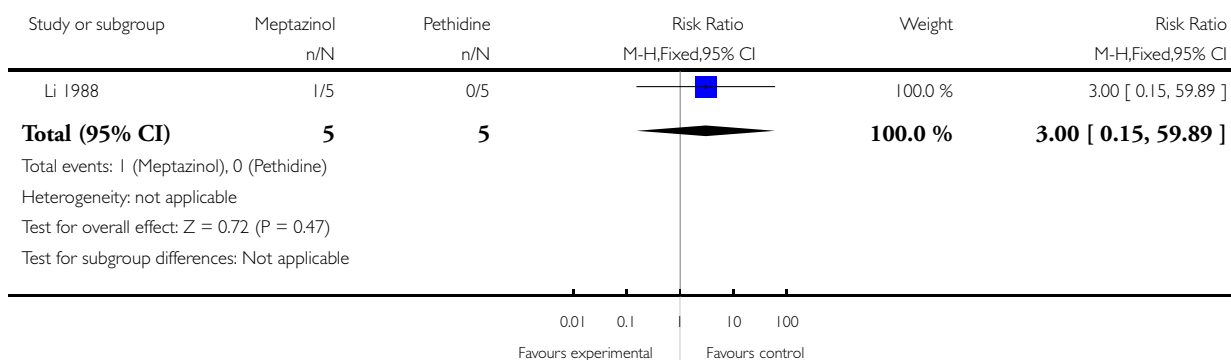


Analysis 3.3. Comparison 3 PCA (IM) meptazinol versus PCA (IM) pethidine, Outcome 3 Epidural.

Review: Parenteral opioids for maternal pain management in labour

Comparison: 3 PCA (IM) meptazinol versus PCA (IM) pethidine

Outcome: 3 Epidural

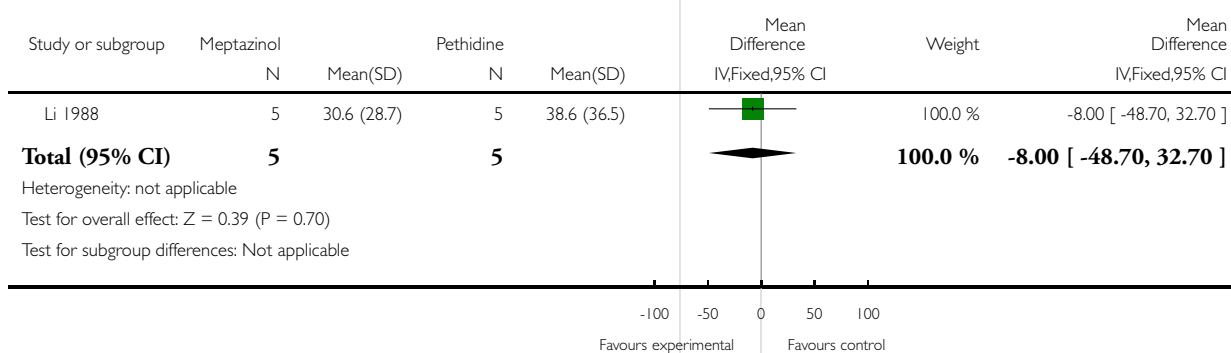


Analysis 3.4. Comparison 3 PCA (IM) meptazinol versus PCA (IM) pethidine, Outcome 4 Nausea score in labour (rated 1 day after delivery).

Review: Parenteral opioids for maternal pain management in labour

Comparison: 3 PCA (IM) meptazinol versus PCA (IM) pethidine

Outcome: 4 Nausea score in labour (rated 1 day after delivery)

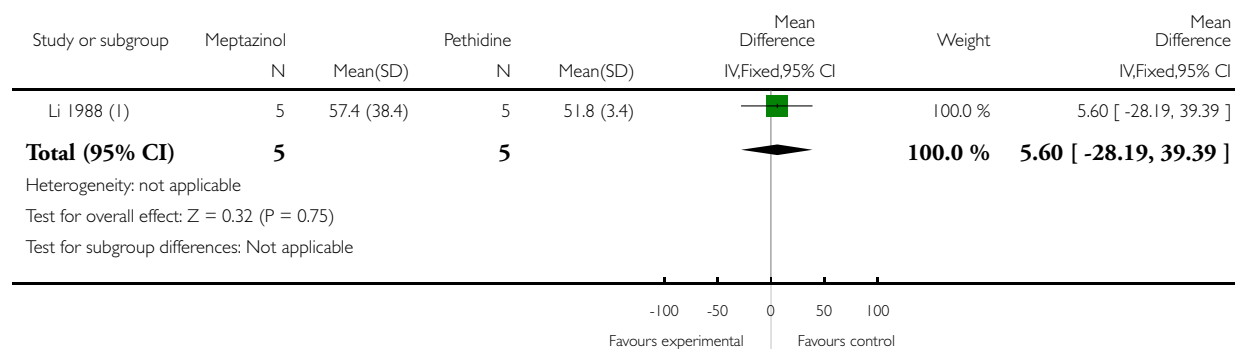


Analysis 3.5. Comparison 3 PCA (IM) meptazinol versus PCA (IM) pethidine, Outcome 5 Drowsiness score in labour (rated 1 day after delivery).

Review: Parenteral opioids for maternal pain management in labour

Comparison: 3 PCA (IM) meptazinol versus PCA (IM) pethidine

Outcome: 5 Drowsiness score in labour (rated 1 day after delivery)



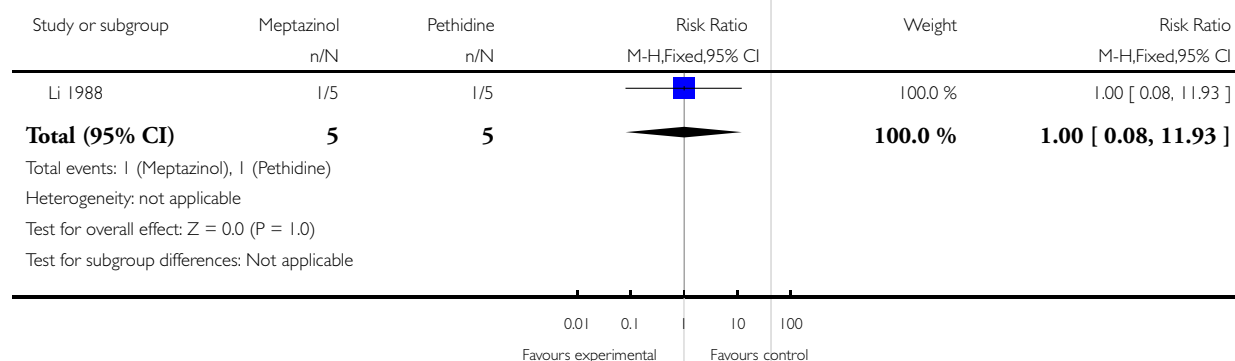
(1) SD in pethidine group as reported in published paper (extremely small)

Analysis 3.6. Comparison 3 PCA (IM) meptazinol versus PCA (IM) pethidine, Outcome 6 Naloxone administered.

Review: Parenteral opioids for maternal pain management in labour

Comparison: 3 PCA (IM) meptazinol versus PCA (IM) pethidine

Outcome: 6 Naloxone administered

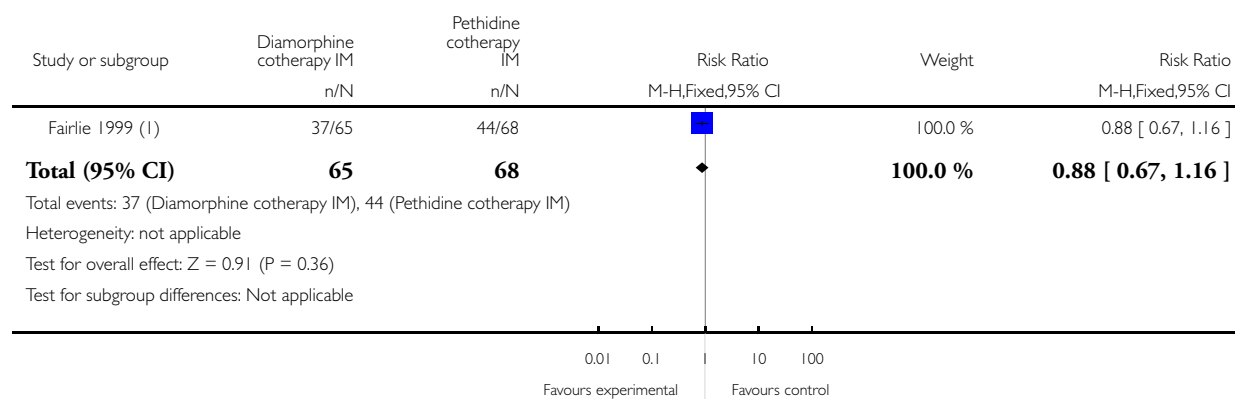


Analysis 4.1. Comparison 4 Diamorphine + prochloprerazine versus pethidine + prochloprerazine, Outcome 1 Global assessment of pain relief at 24 hours.

Review: Parenteral opioids for maternal pain management in labour

Comparison: 4 Diamorphine + prochloprerazine versus pethidine + prochloprerazine

Outcome: 1 Global assessment of pain relief at 24 hours



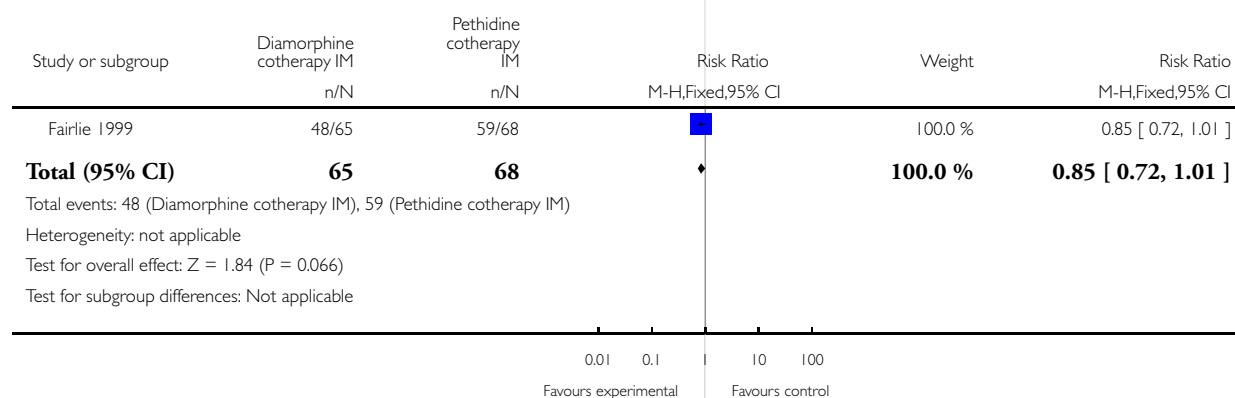
(1) Pain relief as rated as poor or fair

Analysis 4.2. Comparison 4 Diamorphine + prochloprerazine versus pethidine + prochloprerazine, Outcome 2 Pain intensity at 1 hour (moderate or severe).

Review: Parenteral opioids for maternal pain management in labour

Comparison: 4 Diamorphine + prochloprerazine versus pethidine + prochloprerazine

Outcome: 2 Pain intensity at 1 hour (moderate or severe)

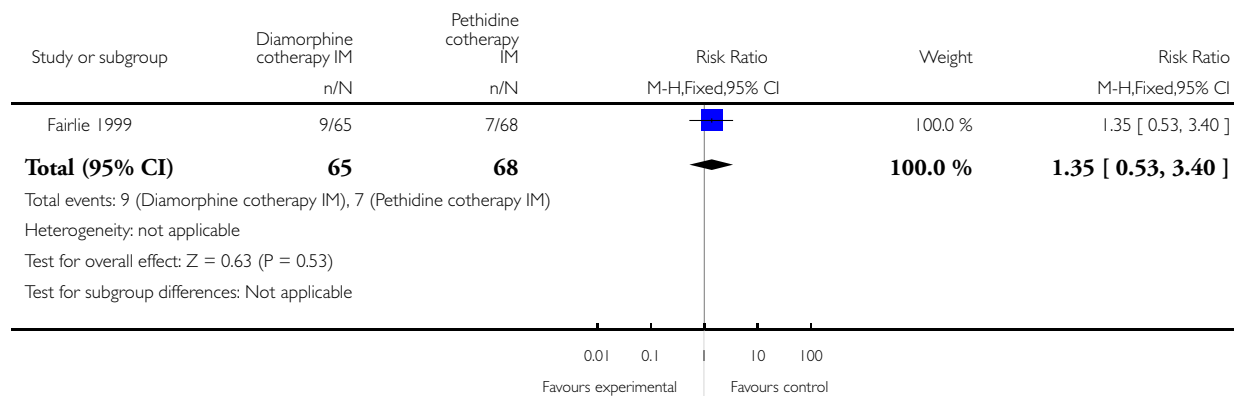


Analysis 4.3. Comparison 4 Diamorphine + prochloprerazine versus pethidine + prochloprerazine, Outcome 3 Additional analgesia required.

Review: Parenteral opioids for maternal pain management in labour

Comparison: 4 Diamorphine + prochloprerazine versus pethidine + prochloprerazine

Outcome: 3 Additional analgesia required

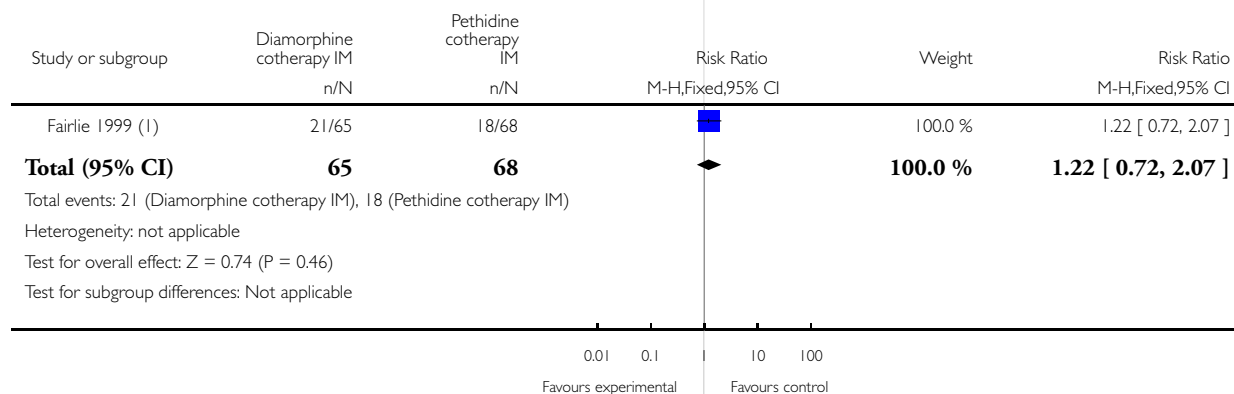


Analysis 4.4. Comparison 4 Diamorphine + prochloprerazine versus pethidine + prochloprerazine, Outcome 4 Epidural.

Review: Parenteral opioids for maternal pain management in labour

Comparison: 4 Diamorphine + prochloprerazine versus pethidine + prochloprerazine

Outcome: 4 Epidural



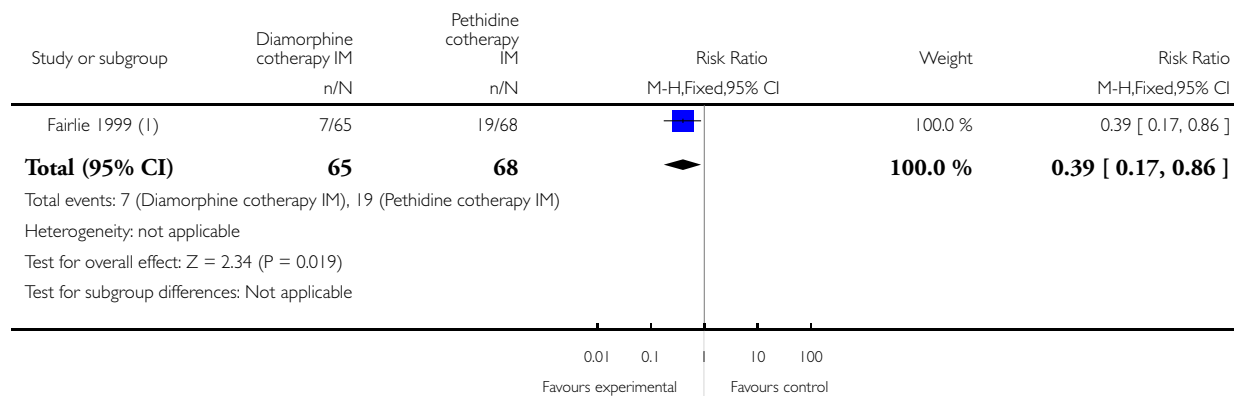
(1) 2nd dose of study drug

Analysis 4.5. Comparison 4 Diamorphine + prochloprerazine versus pethidine + prochloprerazine, Outcome 5 Vomiting.

Review: Parenteral opioids for maternal pain management in labour

Comparison: 4 Diamorphine + prochloprerazine versus pethidine + prochloprerazine

Outcome: 5 Vomiting



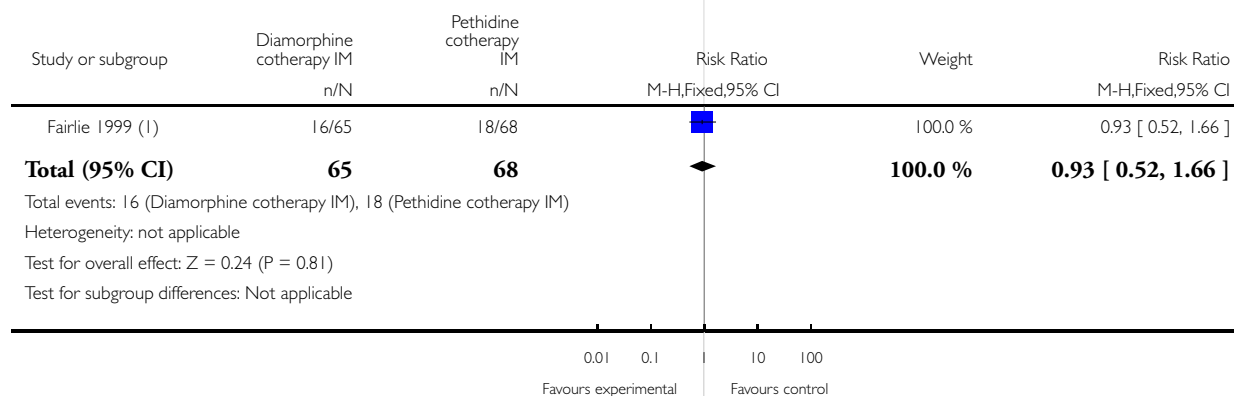
(1) 1 hour post-administration

Analysis 4.6. Comparison 4 Diamorphine + prochloprerazine versus pethidine + prochloprerazine, Outcome 6 Maternal sleepiness.

Review: Parenteral opioids for maternal pain management in labour

Comparison: 4 Diamorphine + prochloprerazine versus pethidine + prochloprerazine

Outcome: 6 Maternal sleepiness



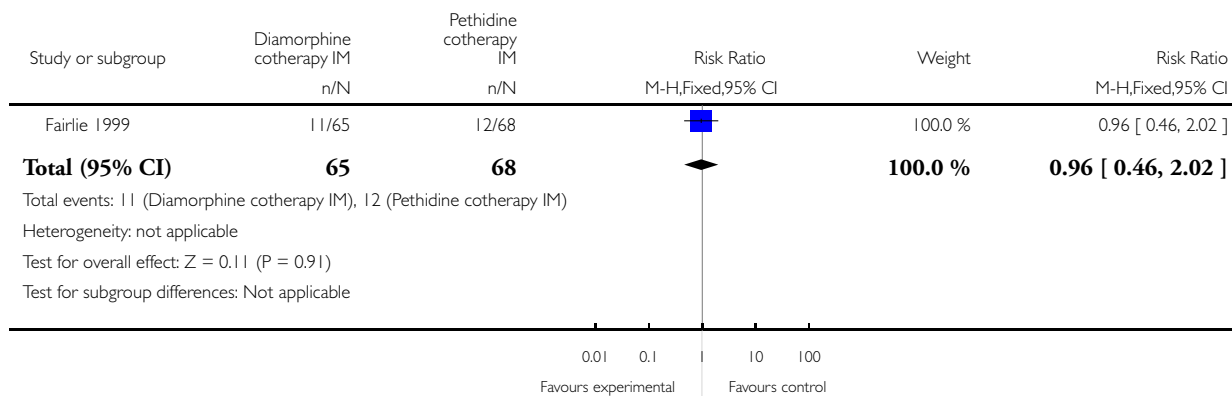
(1) Moderately drowsy or asleep at 60 minutes post-injection

Analysis 4.7. Comparison 4 Diamorphine + prochloprerazine versus pethidine + prochloprerazine, Outcome 7 Assisted vaginal delivery.

Review: Parenteral opioids for maternal pain management in labour

Comparison: 4 Diamorphine + prochloprerazine versus pethidine + prochloprerazine

Outcome: 7 Assisted vaginal delivery

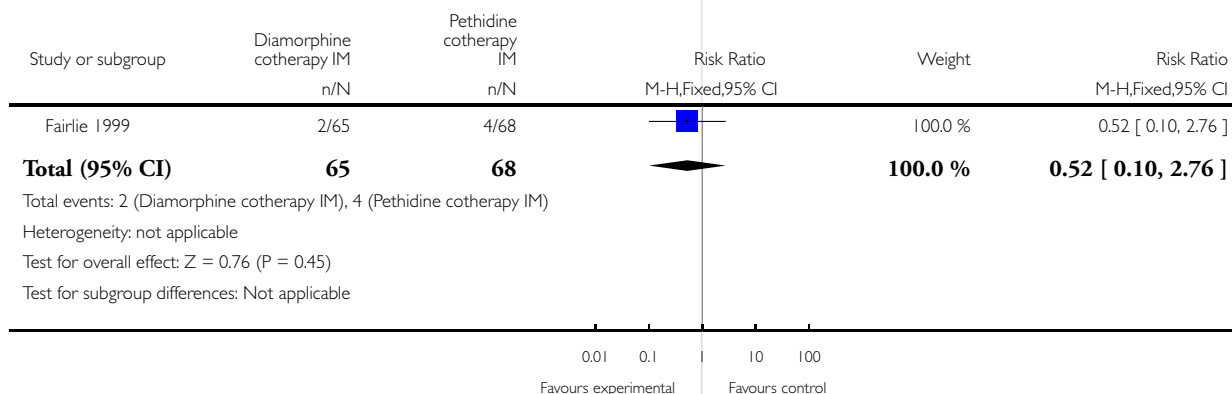


Analysis 4.8. Comparison 4 Diamorphine + prochloprerazine versus pethidine + prochloprerazine, Outcome 8 Caesarean section.

Review: Parenteral opioids for maternal pain management in labour

Comparison: 4 Diamorphine + prochloprerazine versus pethidine + prochloprerazine

Outcome: 8 Caesarean section

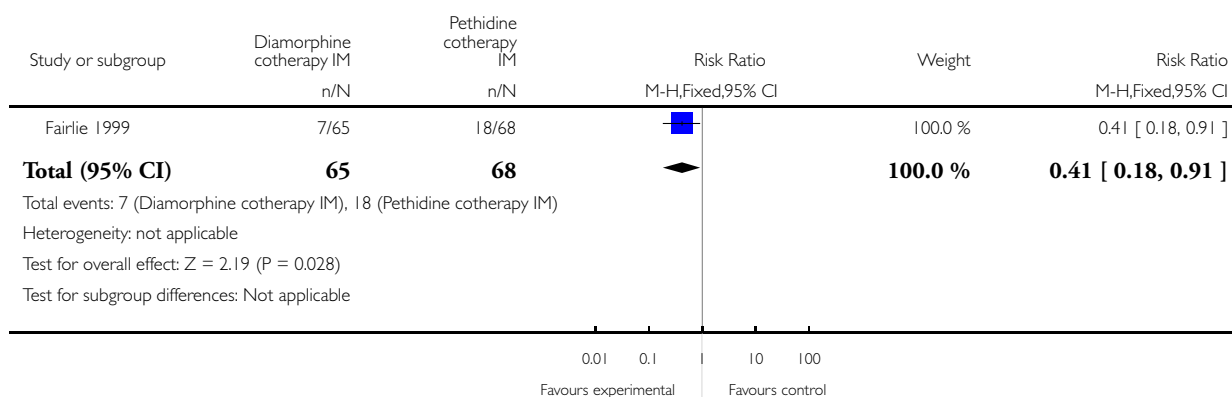


Analysis 4.9. Comparison 4 Diamorphine + prochloprerazine versus pethidine + prochloprerazine, Outcome 9 Apgar < 7 at 1 minute.

Review: Parenteral opioids for maternal pain management in labour

Comparison: 4 Diamorphine + prochloprerazine versus pethidine + prochloprerazine

Outcome: 9 Apgar < 7 at 1 minute

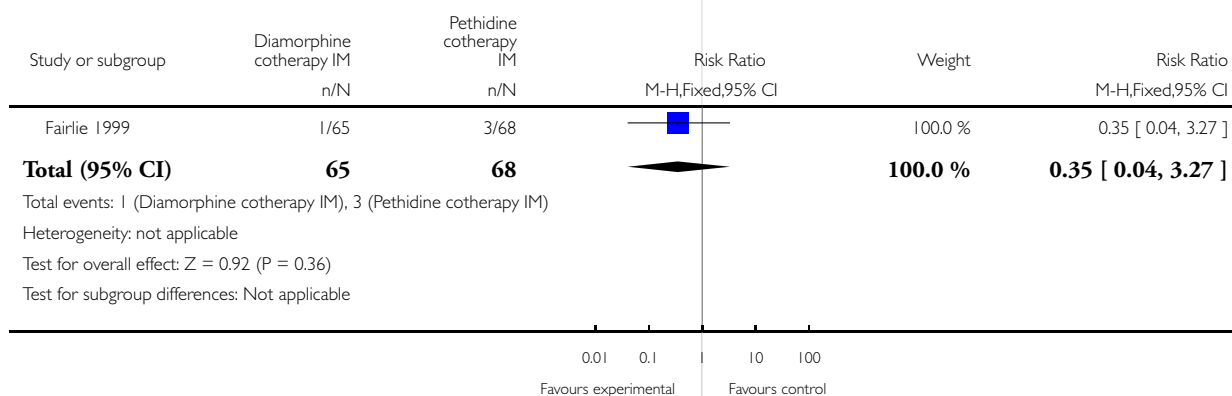


Analysis 4.10. Comparison 4 Diamorphine + prochloprerazine versus pethidine + prochloprerazine, Outcome 10 Apgar < 7 at 5 minutes.

Review: Parenteral opioids for maternal pain management in labour

Comparison: 4 Diamorphine + prochloprerazine versus pethidine + prochloprerazine

Outcome: 10 Apgar < 7 at 5 minutes

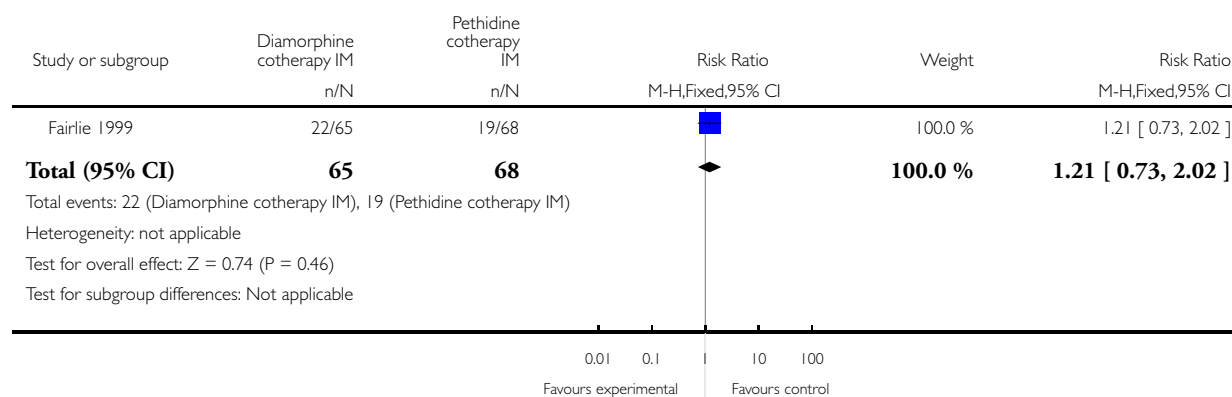


Analysis 4.11. Comparison 4 Diamorphine + prochloprerazine versus pethidine + prochloprerazine, Outcome 11 Neonatal resuscitation.

Review: Parenteral opioids for maternal pain management in labour

Comparison: 4 Diamorphine + prochloprerazine versus pethidine + prochloprerazine

Outcome: 11 Neonatal resuscitation

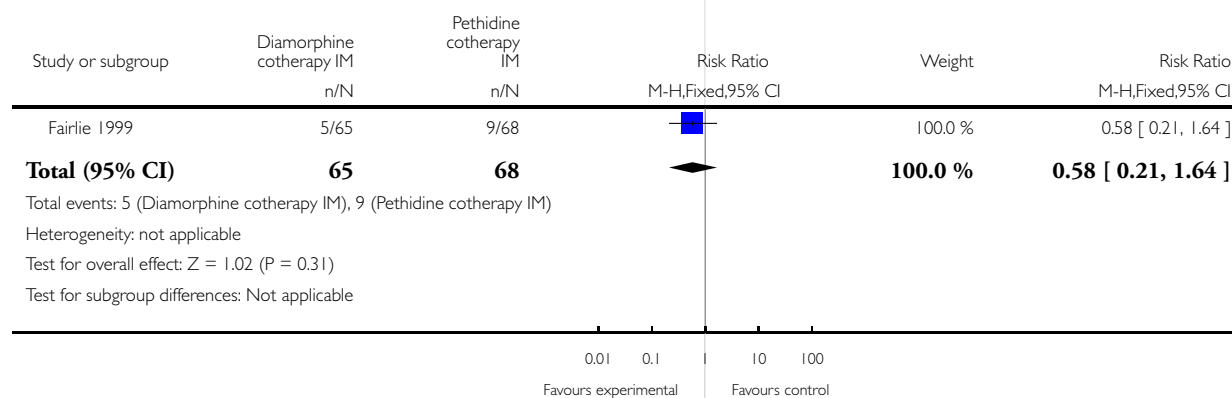


Analysis 4.12. Comparison 4 Diamorphine + prochloprerazine versus pethidine + prochloprerazine, Outcome 12 Admission to NICU.

Review: Parenteral opioids for maternal pain management in labour

Comparison: 4 Diamorphine + prochloprerazine versus pethidine + prochloprerazine

Outcome: 12 Admission to NICU

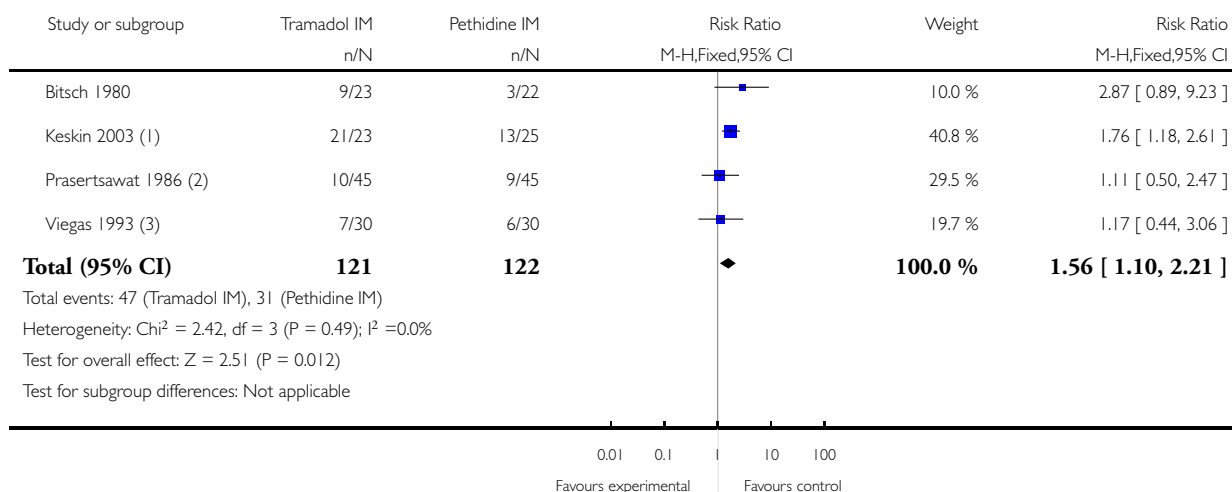


Analysis 5.1. Comparison 5 Tramadol versus pethidine, Outcome 1 Pain intensity: women with poor pain relief.

Review: Parenteral opioids for maternal pain management in labour

Comparison: 5 Tramadol versus pethidine

Outcome: 1 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.

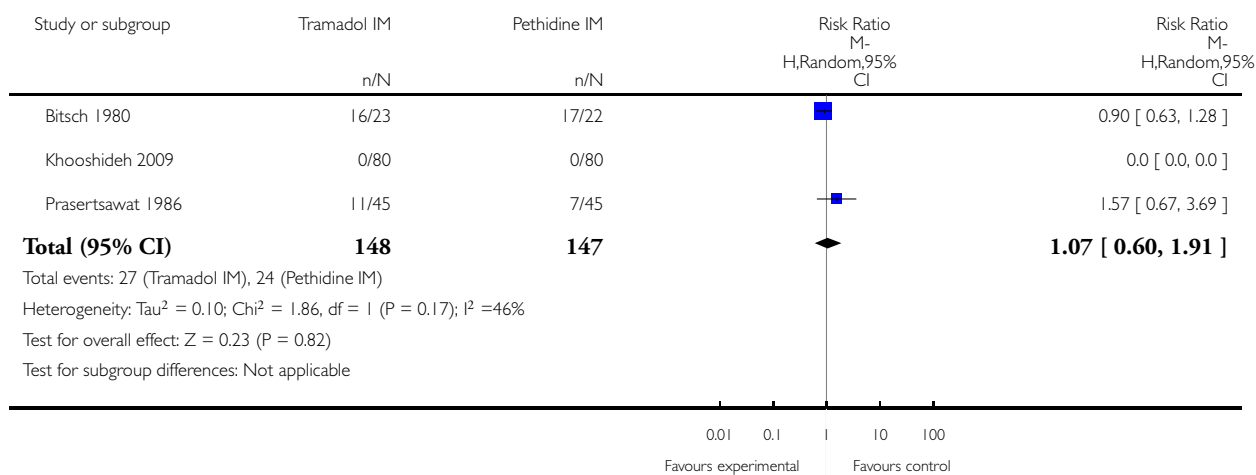
(3) Viegas none or insufficient relief

Analysis 5.2. Comparison 5 Tramadol versus pethidine, Outcome 2 Additional analgesia required.

Review: Parenteral opioids for maternal pain management in labour

Comparison: 5 Tramadol versus pethidine

Outcome: 2 Additional analgesia required

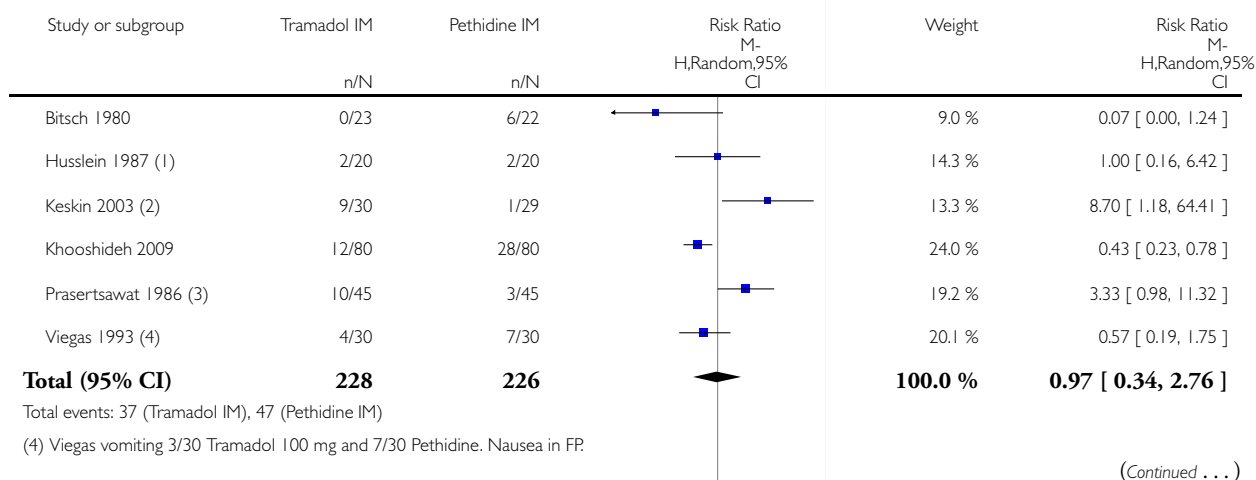


Analysis 5.3. Comparison 5 Tramadol versus pethidine, Outcome 3 Nausea and vomiting.

Review: Parenteral opioids for maternal pain management in labour

Comparison: 5 Tramadol versus pethidine

Outcome: 3 Nausea and vomiting



(... Continued)

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
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Heterogeneity: $\tau^2 = 1.09$; $\chi^2 = 17.89$, $df = 5$ ($P = 0.003$); $I^2 = 72\%$
 Test for overall effect: $Z = 0.06$ ($P = 0.95$)
 Test for subgroup differences: Not applicable

0.01 0.1 10 100
 Favours experimental Favours control

- (1) Husslein is nausea only or vomiting only as the data are identical
- (2) Keskin: nausea at 60 mins - vomiting 1 case in pethidine 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 5.4. Comparison 5 Tramadol versus pethidine, Outcome 4 Maternal sleepiness.

Review: Parenteral opioids for maternal pain management in labour

Comparison: 5 Tramadol versus pethidine

Outcome: 4 Maternal sleepiness

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
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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

0.01 0.1 10 100
 Favours experimental Favours control

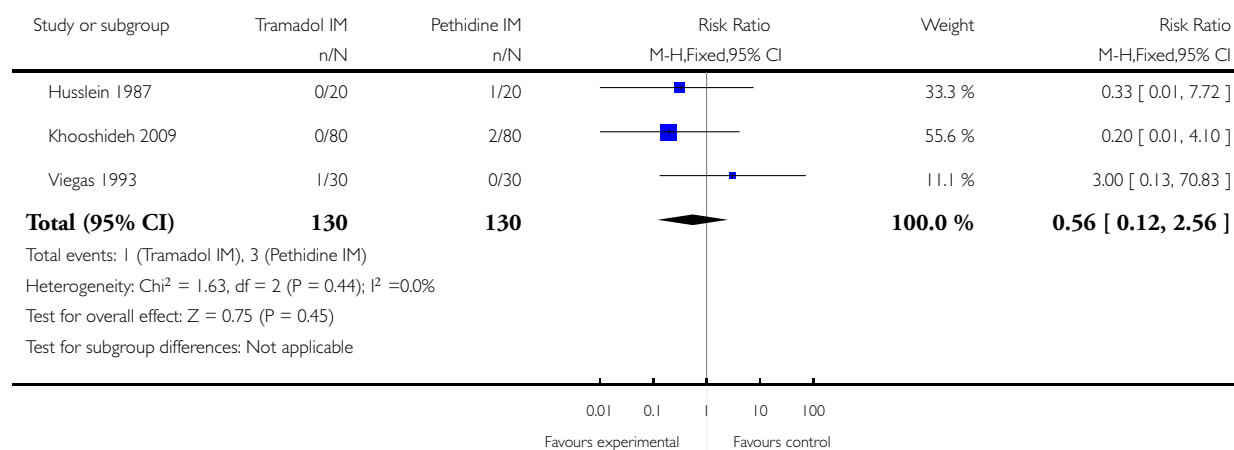
- (1) Keskin - assessed at 60 mins.

Analysis 5.5. Comparison 5 Tramadol versus pethidine, Outcome 5 Assisted vaginal delivery.

Review: Parenteral opioids for maternal pain management in labour

Comparison: 5 Tramadol versus pethidine

Outcome: 5 Assisted vaginal delivery

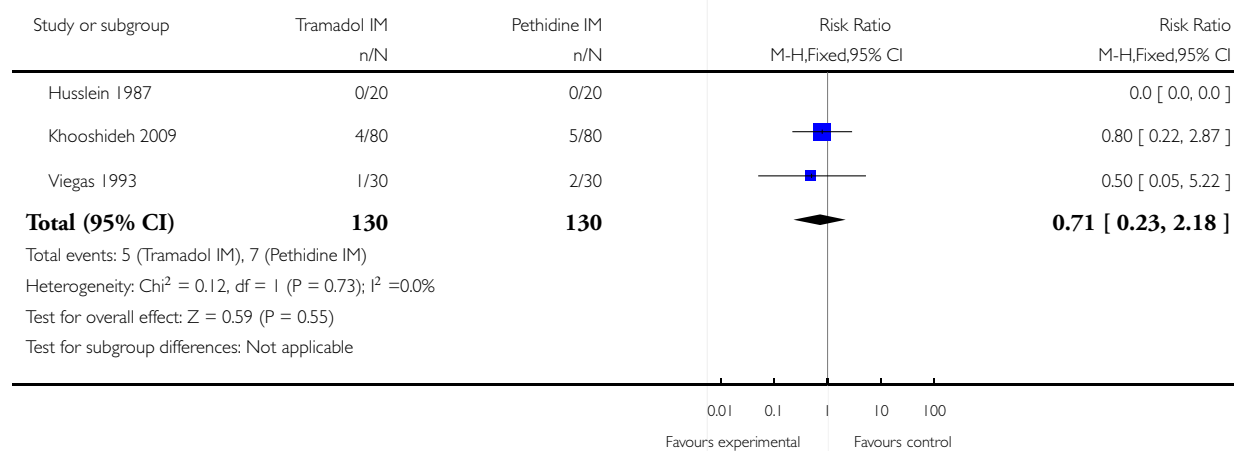


Analysis 5.6. Comparison 5 Tramadol versus pethidine, Outcome 6 Caesarean section.

Review: Parenteral opioids for maternal pain management in labour

Comparison: 5 Tramadol versus pethidine

Outcome: 6 Caesarean section



Analysis 5.7. Comparison 5 Tramadol versus pethidine, Outcome 7 Low Apgar scores (≤ 7) at 1 and 5 minutes.

Review: Parenteral opioids for maternal pain management in labour

Comparison: 5 Tramadol versus pethidine

Outcome: 7 Low 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	Risk Ratio M-H,Fixed,95% CI
1 Low scores at 1 minute				
Khooshideh 2009	0/80	0/80		0.0 [0.0, 0.0]
Prasertsawat 1986	0/45	0/45		0.0 [0.0, 0.0]
Subtotal (95% CI)	125	125		0.0 [0.0, 0.0]
Total events: 0 (Tramadol IM), 0 (Pethidine IM)				
Heterogeneity: Chi ² = 0.0, df = 0 (P<0.00001); I ² = 0.0%				
Test for overall effect: Z = 0.0 (P < 0.00001)				
2 Low scores at 5 minutes				
Khooshideh 2009	0/80	0/80		0.0 [0.0, 0.0]
Subtotal (95% CI)	80	80		0.0 [0.0, 0.0]
Total events: 0 (Tramadol IM), 0 (Pethidine IM)				
Heterogeneity: not applicable				
Test for overall effect: Z = 0.0 (P < 0.00001)				

0.01 0.1 | 10 100
Favours experimental Favours control

Analysis 5.8. Comparison 5 Tramadol versus pethidine, Outcome 8 Neonatal resuscitation.

Review: Parenteral opioids for maternal pain management in labour

Comparison: 5 Tramadol versus pethidine

Outcome: 8 Neonatal resuscitation

Study or subgroup	Tramadol IM n/N	Pethidine IM n/N	Risk Ratio M-H,Fixed,95% CI	Risk Ratio M-H,Fixed,95% CI
Prasertsawat 1986	0/45	0/45		0.0 [0.0, 0.0]
Total (95% CI)	45	45		0.0 [0.0, 0.0]
Total events: 0 (Tramadol IM), 0 (Pethidine IM)				
Heterogeneity: not applicable				
Test for overall effect: Z = 0.0 (P < 0.00001)				
Test for subgroup differences: Not applicable				

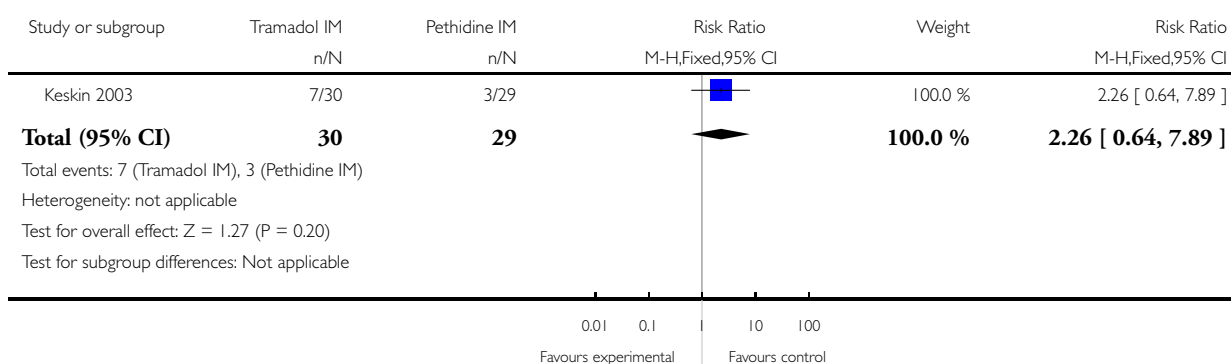
0.01 0.1 | 10 100
Favours experimental Favours control

Analysis 5.9. Comparison 5 Tramadol versus pethidine, Outcome 9 Neonatal respiratory distress.

Review: Parenteral opioids for maternal pain management in labour

Comparison: 5 Tramadol versus pethidine

Outcome: 9 Neonatal respiratory distress

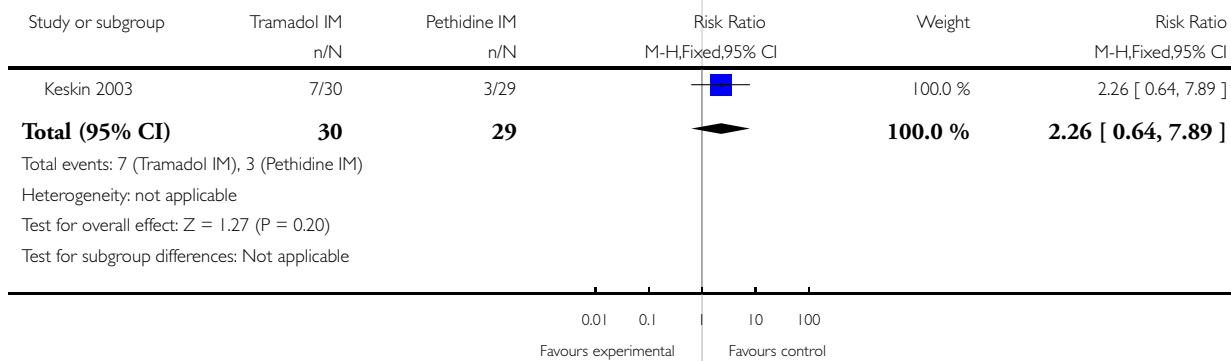


Analysis 5.10. Comparison 5 Tramadol versus pethidine, Outcome 10 Admission to NICU.

Review: Parenteral opioids for maternal pain management in labour

Comparison: 5 Tramadol versus pethidine

Outcome: 10 Admission to NICU

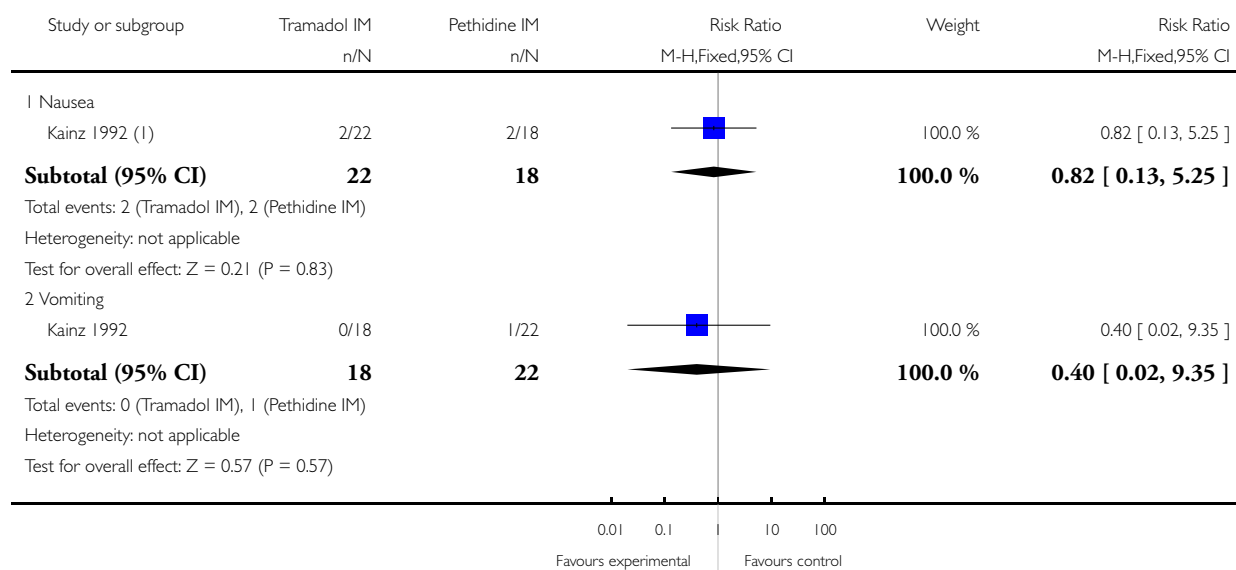


Analysis 6.1. Comparison 6 Tramadol + triflupromazine versus pethidine + triflupromazine, Outcome 1 Nausea and vomiting.

Review: Parenteral opioids for maternal pain management in labour

Comparison: 6 Tramadol + triflupromazine versus pethidine + triflupromazine

Outcome: 1 Nausea and vomiting



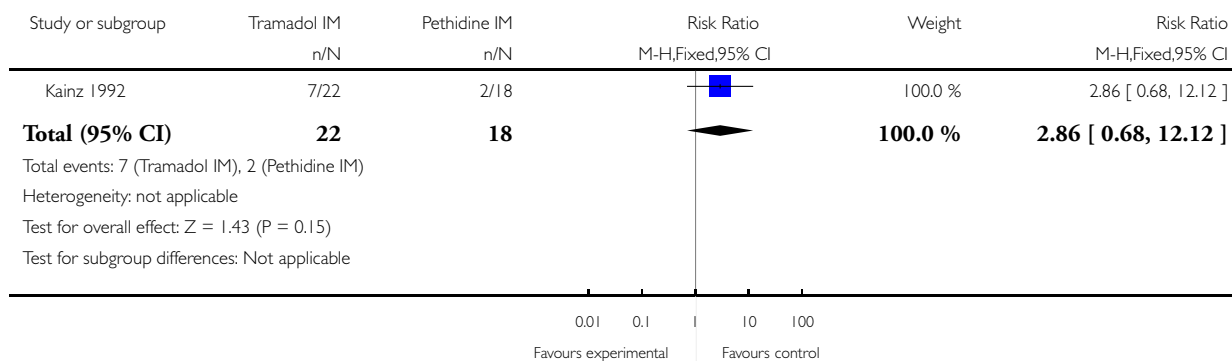
(1) assessment at 60 minutes

Analysis 6.2. Comparison 6 Tramadol + triflupromazine versus pethidine + triflupromazine, Outcome 2 Maternal sleepiness.

Review: Parenteral opioids for maternal pain management in labour

Comparison: 6 Tramadol + triflupromazine versus pethidine + triflupromazine

Outcome: 2 Maternal sleepiness

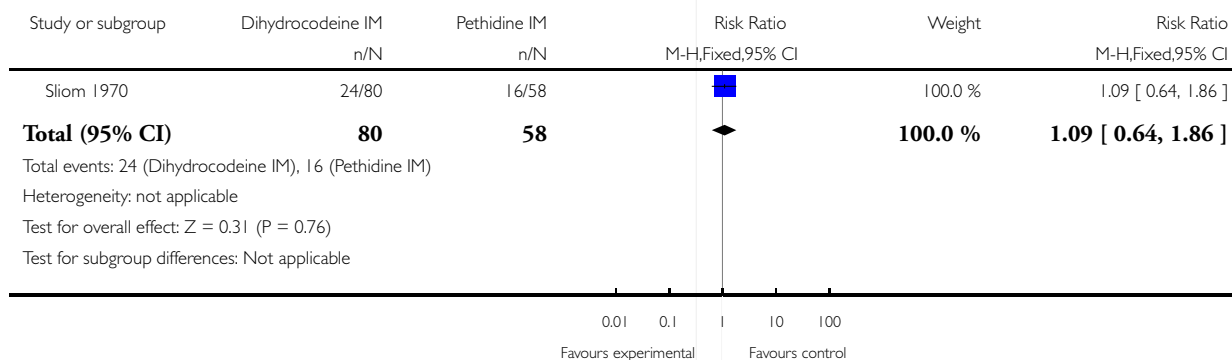


Analysis 7.1. Comparison 7 Dihydrocodeine 50 mg IM versus pethidine 100 mg IM, Outcome 1 Maternal pain relief poor (1 hour).

Review: Parenteral opioids for maternal pain management in labour

Comparison: 7 Dihydrocodeine 50 mg IM versus pethidine 100 mg IM

Outcome: 1 Maternal pain relief poor (1 hour)

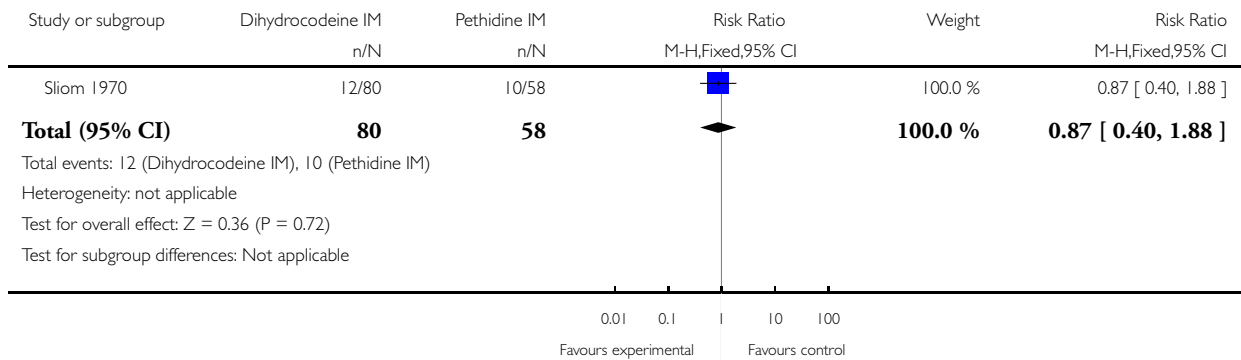


Analysis 7.2. Comparison 7 Dihydrocodeine 50 mg IM versus pethidine 100 mg IM, Outcome 2 Nausea and vomiting.

Review: Parenteral opioids for maternal pain management in labour

Comparison: 7 Dihydrocodeine 50 mg IM versus pethidine 100 mg IM

Outcome: 2 Nausea and vomiting

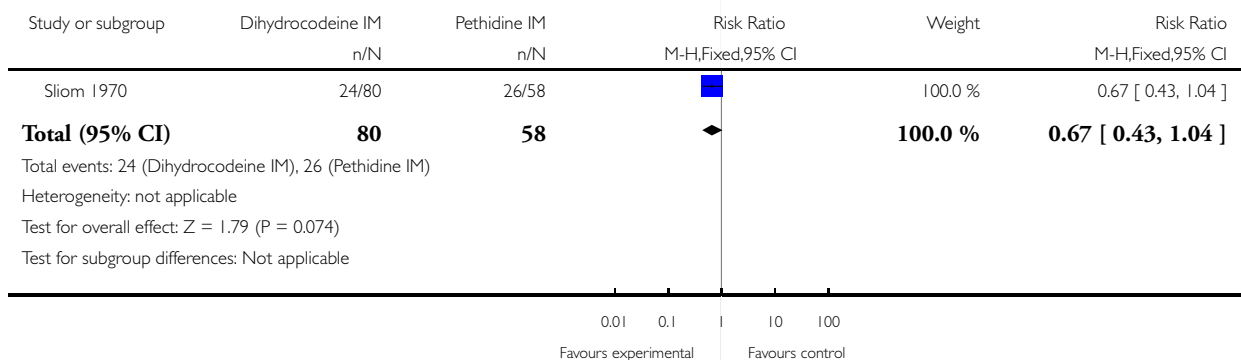


Analysis 7.3. Comparison 7 Dihydrocodeine 50 mg IM versus pethidine 100 mg IM, Outcome 3 Maternal sleepiness.

Review: Parenteral opioids for maternal pain management in labour

Comparison: 7 Dihydrocodeine 50 mg IM versus pethidine 100 mg IM

Outcome: 3 Maternal sleepiness

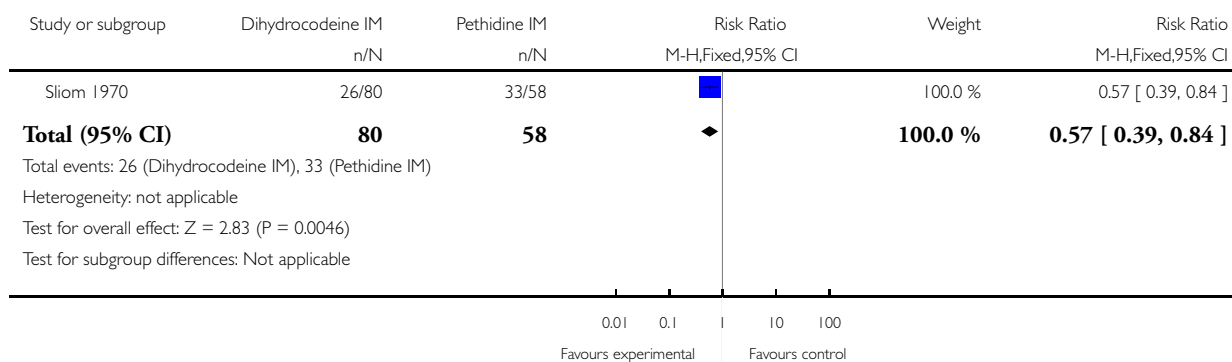


Analysis 7.4. Comparison 7 Dihydrocodeine 50 mg IM versus pethidine 100 mg IM, Outcome 4 Apgar \leq 7 at 1 minute.

Review: Parenteral opioids for maternal pain management in labour

Comparison: 7 Dihydrocodeine 50 mg IM versus pethidine 100 mg IM

Outcome: 4 Apgar \leq 7 at 1 minute

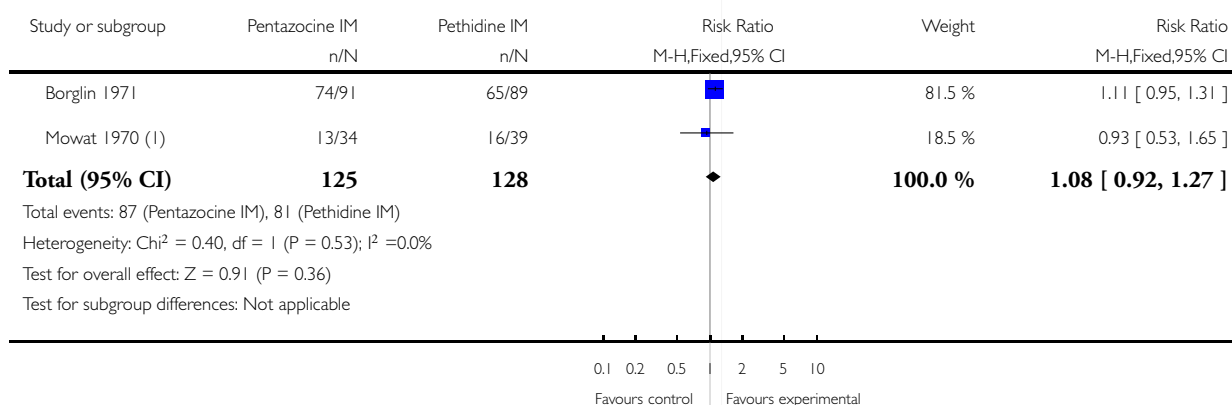


Analysis 8.1. Comparison 8 Pentazocine IM versus pethidine IM, Outcome 1 Pain relief (good or very good) at delivery.

Review: Parenteral opioids for maternal pain management in labour

Comparison: 8 Pentazocine IM versus pethidine IM

Outcome: 1 Pain relief (good or very good) at delivery



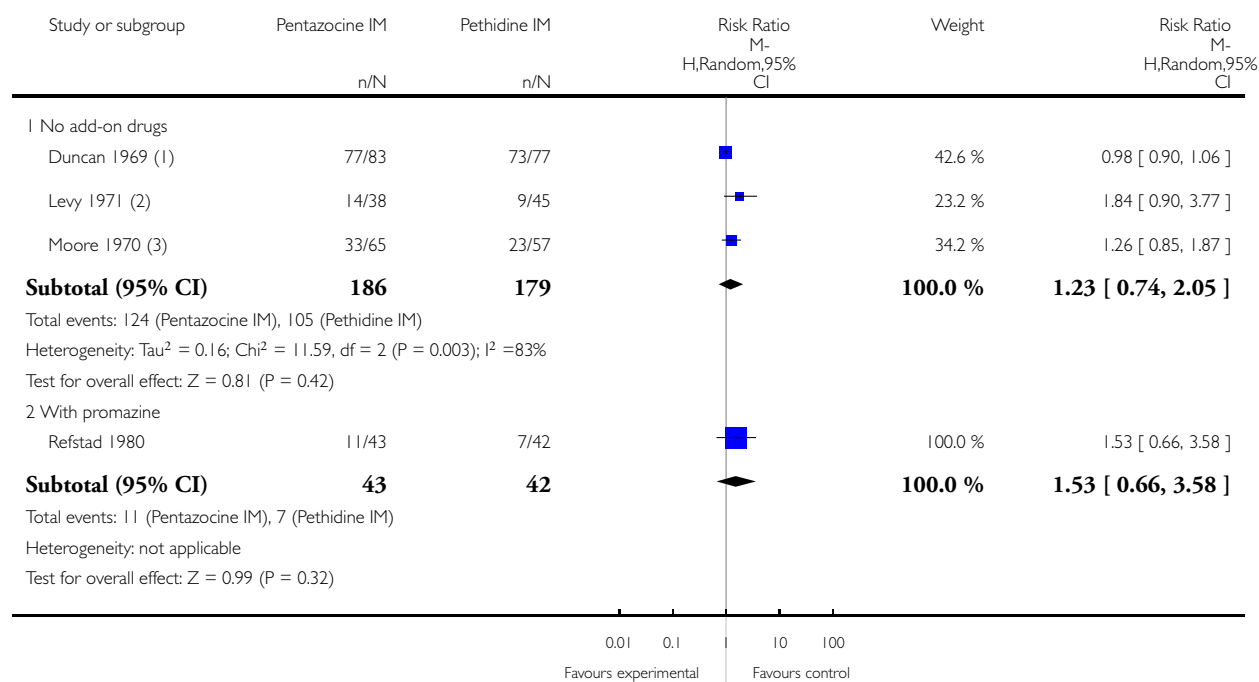
(1) Obtained relief after 1st injection.

Analysis 8.2. Comparison 8 Pentazocine IM versus pethidine IM, Outcome 2 Pain relief poor (partial, none or worse).

Review: Parenteral opioids for maternal pain management in labour

Comparison: 8 Pentazocine IM versus pethidine IM

Outcome: 2 Pain relief poor (partial, none or worse)



(1) After 1st injection only.

(2) Unclear when pain assessed but following first dose.

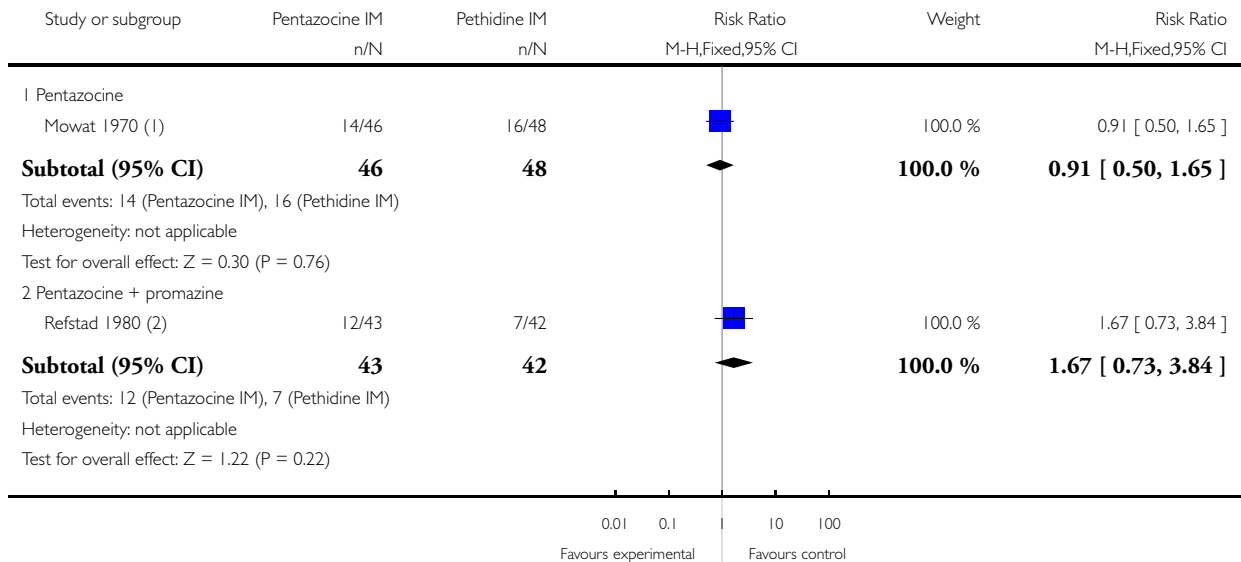
(3) Severe pain at 60 minutes.

Analysis 8.3. Comparison 8 Pentazocine IM versus pethidine IM, Outcome 3 Additional analgesia required.

Review: Parenteral opioids for maternal pain management in labour

Comparison: 8 Pentazocine IM versus pethidine IM

Outcome: 3 Additional analgesia required



(1) Additional doses of study drug.

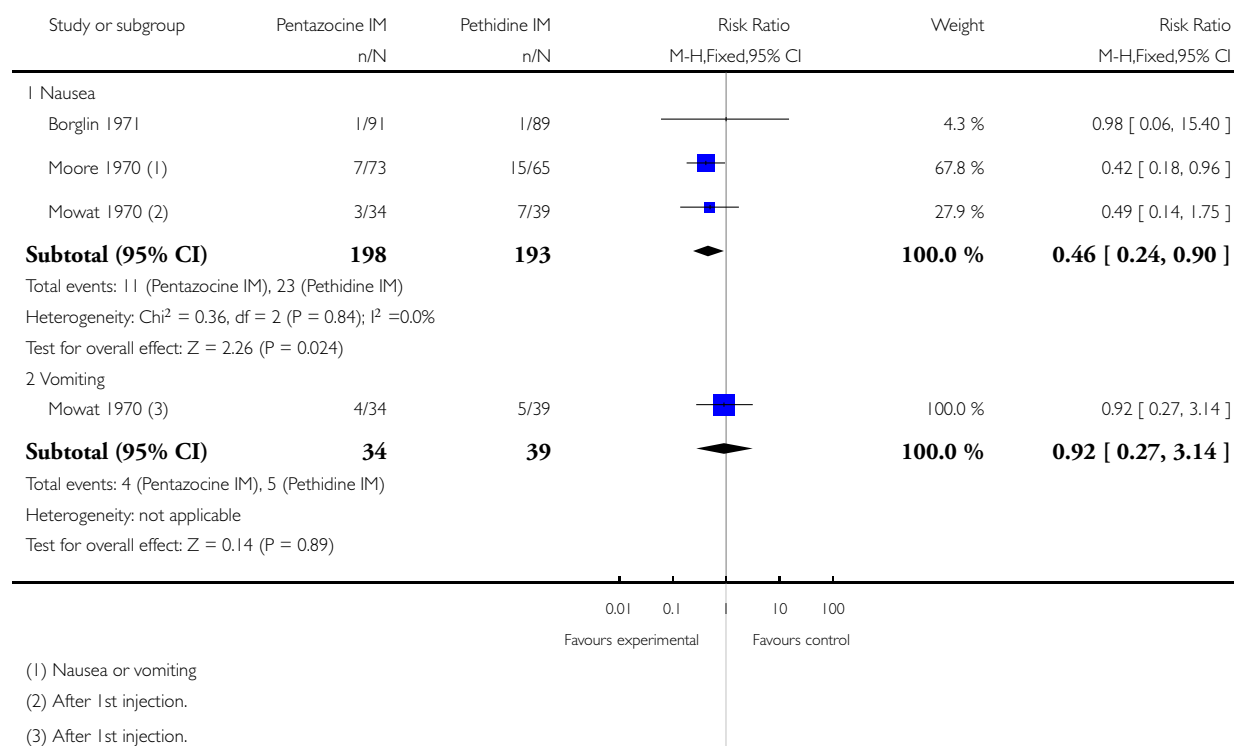
(2) 2nd dose of study drug

Analysis 8.4. Comparison 8 Pentazocine IM versus pethidine IM, Outcome 4 Nausea and vomiting.

Review: Parenteral opioids for maternal pain management in labour

Comparison: 8 Pentazocine IM versus pethidine IM

Outcome: 4 Nausea and vomiting

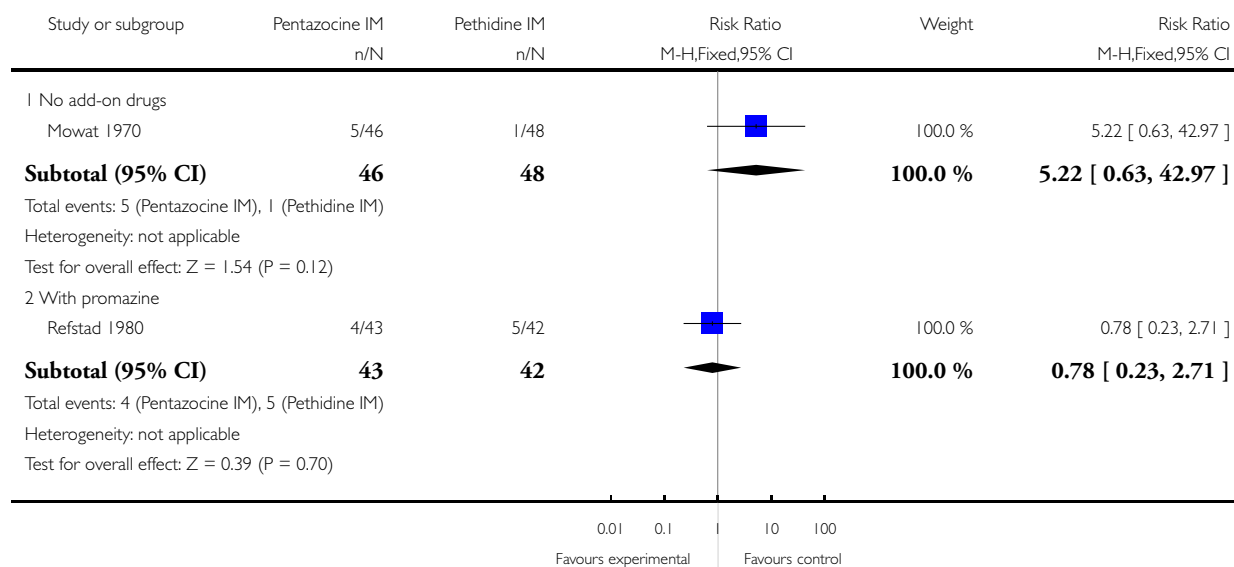


Analysis 8.5. Comparison 8 Pentazocine IM versus pethidine IM, Outcome 5 Assisted vaginal delivery.

Review: Parenteral opioids for maternal pain management in labour

Comparison: 8 Pentazocine IM versus pethidine IM

Outcome: 5 Assisted vaginal delivery

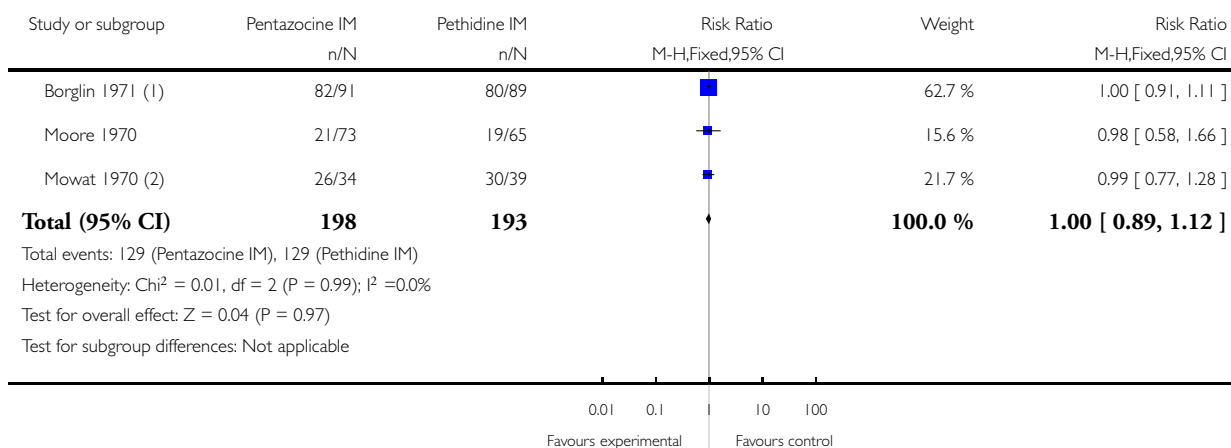


Analysis 8.6. Comparison 8 Pentazocine IM versus pethidine IM, Outcome 6 Maternal sleepiness.

Review: Parenteral opioids for maternal pain management in labour

Comparison: 8 Pentazocine IM versus pethidine IM

Outcome: 6 Maternal sleepiness



(1) Borglin 1971 - Sedating and relaxing effects

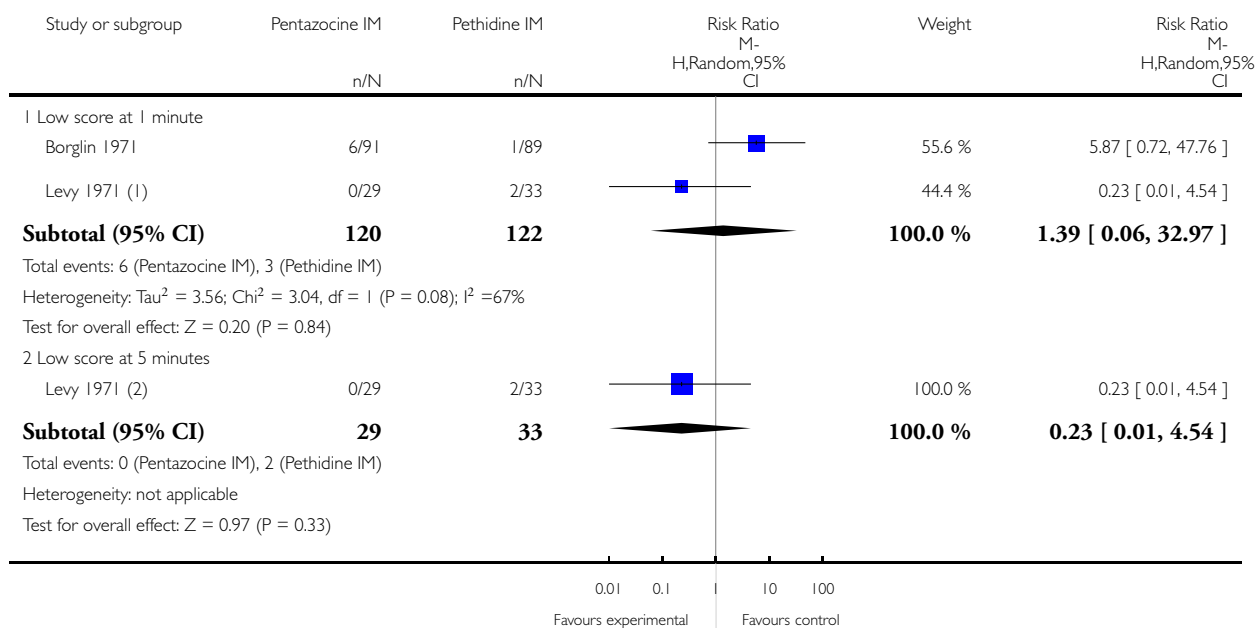
(2) After 1st injection

Analysis 8.7. Comparison 8 Pentazocine IM versus pethidine IM, Outcome 7 Low Apgar score (≤ 7) at 1 and 5 minutes.

Review: Parenteral opioids for maternal pain management in labour

Comparison: 8 Pentazocine IM versus pethidine IM

Outcome: 7 Low Apgar score (≤ 7) at 1 and 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

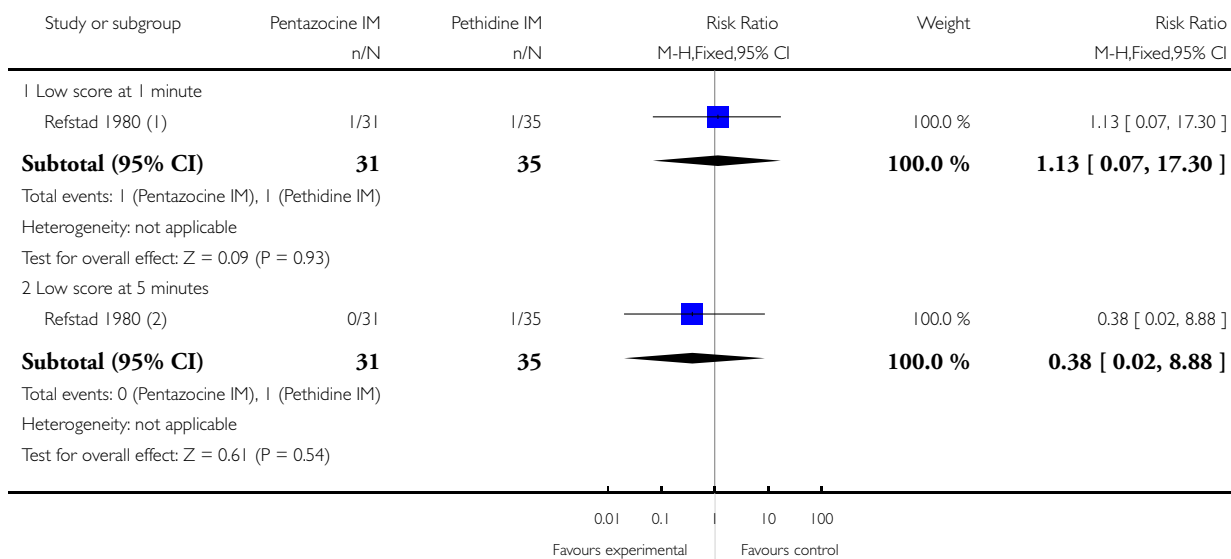
(2) Apgar is for babies that had 1 dose only and does not include data for 1st dose of women who had 2 doses

Analysis 9.1. Comparison 9 Pentazocine + promazine versus pethidine + promazine, Outcome 1 Low Apgar score (≤ 7) at 1 and 5 minutes (with promazine).

Review: Parenteral opioids for maternal pain management in labour

Comparison: 9 Pentazocine + promazine versus pethidine + promazine

Outcome: 1 Low Apgar score (≤ 7) at 1 and 5 minutes (with promazine)



(1) After 1 dose only

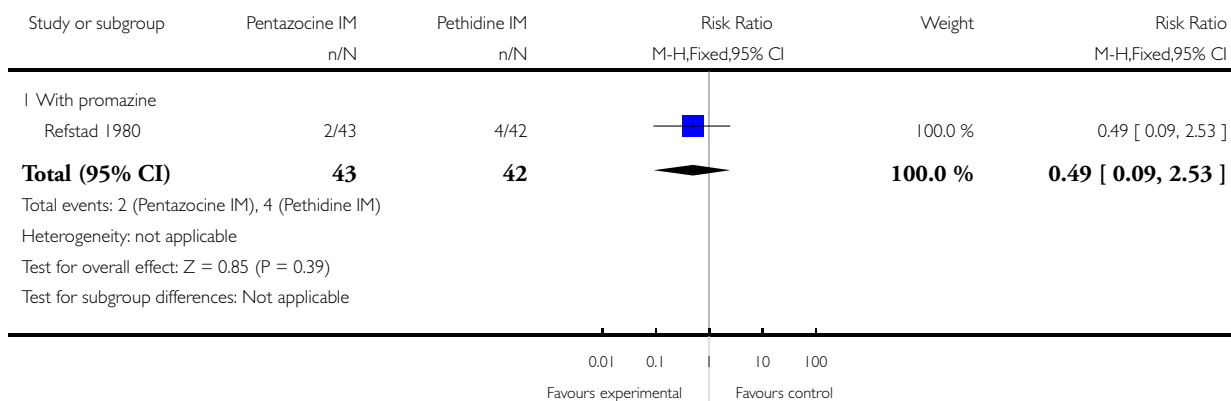
(2) After 1st dose only

Analysis 9.2. Comparison 9 Pentazocine + promazine versus pethidine + promazine, Outcome 2 Naloxone administration (neonatal).

Review: Parenteral opioids for maternal pain management in labour

Comparison: 9 Pentazocine + promazine versus pethidine + promazine

Outcome: 2 Naloxone administration (neonatal)

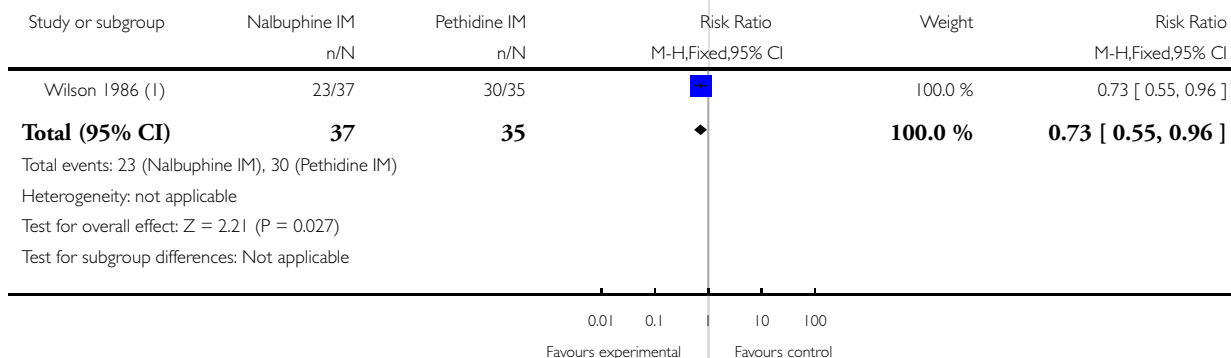


Analysis 10.1. Comparison 10 Nalbuphine versus pethidine, Outcome 1 Maternal satisfaction with analgesia at 24 hours; numbers dissatisfied.

Review: Parenteral opioids for maternal pain management in labour

Comparison: 10 Nalbuphine versus pethidine

Outcome: 1 Maternal satisfaction with analgesia at 24 hours; numbers dissatisfied



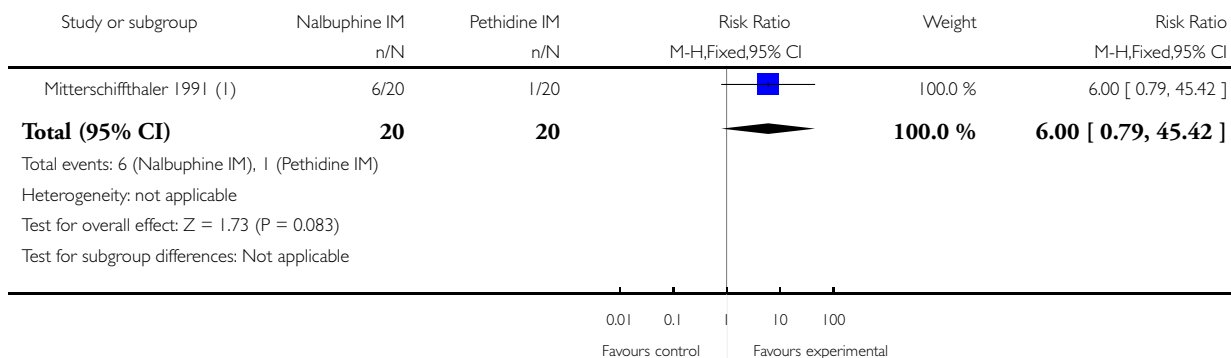
(1) Rated as minimally effective.

Analysis 10.2. Comparison 10 Nalbuphine versus pethidine, Outcome 2 Pain free.

Review: Parenteral opioids for maternal pain management in labour

Comparison: 10 Nalbuphine versus pethidine

Outcome: 2 Pain free



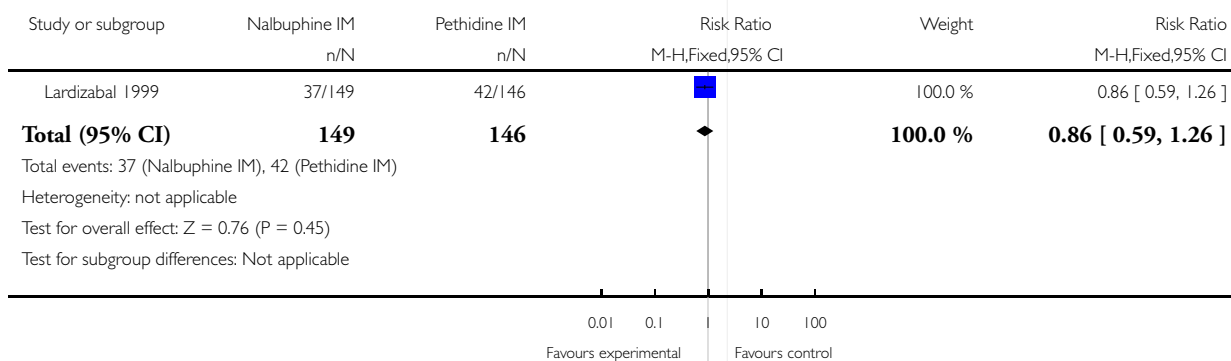
(1) Unclear when pain assessed

Analysis 10.3. Comparison 10 Nalbuphine versus pethidine, Outcome 3 Pain intensity at 30 minutes: women with severe pain.

Review: Parenteral opioids for maternal pain management in labour

Comparison: 10 Nalbuphine versus pethidine

Outcome: 3 Pain intensity at 30 minutes: women with severe pain

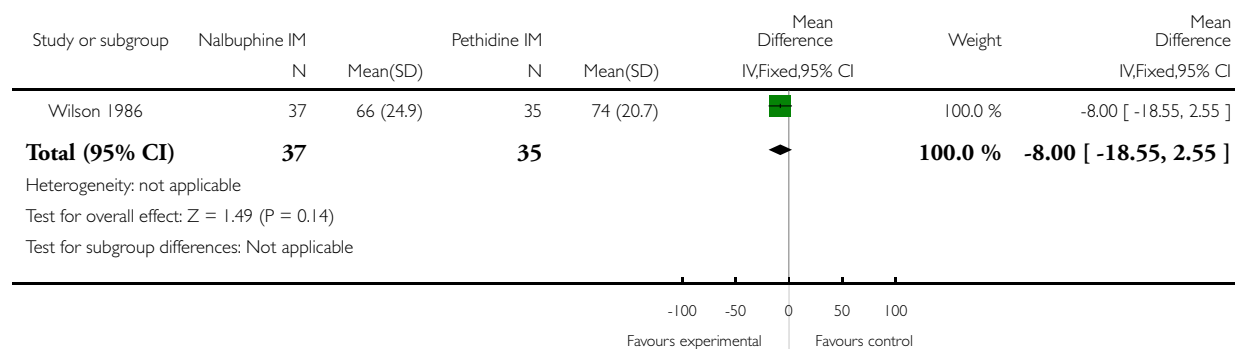


Analysis 10.4. Comparison 10 Nalbuphine versus pethidine, Outcome 4 VAS at 60 minutes (at peak of contraction).

Review: Parenteral opioids for maternal pain management in labour

Comparison: 10 Nalbuphine versus pethidine

Outcome: 4 VAS at 60 minutes (at peak of contraction)

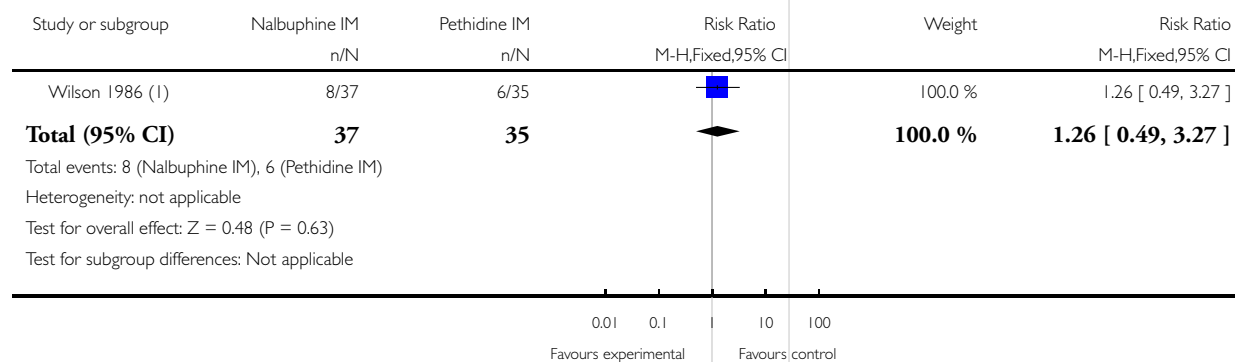


Analysis 10.5. Comparison 10 Nalbuphine versus pethidine, Outcome 5 Additional analgesia required.

Review: Parenteral opioids for maternal pain management in labour

Comparison: 10 Nalbuphine versus pethidine

Outcome: 5 Additional analgesia required



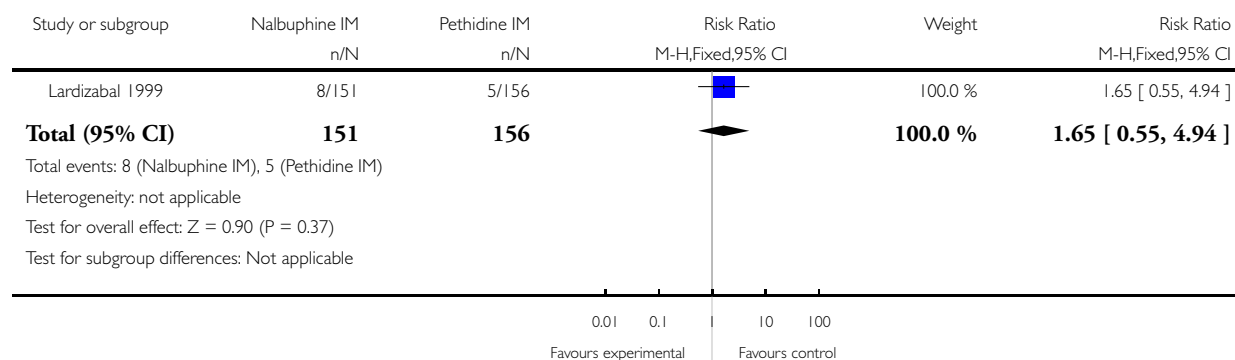
(1) 2nd dose of study drug

Analysis 10.6. Comparison 10 Nalbuphine versus pethidine, Outcome 6 Epidural.

Review: Parenteral opioids for maternal pain management in labour

Comparison: 10 Nalbuphine versus pethidine

Outcome: 6 Epidural

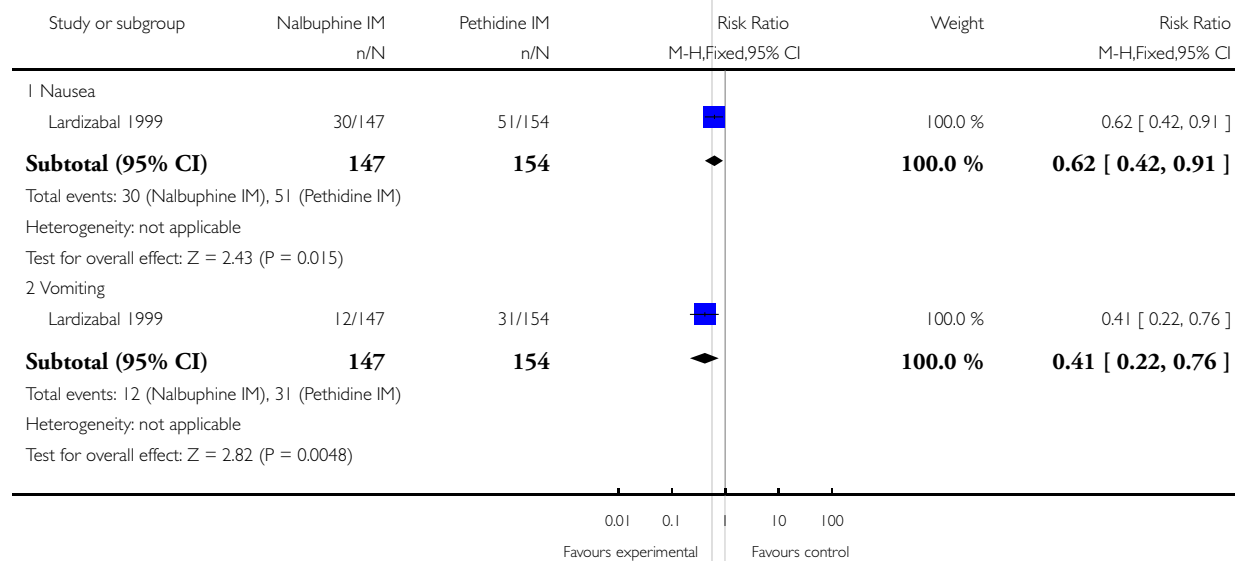


Analysis 10.7. Comparison 10 Nalbuphine versus pethidine, Outcome 7 Nausea and vomiting.

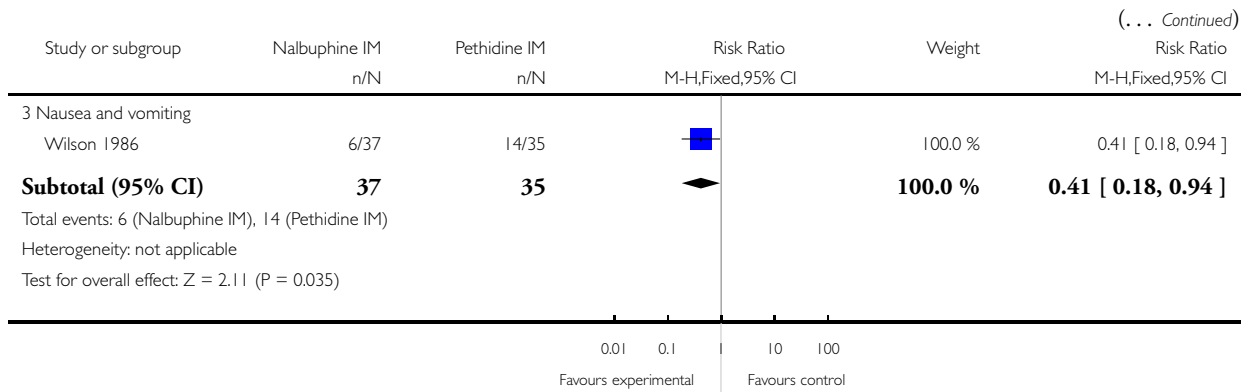
Review: Parenteral opioids for maternal pain management in labour

Comparison: 10 Nalbuphine versus pethidine

Outcome: 7 Nausea and vomiting



(Continued . . .)

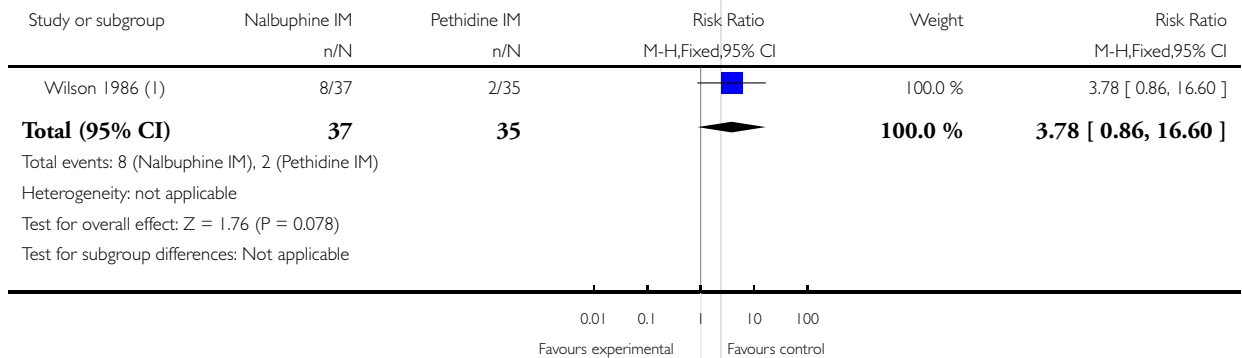


Analysis 10.8. Comparison 10 Nalbuphine versus pethidine, Outcome 8 Maternal sleepiness.

Review: Parenteral opioids for maternal pain management in labour

Comparison: 10 Nalbuphine versus pethidine

Outcome: 8 Maternal sleepiness



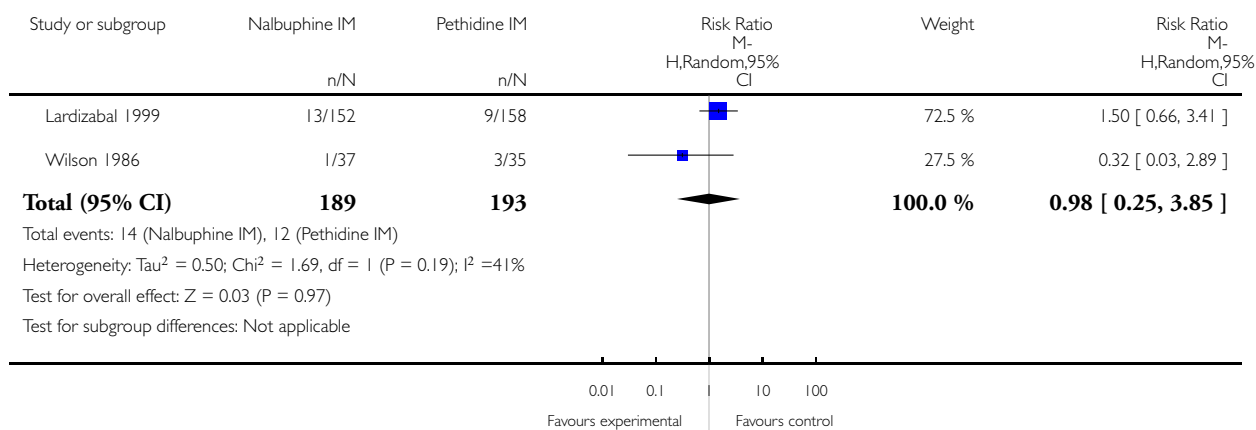
(1) Excessive sedation

Analysis 10.9. Comparison 10 Nalbuphine versus pethidine, Outcome 9 Assisted vaginal delivery.

Review: Parenteral opioids for maternal pain management in labour

Comparison: 10 Nalbuphine versus pethidine

Outcome: 9 Assisted vaginal delivery

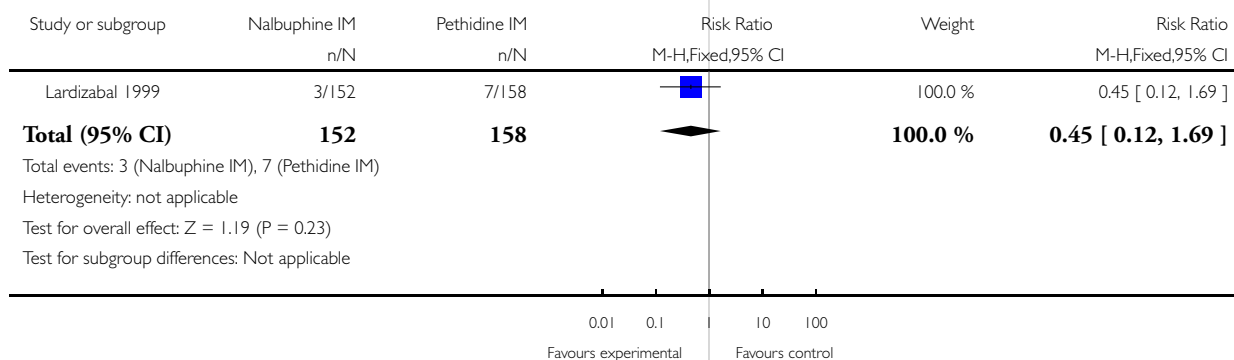


Analysis 10.10. Comparison 10 Nalbuphine versus pethidine, Outcome 10 Caesarean section.

Review: Parenteral opioids for maternal pain management in labour

Comparison: 10 Nalbuphine versus pethidine

Outcome: 10 Caesarean section

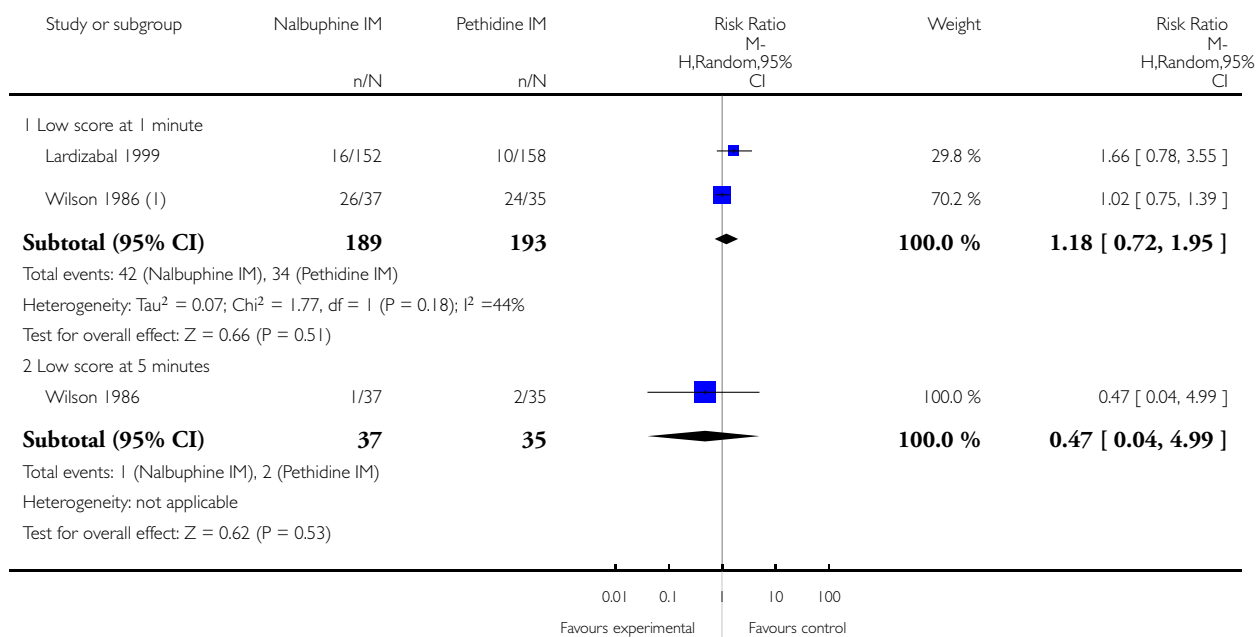


Analysis 10.11. Comparison 10 Nalbuphine versus pethidine, Outcome 11 Low Apgar score (≤ 7) at 1 and 5 minutes.

Review: Parenteral opioids for maternal pain management in labour

Comparison: 10 Nalbuphine versus pethidine

Outcome: 11 Low Apgar score (≤ 7) at 1 and 5 minutes



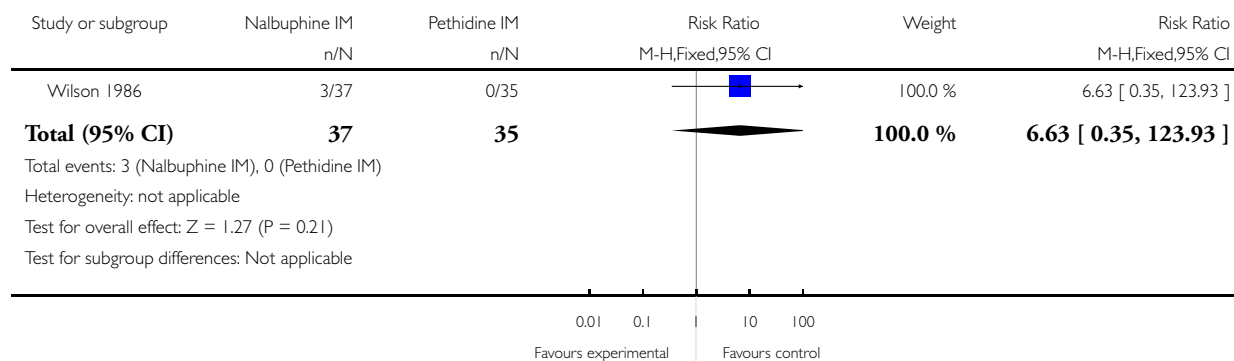
(1) Apgar modified: minus colour score

Analysis 10.12. Comparison 10 Nalbuphine versus pethidine, Outcome 12 Naloxone administration (neonatal).

Review: Parenteral opioids for maternal pain management in labour

Comparison: 10 Nalbuphine versus pethidine

Outcome: 12 Naloxone administration (neonatal)

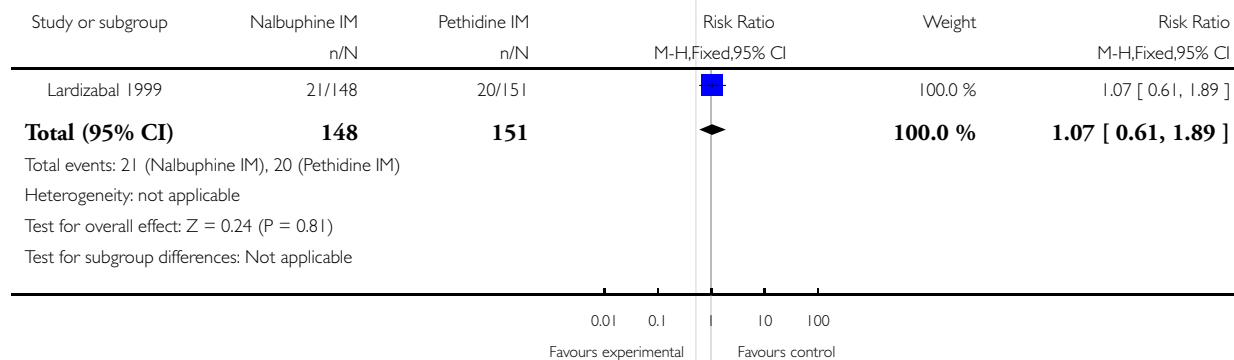


Analysis 10.13. Comparison 10 Nalbuphine versus pethidine, Outcome 13 Admission to NICU.

Review: Parenteral opioids for maternal pain management in labour

Comparison: 10 Nalbuphine versus pethidine

Outcome: 13 Admission to NICU

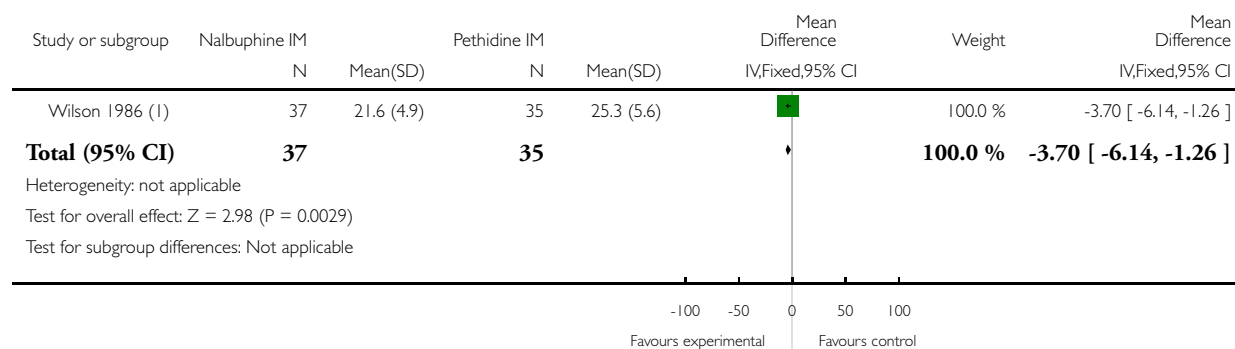


Analysis 10.14. Comparison 10 Nalbuphine versus pethidine, Outcome 14 Neonatal neurobehavioural (Scanlon) 2-4 hours PN.

Review: Parenteral opioids for maternal pain management in labour

Comparison: 10 Nalbuphine versus pethidine

Outcome: 14 Neonatal neurobehavioural (Scanlon) 2-4 hours PN



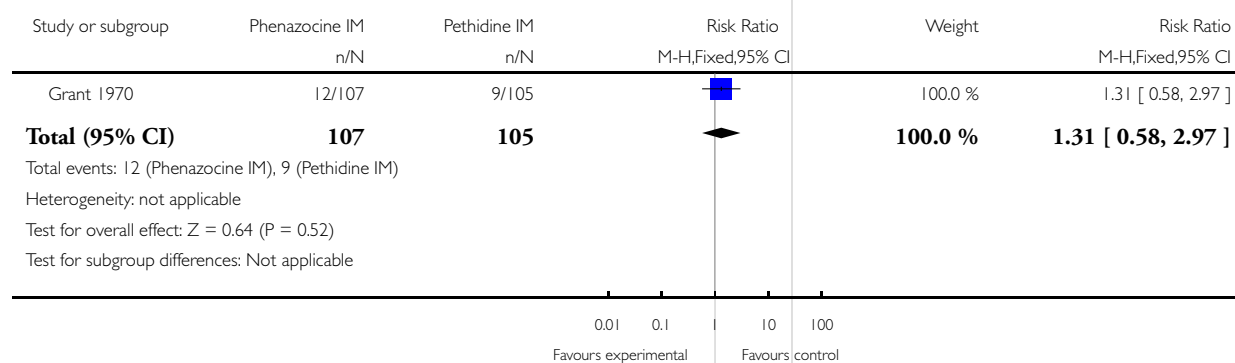
(1) Lower scores on Scanlon scale = poorer outcome

Analysis 11.1. Comparison 11 Phenazocine versus pethidine, Outcome 1 Epidural.

Review: Parenteral opioids for maternal pain management in labour

Comparison: 11 Phenazocine versus pethidine

Outcome: 1 Epidural

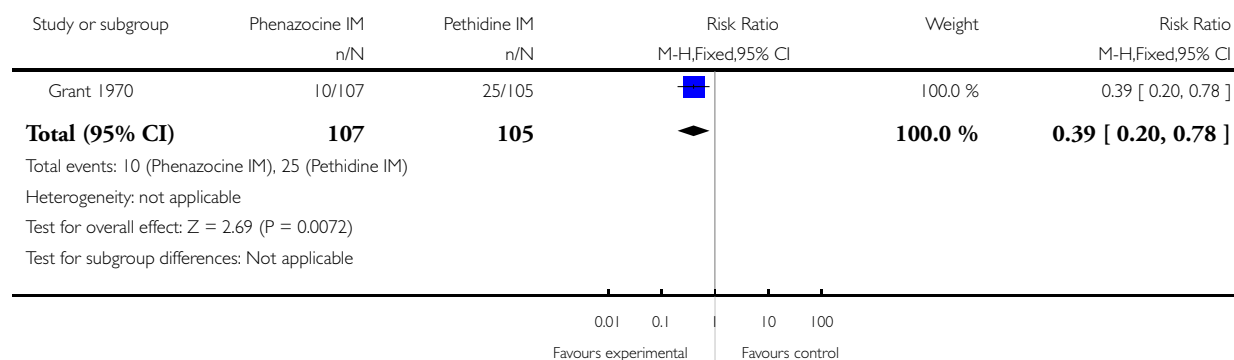


Analysis 11.2. Comparison 11 Phenazocine versus pethidine, Outcome 2 Vomiting.

Review: Parenteral opioids for maternal pain management in labour

Comparison: 11 Phenazocine versus pethidine

Outcome: 2 Vomiting

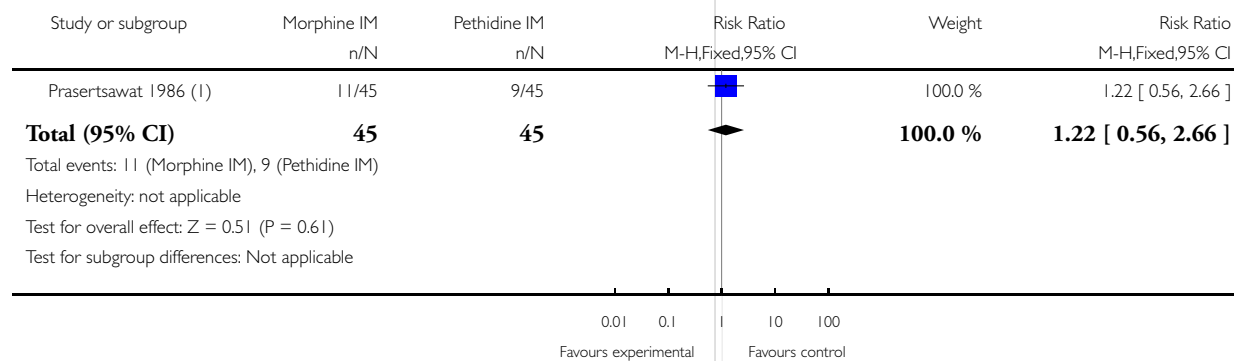


Analysis 12.1. Comparison 12 Morphine versus pethidine, Outcome 1 Pain relief described as poor.

Review: Parenteral opioids for maternal pain management in labour

Comparison: 12 Morphine versus pethidine

Outcome: 1 Pain relief described as poor



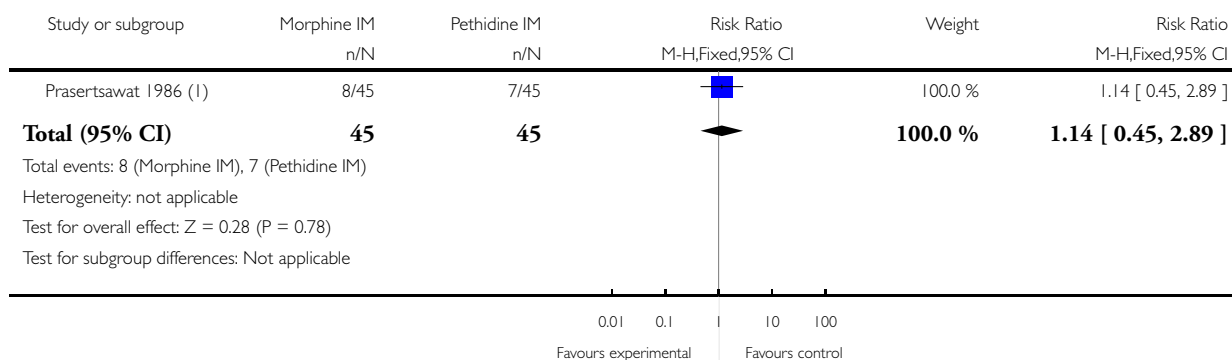
(1) Poor response after 1st dose.

Analysis 12.2. Comparison 12 Morphine versus pethidine, Outcome 2 Additional analgesia required.

Review: Parenteral opioids for maternal pain management in labour

Comparison: 12 Morphine versus pethidine

Outcome: 2 Additional analgesia required



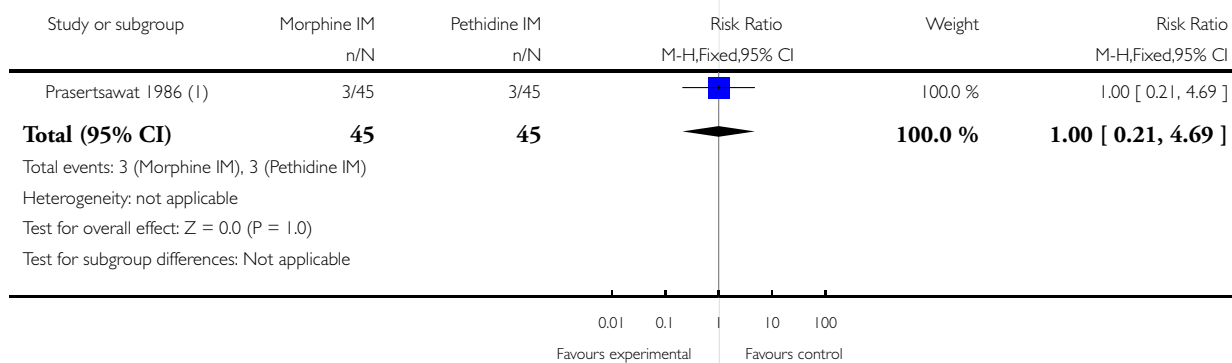
(1) 2nd dose of study drug but half initial amount

Analysis 12.3. Comparison 12 Morphine versus pethidine, Outcome 3 Nausea and vomiting.

Review: Parenteral opioids for maternal pain management in labour

Comparison: 12 Morphine versus pethidine

Outcome: 3 Nausea and vomiting



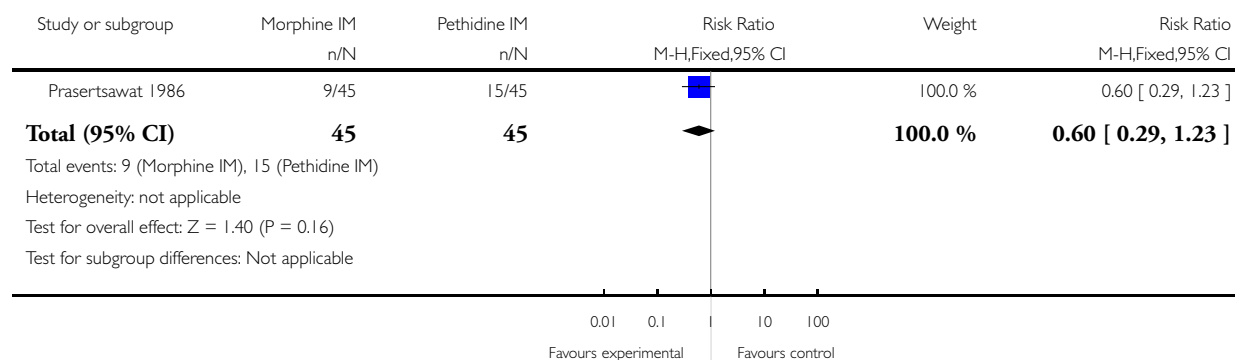
(1) Prasertsawat nausea - vomiting in 1/45 morphine and 2/45 pethidine.

Analysis 12.4. Comparison 12 Morphine versus pethidine, Outcome 4 Maternal sleepiness.

Review: Parenteral opioids for maternal pain management in labour

Comparison: 12 Morphine versus pethidine

Outcome: 4 Maternal sleepiness

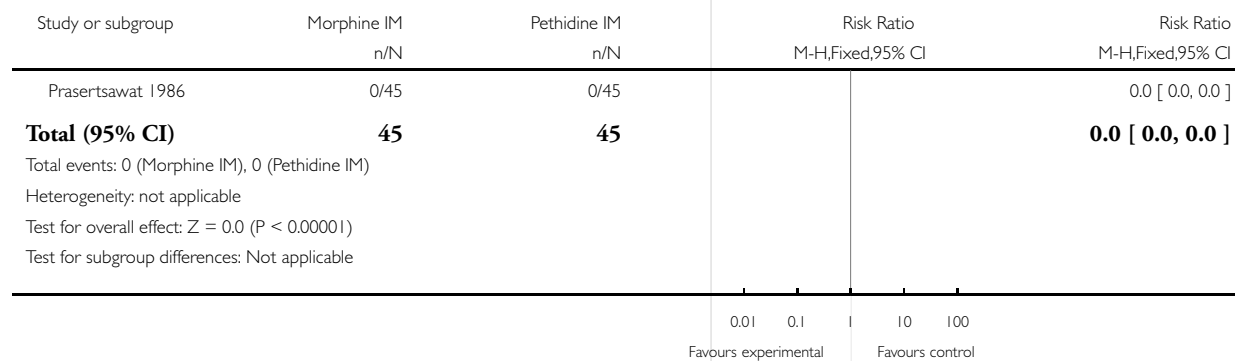


Analysis 12.5. Comparison 12 Morphine versus pethidine, Outcome 5 Apgar < 7 at 1 minute.

Review: Parenteral opioids for maternal pain management in labour

Comparison: 12 Morphine versus pethidine

Outcome: 5 Apgar < 7 at 1 minute

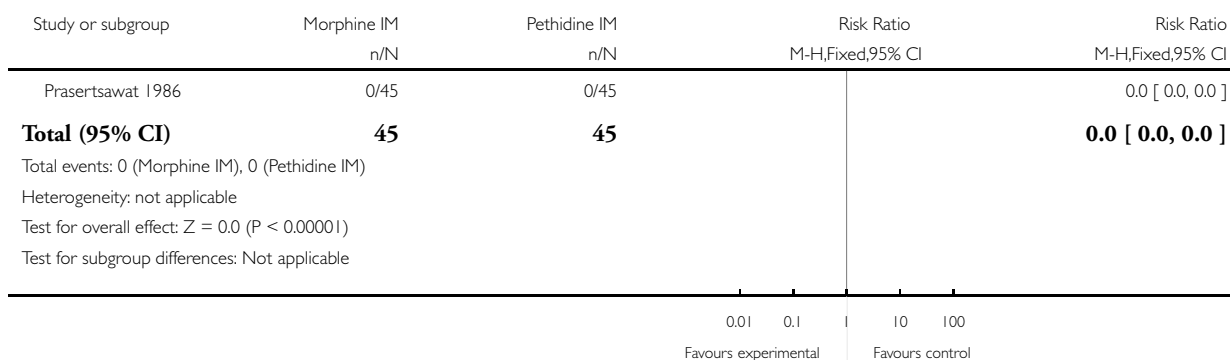


Analysis 12.6. Comparison 12 Morphine versus pethidine, Outcome 6 Neonatal resuscitation.

Review: Parenteral opioids for maternal pain management in labour

Comparison: 12 Morphine versus pethidine

Outcome: 6 Neonatal resuscitation

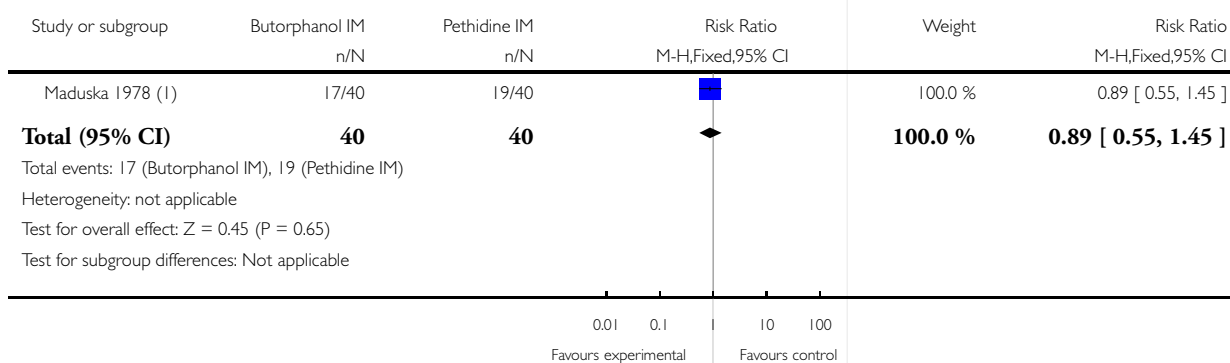


Analysis 13.1. Comparison 13 Butorphanol versus pethidine, Outcome 1 Additional analgesia required.

Review: Parenteral opioids for maternal pain management in labour

Comparison: 13 Butorphanol versus pethidine

Outcome: 1 Additional analgesia required



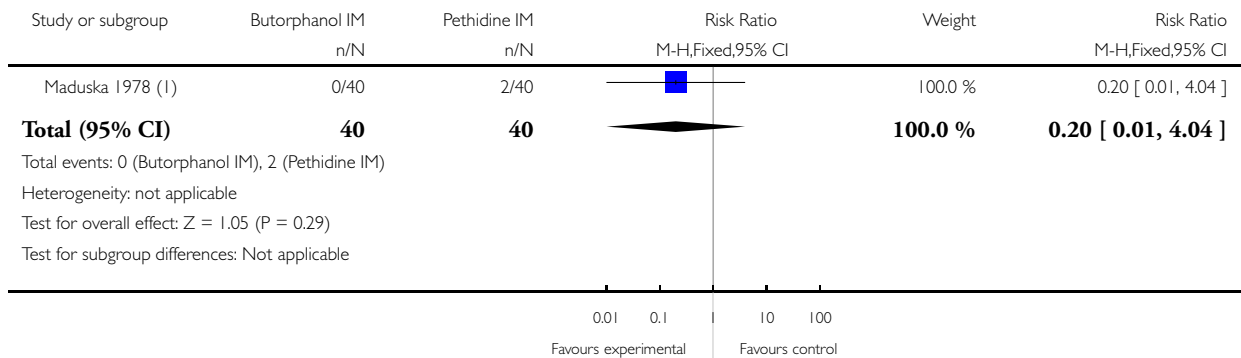
(1) 2nd dose of study drug

Analysis 13.2. Comparison 13 Butorphanol versus pethidine, Outcome 2 Nausea.

Review: Parenteral opioids for maternal pain management in labour

Comparison: 13 Butorphanol versus pethidine

Outcome: 2 Nausea



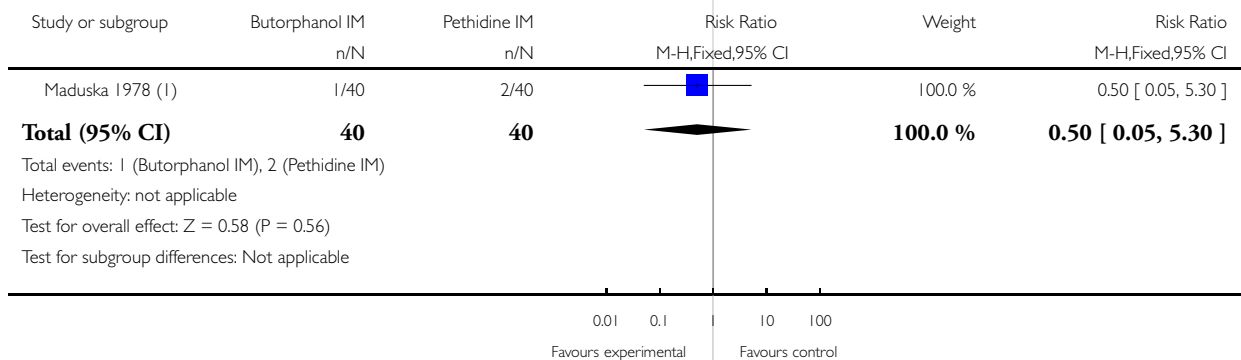
(1) Unclear when assessed

Analysis 13.3. Comparison 13 Butorphanol versus pethidine, Outcome 3 Vomiting.

Review: Parenteral opioids for maternal pain management in labour

Comparison: 13 Butorphanol versus pethidine

Outcome: 3 Vomiting



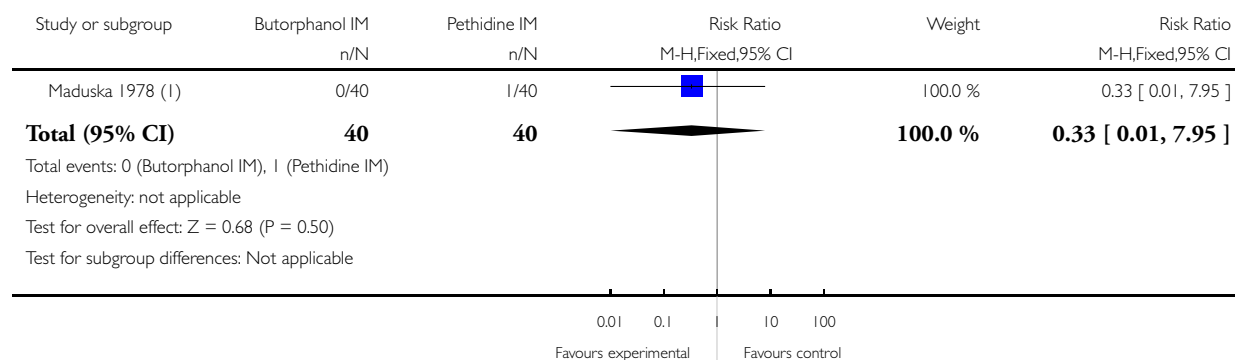
(1) Unclear when assessed

Analysis 13.4. Comparison 13 Butorphanol versus pethidine, Outcome 4 Neonatal resuscitation.

Review: Parenteral opioids for maternal pain management in labour

Comparison: 13 Butorphanol versus pethidine

Outcome: 4 Neonatal resuscitation



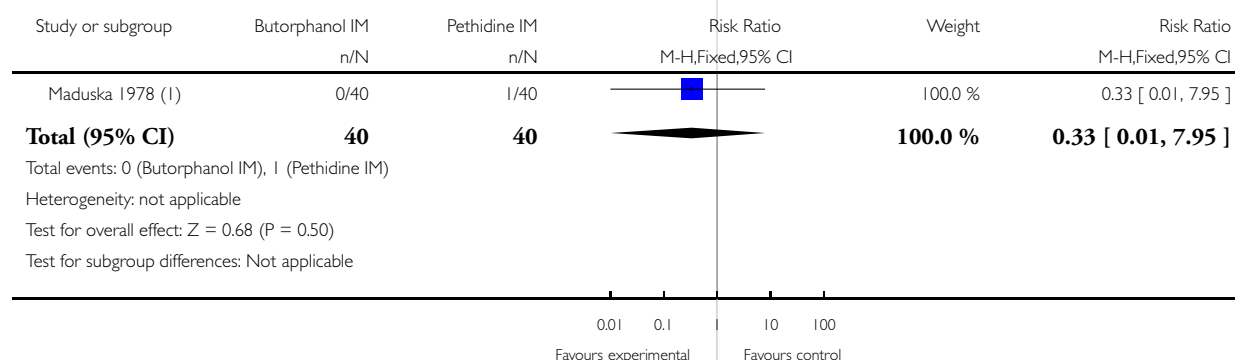
(1) received 2 doses of pethidine (40 mg x 2)

Analysis 13.5. Comparison 13 Butorphanol versus pethidine, Outcome 5 Naloxone administration (neonatal).

Review: Parenteral opioids for maternal pain management in labour

Comparison: 13 Butorphanol versus pethidine

Outcome: 5 Naloxone administration (neonatal)



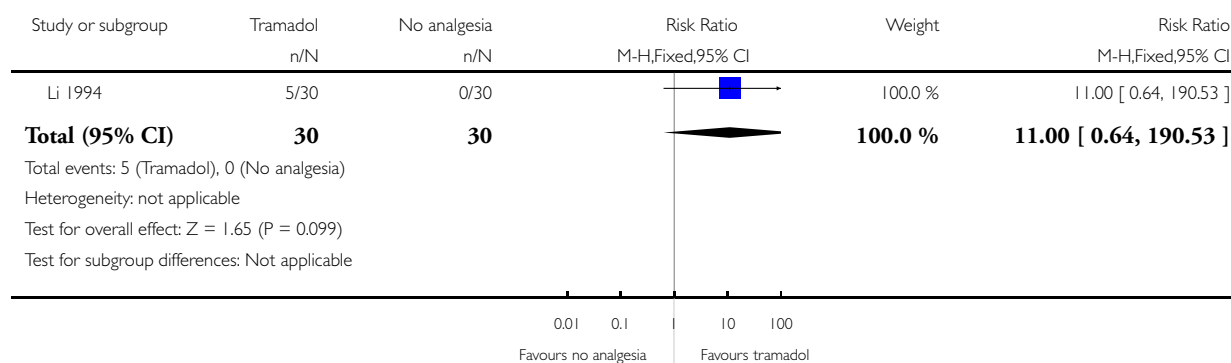
(1) received 2 doses of pethidine (40 mg x 2)

Analysis 14.1. Comparison 14 IM tramadol versus no treatment, Outcome 1 Analgesic effect described as satisfactory (not clear when measured).

Review: Parenteral opioids for maternal pain management in labour

Comparison: 14 IM tramadol versus no treatment

Outcome: 1 Analgesic effect described as satisfactory (not clear when measured)

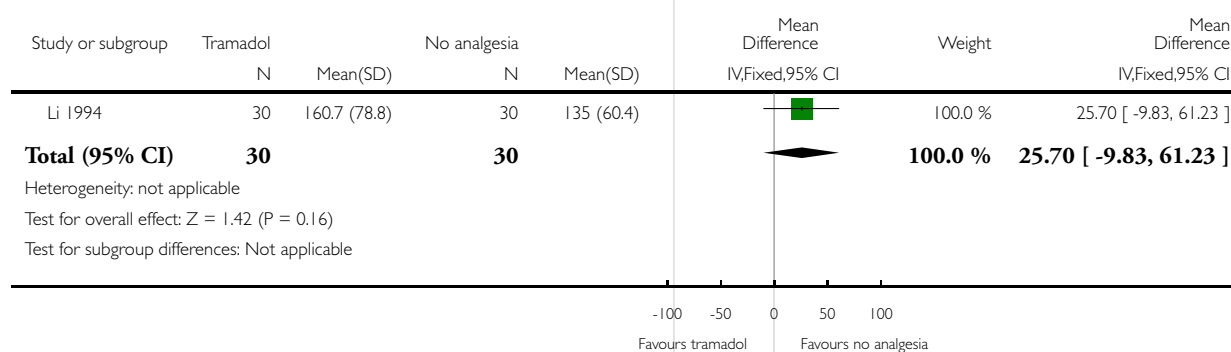


Analysis 14.2. Comparison 14 IM tramadol versus no treatment, Outcome 2 Mean blood loss at delivery (ml).

Review: Parenteral opioids for maternal pain management in labour

Comparison: 14 IM tramadol versus no treatment

Outcome: 2 Mean blood loss at delivery (ml)

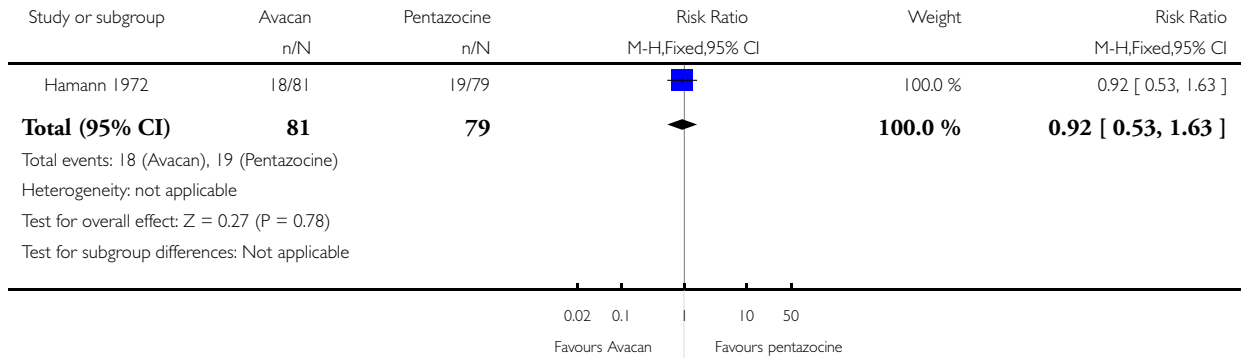


Analysis 15.1. Comparison 15 IM Avacan® versus IM pentazocine, Outcome 1 Further analgesia required (nitrous oxide).

Review: Parenteral opioids for maternal pain management in labour

Comparison: 15 IM Avacan versus IM pentazocine

Outcome: 1 Further analgesia required (nitrous oxide)

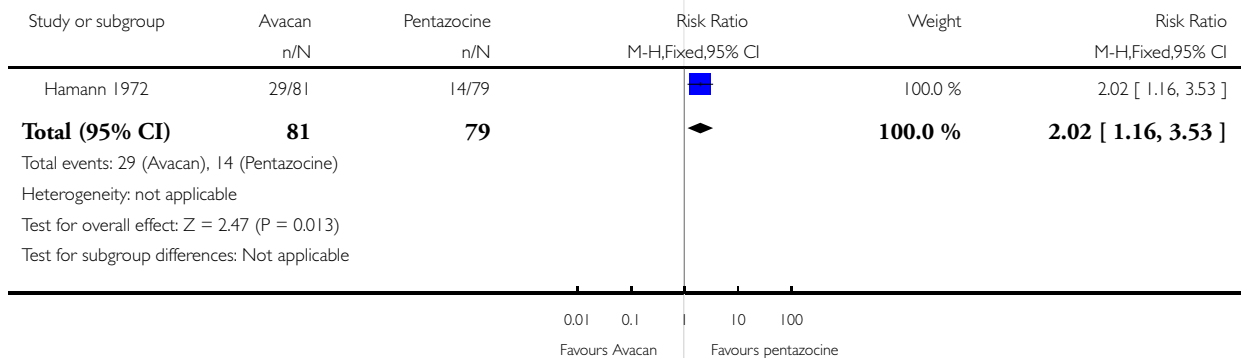


Analysis 15.2. Comparison 15 IM Avacan® versus IM pentazocine, Outcome 2 Further analgesia required (pudendal-paracervical block).

Review: Parenteral opioids for maternal pain management in labour

Comparison: 15 IM Avacan versus IM pentazocine

Outcome: 2 Further analgesia required (pudendal-paracervical block)

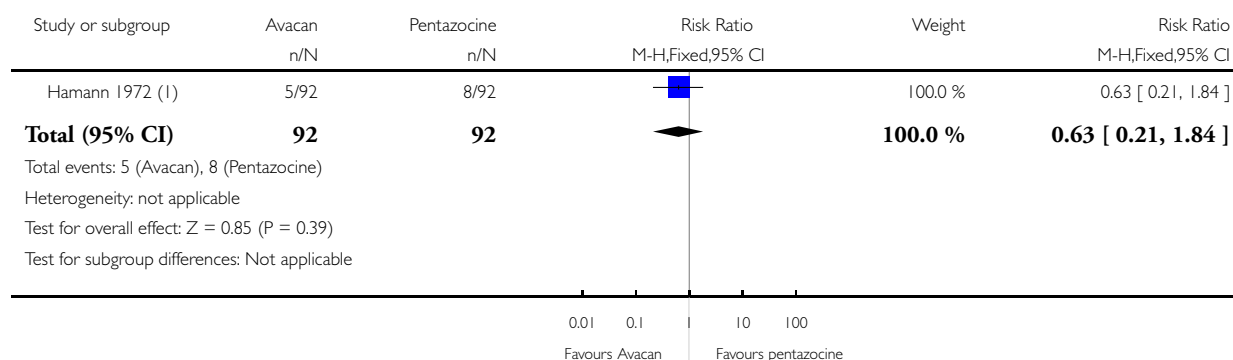


Analysis 15.3. Comparison 15 IM Avacan® versus IM pentazocine, Outcome 3 Caesarean section.

Review: Parenteral opioids for maternal pain management in labour

Comparison: 15 IM Avacan versus IM pentazocine

Outcome: 3 Caesarean section



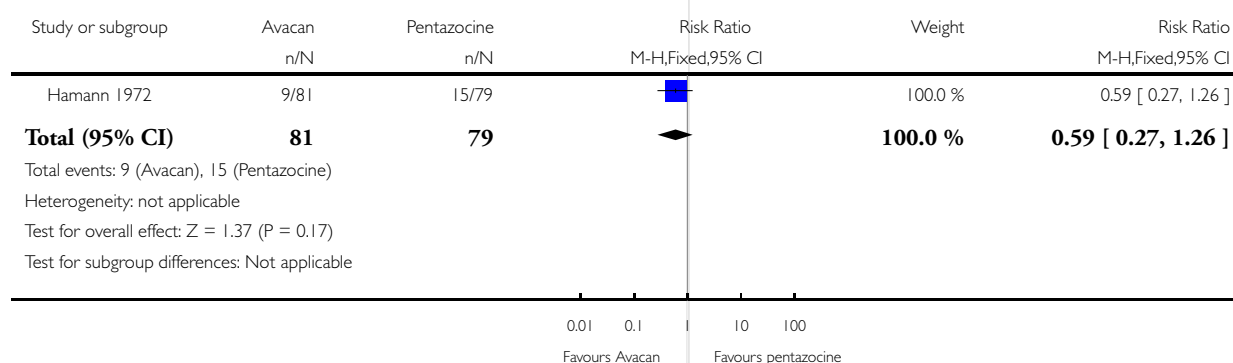
(1) Denominators not clear (women having CS were excluded from analyses in study report).

Analysis 15.4. Comparison 15 IM Avacan® versus IM pentazocine, Outcome 4 Low Apgar score (< 7) "at birth".

Review: Parenteral opioids for maternal pain management in labour

Comparison: 15 IM Avacan versus IM pentazocine

Outcome: 4 Low Apgar score (< 7) "at birth"

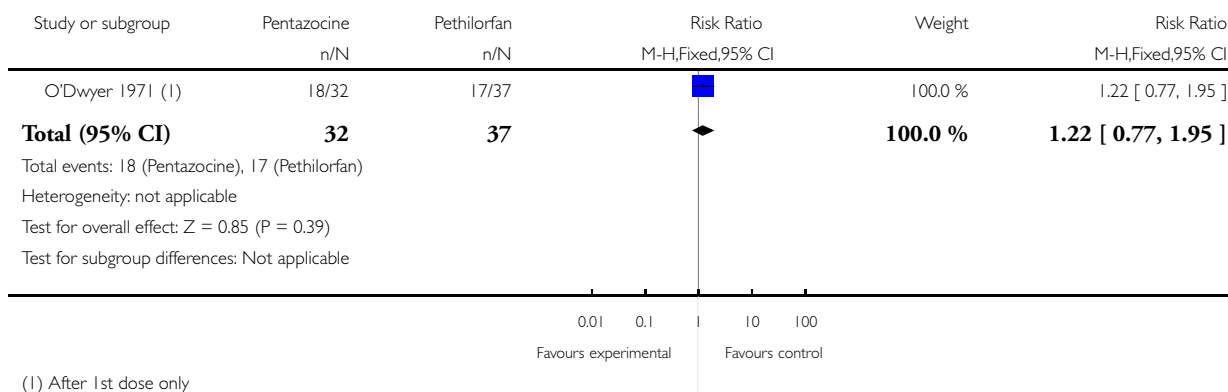


Analysis 16.1. Comparison 16 IM pentazocine versus IM pethilorfan, Outcome 1 Pain relief (women NOT obtaining pain relief) at 1 hour.

Review: Parenteral opioids for maternal pain management in labour

Comparison: 16 IM pentazocine versus IM pethilorfan

Outcome: 1 Pain relief (women NOT obtaining pain relief) at 1 hour

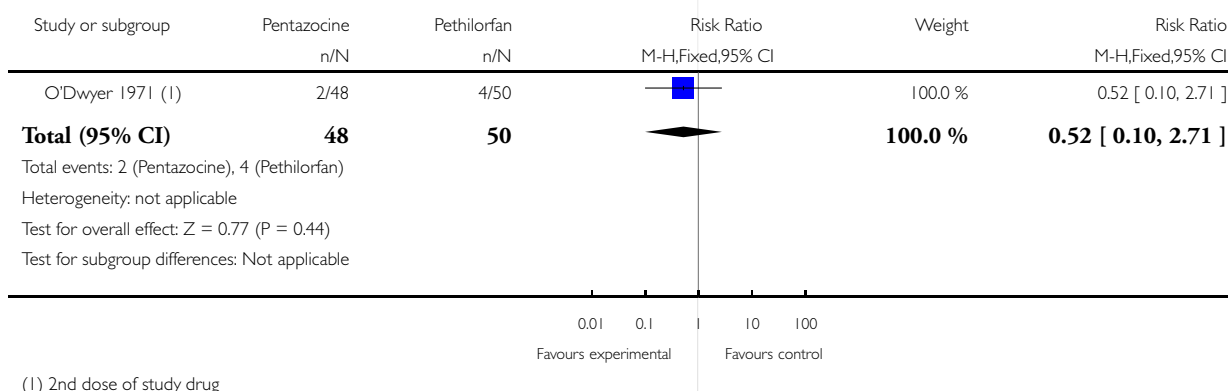


Analysis 16.2. Comparison 16 IM pentazocine versus IM pethilorfan, Outcome 2 Additional analgesia required.

Review: Parenteral opioids for maternal pain management in labour

Comparison: 16 IM pentazocine versus IM pethilorfan

Outcome: 2 Additional analgesia required

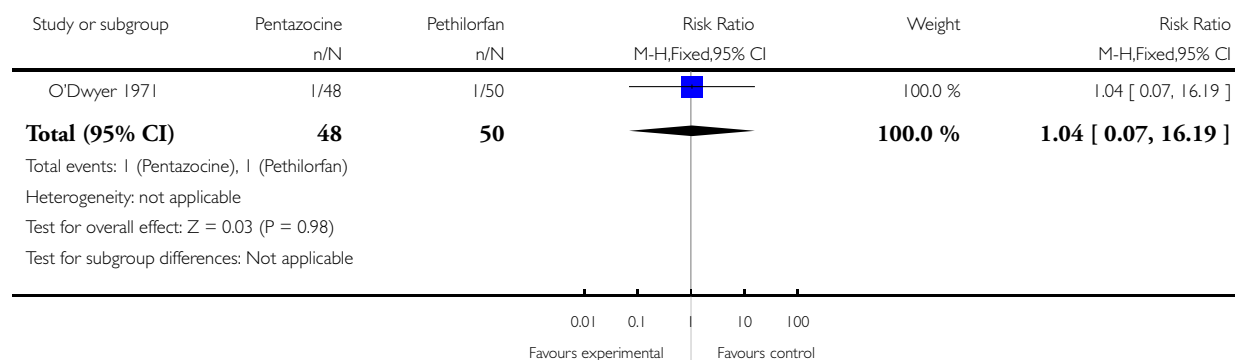


Analysis 16.3. Comparison 16 IM pentazocine versus IM pethilorfan, Outcome 3 Assisted vaginal delivery.

Review: Parenteral opioids for maternal pain management in labour

Comparison: 16 IM pentazocine versus IM pethilorfan

Outcome: 3 Assisted vaginal delivery

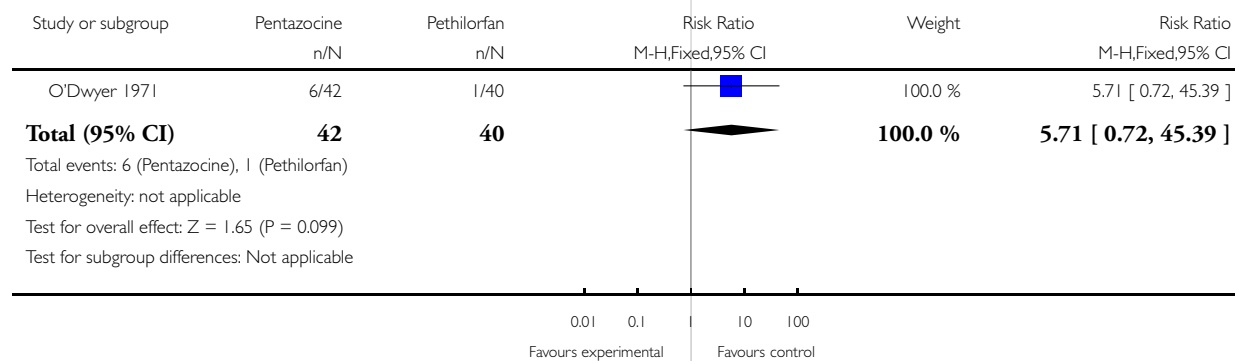


Analysis 16.4. Comparison 16 IM pentazocine versus IM pethilorfan, Outcome 4 Apgar < 8 at 1 minute.

Review: Parenteral opioids for maternal pain management in labour

Comparison: 16 IM pentazocine versus IM pethilorfan

Outcome: 4 Apgar < 8 at 1 minute



Analysis 16.5. Comparison 16 IM pentazocine versus IM pethilorfan, Outcome 5 Apgar < 8 at 5 minutes.

Review: Parenteral opioids for maternal pain management in labour

Comparison: 16 IM pentazocine versus IM pethilorfan

Outcome: 5 Apgar < 8 at 5 minutes

Study or subgroup	Pentazocine		Pethilorfan		Risk Ratio	
	n/N	n/N	n/N	n/N	M-H,Fixed,95% CI	Risk Ratio M-H,Fixed,95% CI
O'Dwyer 1971	0/42	0/40				0.0 [0.0, 0.0]
Total (95% CI)	42	40				0.0 [0.0, 0.0]
Total events: 0 (Pentazocine), 0 (Pethilorfan)						
Heterogeneity: not applicable						
Test for overall effect: Z = 0.0 (P < 0.00001)						
Test for subgroup differences: Not applicable						


0.01 0.1 10 100
Favours experimental Favours control

Analysis 17.1. Comparison 17 IV fentanyl versus IV pethidine, Outcome 1 Pain score (1 hour after drug administration).

Review: Parenteral opioids for maternal pain management in labour

Comparison: 17 IV fentanyl versus IV pethidine

Outcome: 1 Pain score (1 hour after drug administration)

Study or subgroup	Experimental		Pethidine		Mean Difference IV,Fixed,95% CI	Weight	Mean Difference IV,Fixed,95% CI
	N	Mean(SD)	N	Mean(SD)			
Rayburn 1989a (1)	49	5.9 (0.4)	56	6.1 (0.3)		100.0 %	-0.20 [-0.34, -0.06]
Total (95% CI)	49		56			100.0 %	-0.20 [-0.34, -0.06]
Heterogeneity: not applicable							
Test for overall effect: Z = 2.87 (P = 0.0042)							
Test for subgroup differences: Not applicable							

-100 -50 0 50 100
Favours experimental Favours control

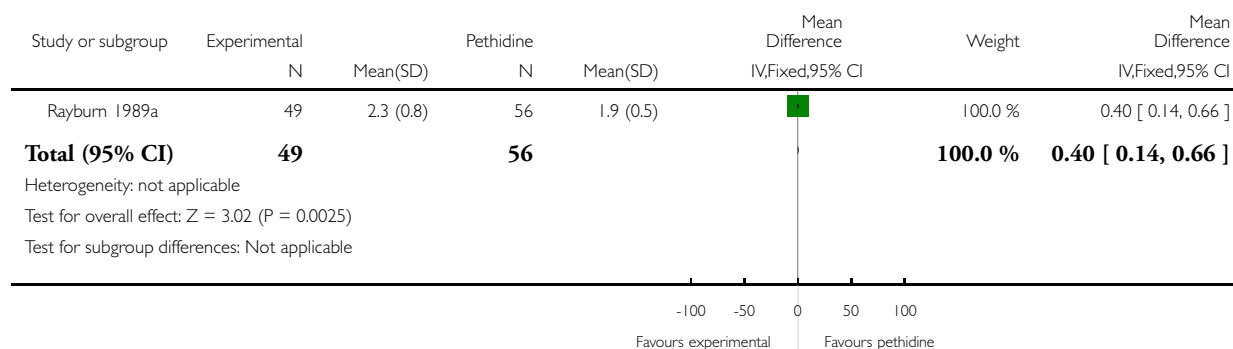
(1) Pain score at 4-7cm dilatation (SD/SE not clear)

Analysis 17.2. Comparison 17 IV fentanyl versus IV pethidine, Outcome 2 Mean doses of analgesia.

Review: Parenteral opioids for maternal pain management in labour

Comparison: 17 IV fentanyl versus IV pethidine

Outcome: 2 Mean doses of analgesia

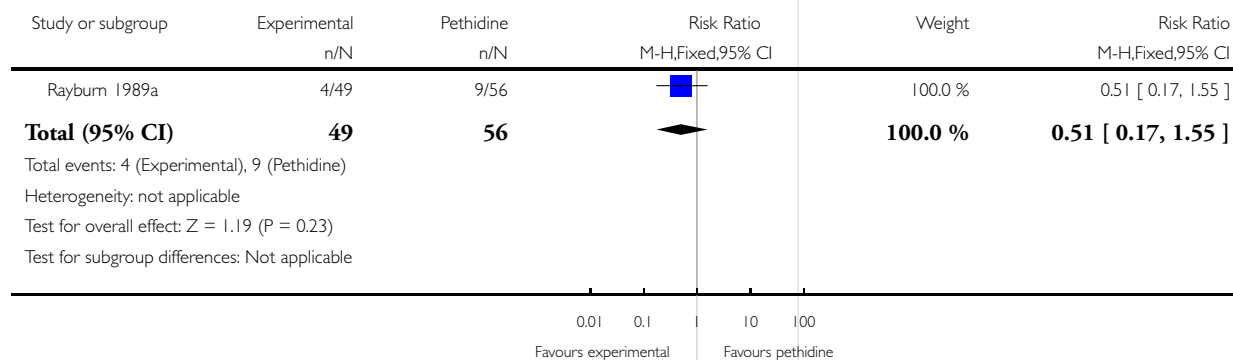


Analysis 17.3. Comparison 17 IV fentanyl versus IV pethidine, Outcome 3 Nausea and/or vomiting.

Review: Parenteral opioids for maternal pain management in labour

Comparison: 17 IV fentanyl versus IV pethidine

Outcome: 3 Nausea and/or vomiting

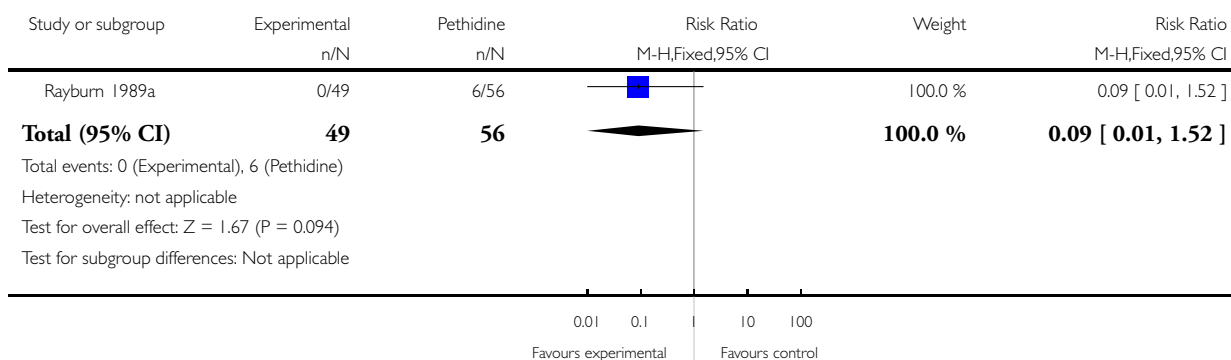


Analysis 17.4. Comparison 17 IV fentanyl versus IV pethidine, Outcome 4 Anti-emetic required.

Review: Parenteral opioids for maternal pain management in labour

Comparison: 17 IV fentanyl versus IV pethidine

Outcome: 4 Anti-emetic required

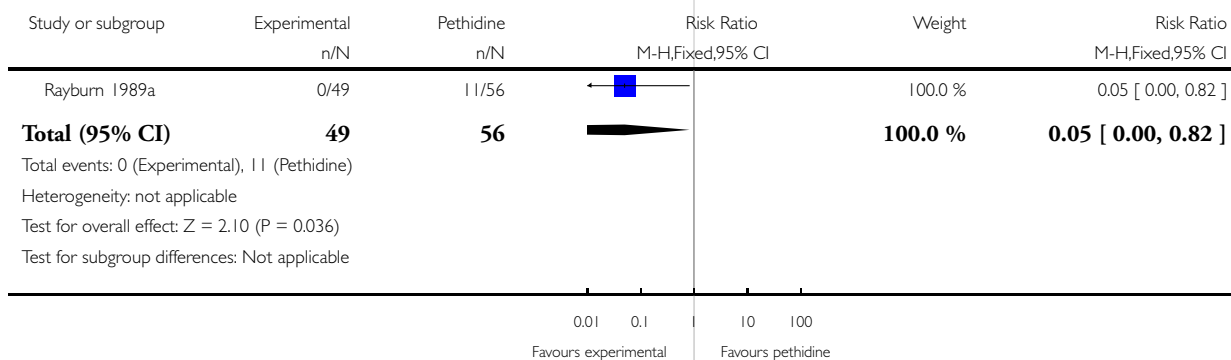


Analysis 17.5. Comparison 17 IV fentanyl versus IV pethidine, Outcome 5 Maternal sedation.

Review: Parenteral opioids for maternal pain management in labour

Comparison: 17 IV fentanyl versus IV pethidine

Outcome: 5 Maternal sedation

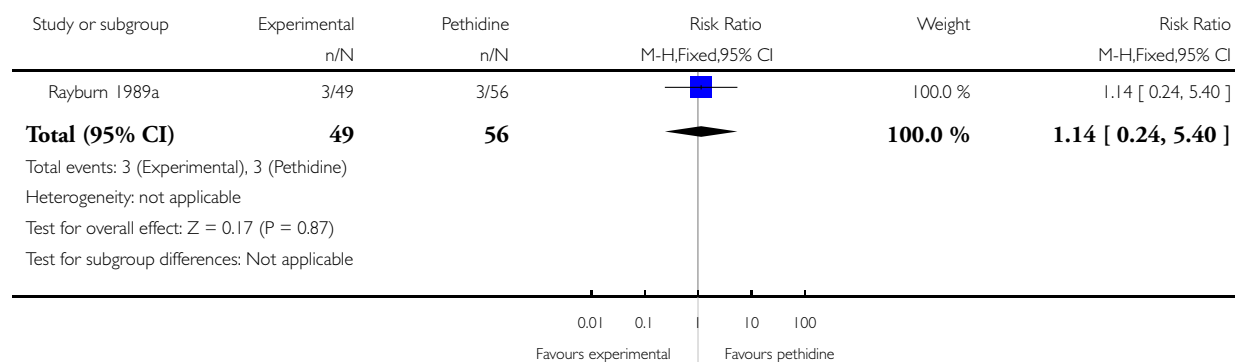


Analysis 17.6. Comparison 17 IV fentanyl versus IV pethidine, Outcome 6 Caesarean section.

Review: Parenteral opioids for maternal pain management in labour

Comparison: 17 IV fentanyl versus IV pethidine

Outcome: 6 Caesarean section

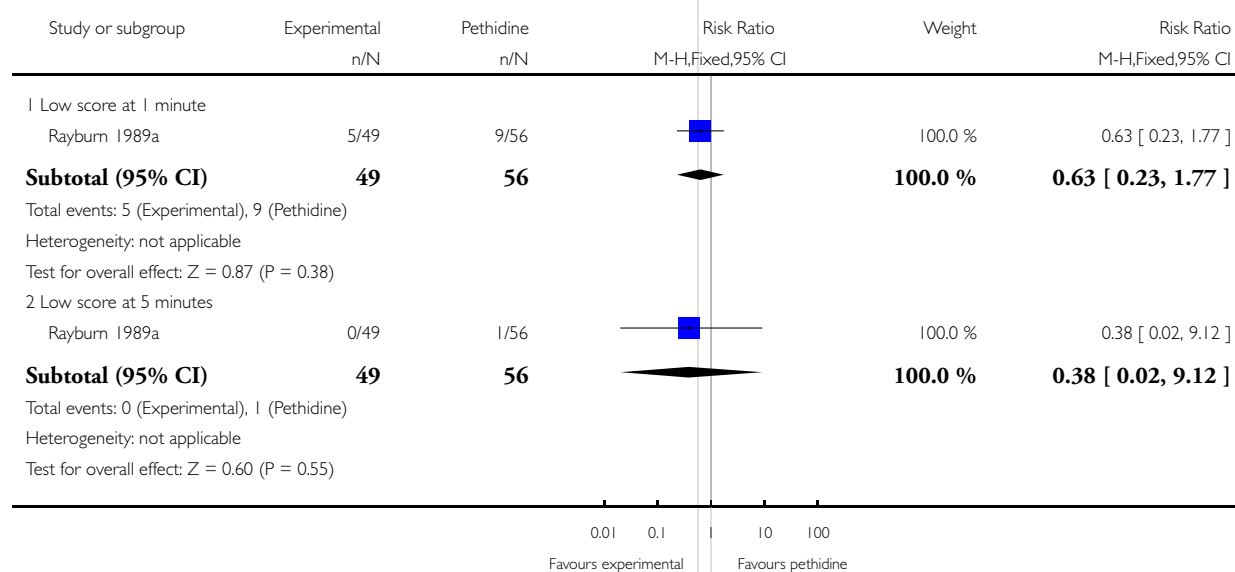


Analysis 17.7. Comparison 17 IV fentanyl versus IV pethidine, Outcome 7 Apgar score < 7 at 1 and 5 minutes.

Review: Parenteral opioids for maternal pain management in labour

Comparison: 17 IV fentanyl versus IV pethidine

Outcome: 7 Apgar score < 7 at 1 and 5 minutes

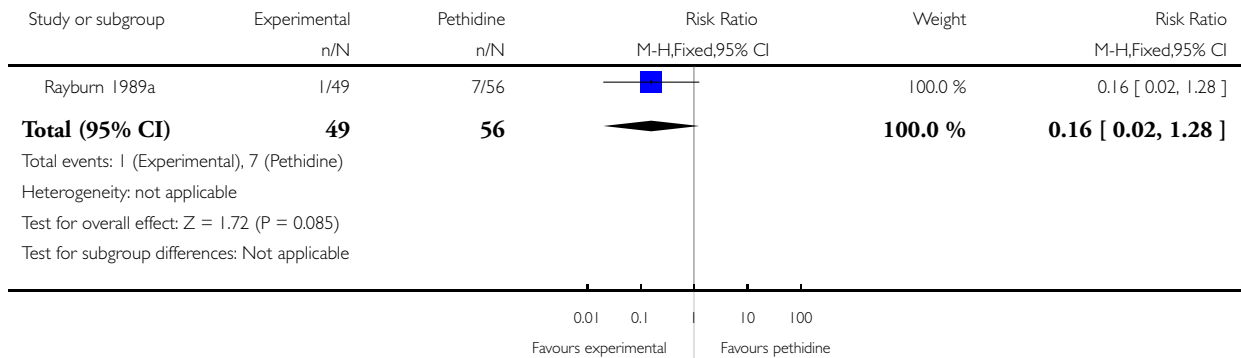


Analysis 17.8. Comparison 17 IV fentanyl versus IV pethidine, Outcome 8 Naloxone administered.

Review: Parenteral opioids for maternal pain management in labour

Comparison: 17 IV fentanyl versus IV pethidine

Outcome: 8 Naloxone administered

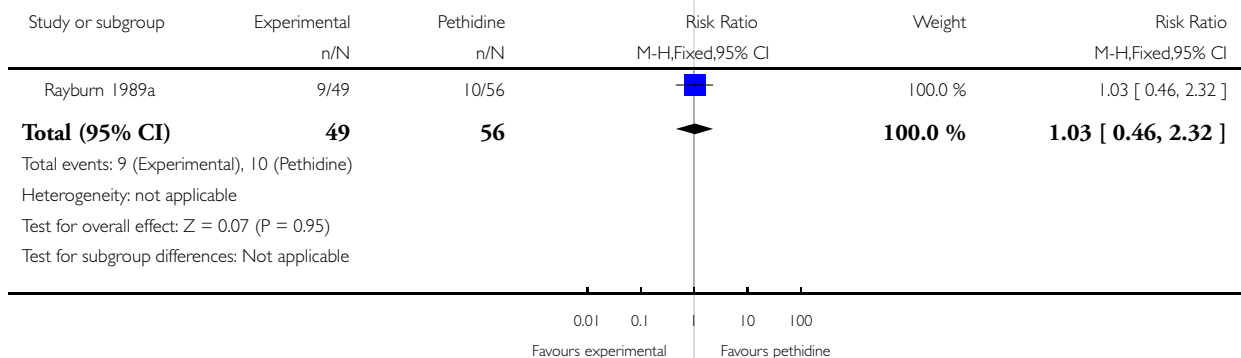


Analysis 17.9. Comparison 17 IV fentanyl versus IV pethidine, Outcome 9 Babies requiring resuscitation/ventilatory support.

Review: Parenteral opioids for maternal pain management in labour

Comparison: 17 IV fentanyl versus IV pethidine

Outcome: 9 Babies requiring resuscitation/ ventilatory support

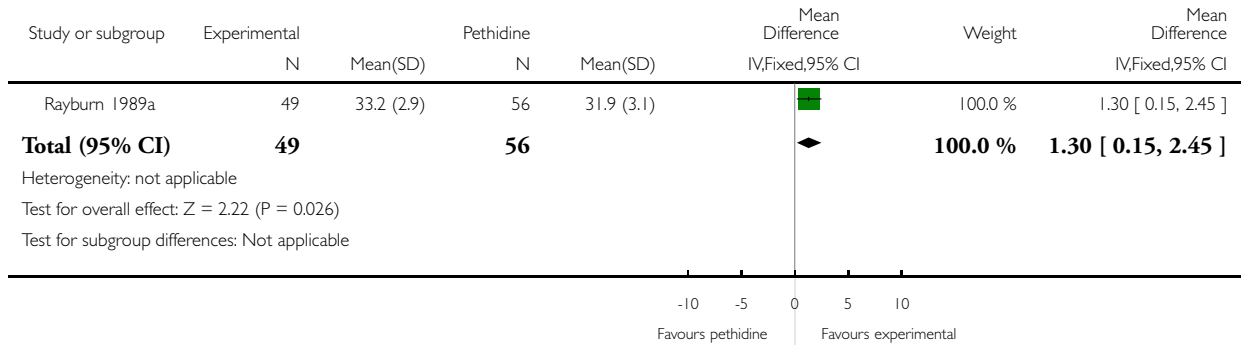


Analysis 17.10. Comparison 17 IV fentanyl versus IV pethidine, Outcome 10 Neurobehavioural score (1 - 2 hours after delivery).

Review: Parenteral opioids for maternal pain management in labour

Comparison: 17 IV fentanyl versus IV pethidine

Outcome: 10 Neurobehavioural score (1 - 2 hours after delivery)

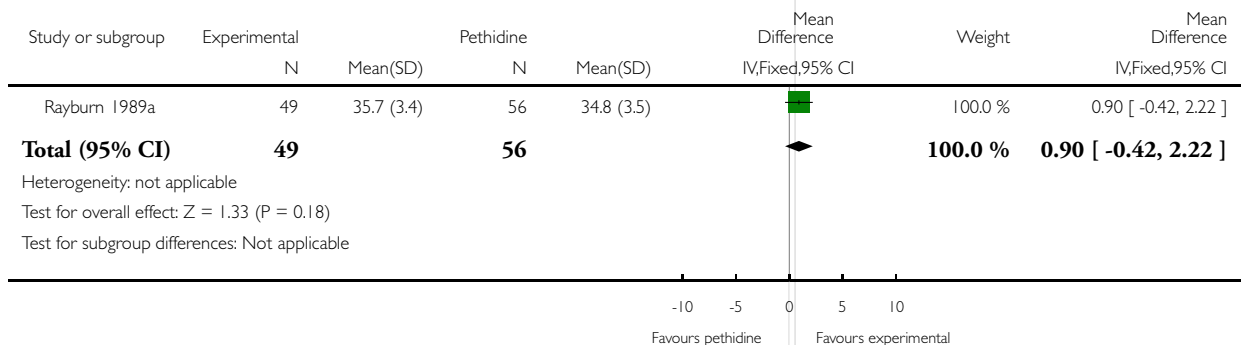


Analysis 17.11. Comparison 17 IV fentanyl versus IV pethidine, Outcome 11 Neurobehavioural score (2 hours - 24 hours).

Review: Parenteral opioids for maternal pain management in labour

Comparison: 17 IV fentanyl versus IV pethidine

Outcome: 11 Neurobehavioural score (2 hours - 24 hours)

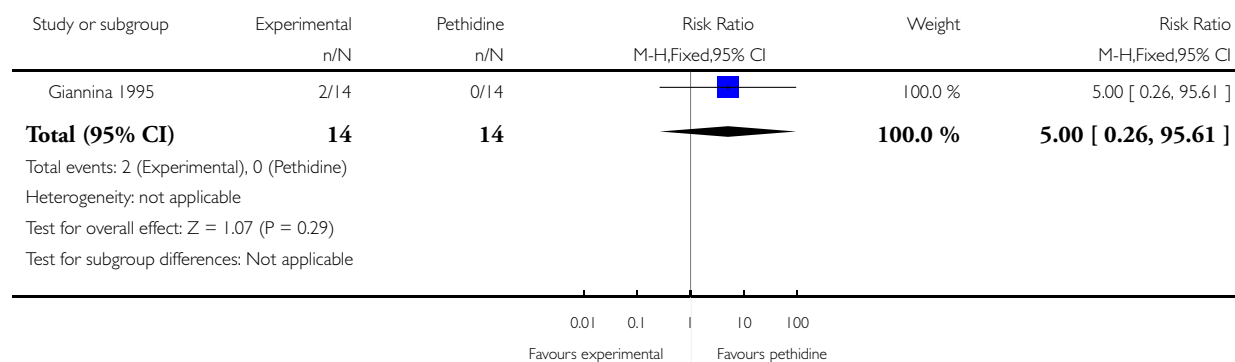


Analysis 18.1. Comparison 18 IV nalbuphine versus IV pethidine, Outcome 1 Caesarean section.

Review: Parenteral opioids for maternal pain management in labour

Comparison: 18 IV nalbuphine versus IV pethidine

Outcome: 1 Caesarean section

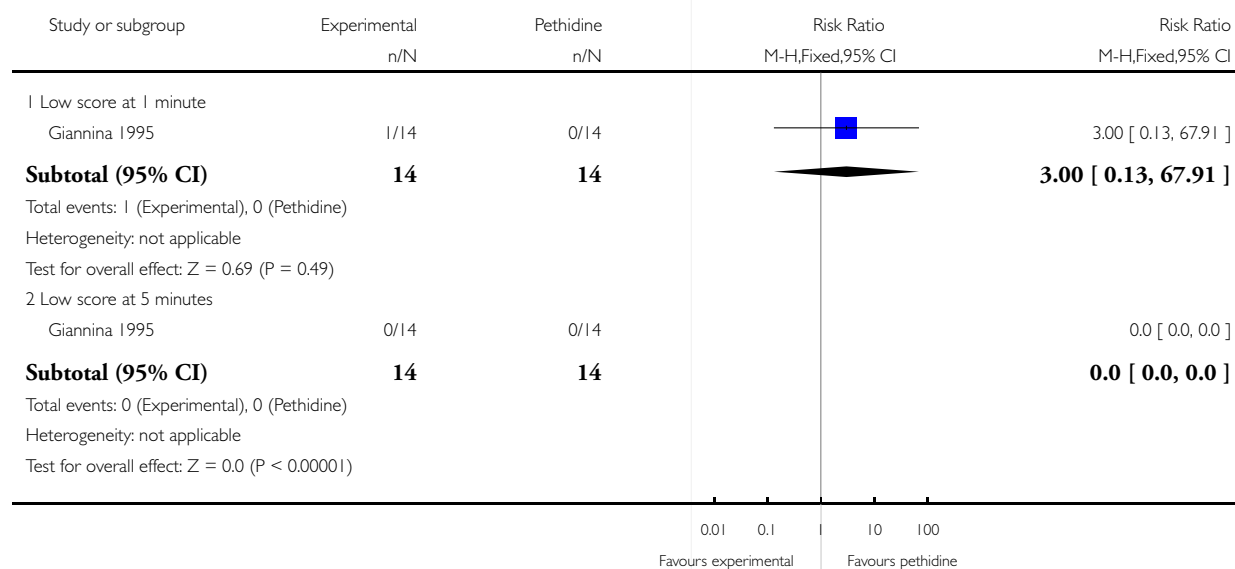


Analysis 18.2. Comparison 18 IV nalbuphine versus IV pethidine, Outcome 2 Apgar score < 7 at 1 and 5 minutes.

Review: Parenteral opioids for maternal pain management in labour

Comparison: 18 IV nalbuphine versus IV pethidine

Outcome: 2 Apgar score < 7 at 1 and 5 minutes

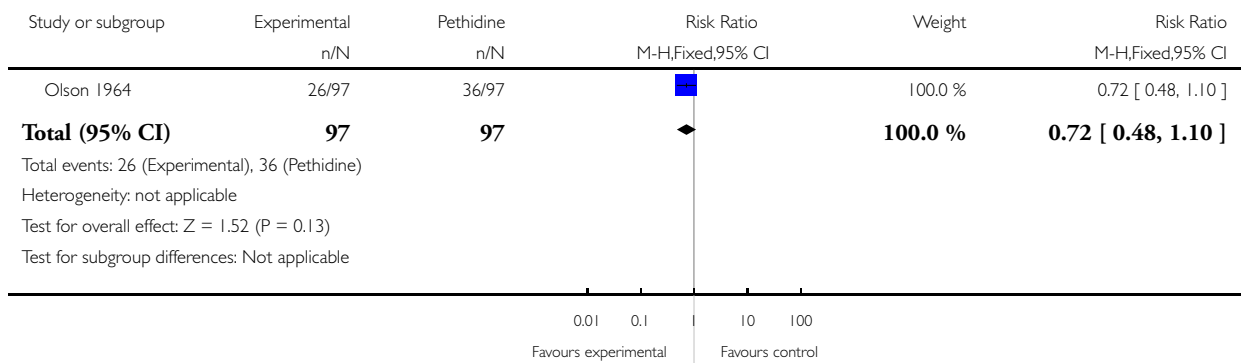


Analysis 19.1. Comparison 19 IV phenazocine versus IV pethidine, Outcome 1 Satisfaction with pain relief (women with fair or poor relief).

Review: Parenteral opioids for maternal pain management in labour

Comparison: 19 IV phenazocine versus IV pethidine

Outcome: 1 Satisfaction with pain relief (women with fair or poor relief)

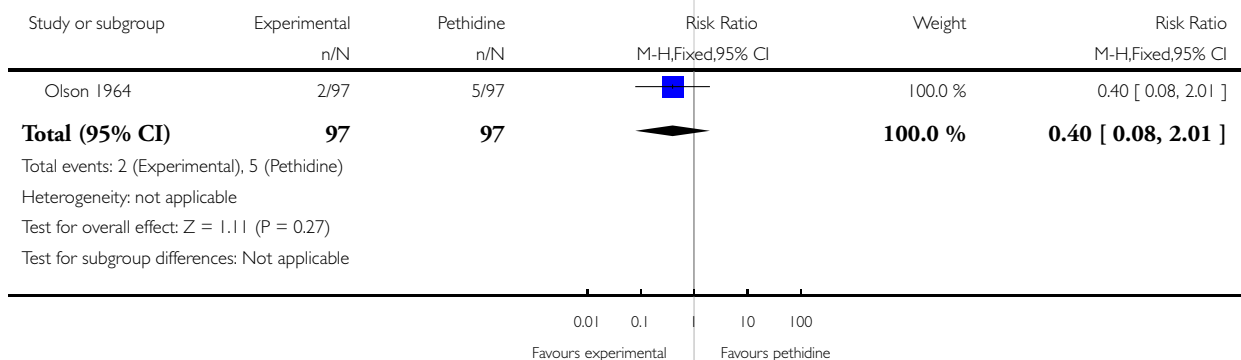


Analysis 19.2. Comparison 19 IV phenazocine versus IV pethidine, Outcome 2 Nausea with vomiting.

Review: Parenteral opioids for maternal pain management in labour

Comparison: 19 IV phenazocine versus IV pethidine

Outcome: 2 Nausea with vomiting



Analysis 19.3. Comparison 19 IV phenazocine versus IV pethidine, Outcome 3 Perinatal death.

Review: Parenteral opioids for maternal pain management in labour

Comparison: 19 IV phenazocine versus IV pethidine

Outcome: 3 Perinatal death

Study or subgroup	Experimental n/N	Pethidine n/N	Risk Ratio M-H,Fixed,95% CI	Risk Ratio M-H,Fixed,95% CI
Olson 1964	0/97	0/97		0.0 [0.0, 0.0]
Total (95% CI)	97	97		0.0 [0.0, 0.0]
Total events: 0 (Experimental), 0 (Pethidine)				
Heterogeneity: not applicable				
Test for overall effect: $Z = 0.0$ ($P < 0.00001$)				
Test for subgroup differences: Not applicable				

0.01 0.1 | 10 100
Favours experimental Favours control

Analysis 19.4. Comparison 19 IV phenazocine versus IV pethidine, Outcome 4 Apgar score < 7 at 1 minute.

Review: Parenteral opioids for maternal pain management in labour

Comparison: 19 IV phenazocine versus IV pethidine

Outcome: 4 Apgar score < 7 at 1 minute

Study or subgroup	Experimental n/N	Pethidine n/N	Risk Ratio M-H,Fixed,95% CI	Risk Ratio M-H,Fixed,95% CI
Prasertsawat 1986	0/97	0/97		0.0 [0.0, 0.0]
Total (95% CI)	97	97		0.0 [0.0, 0.0]
Total events: 0 (Experimental), 0 (Pethidine)				
Heterogeneity: not applicable				
Test for overall effect: $Z = 0.0$ ($P < 0.00001$)				
Test for subgroup differences: Not applicable				

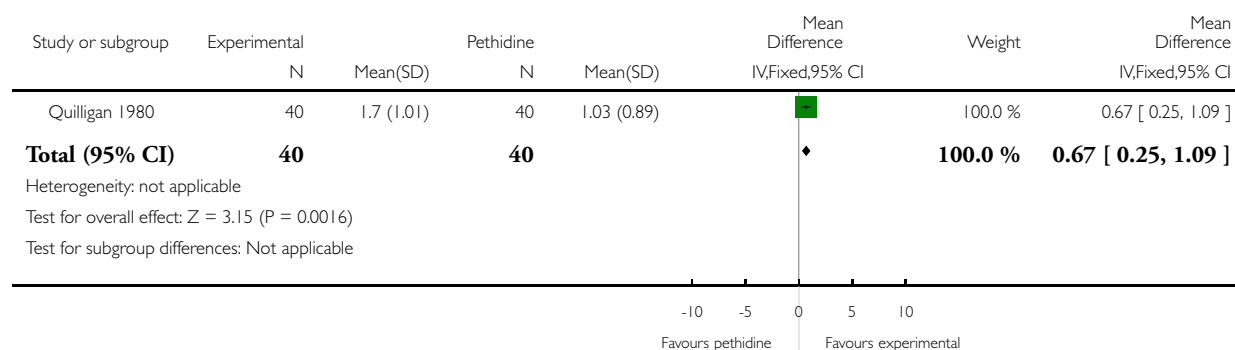
0.01 0.1 | 10 100
Favours experimental Favours pethidine

Analysis 20.1. Comparison 20 IV butorphanol versus IV pethidine, Outcome 1 Pain relief score.

Review: Parenteral opioids for maternal pain management in labour

Comparison: 20 IV butorphanol versus IV pethidine

Outcome: 1 Pain relief score

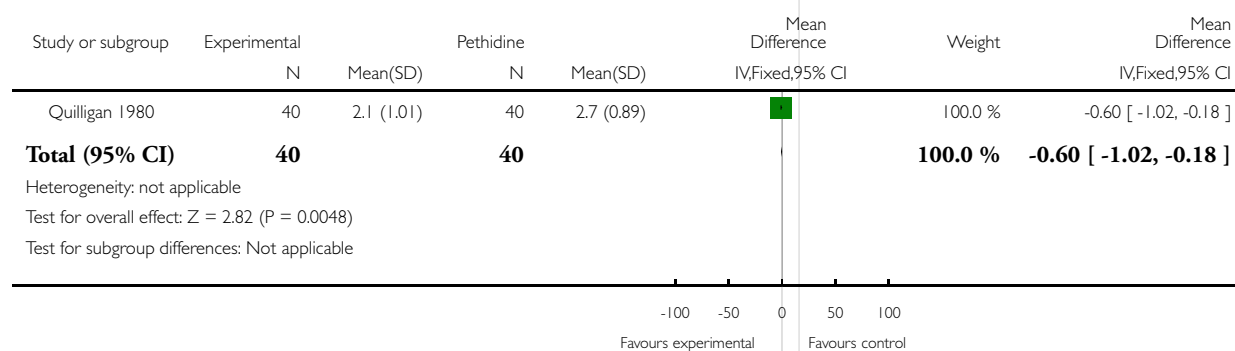


Analysis 20.2. Comparison 20 IV butorphanol versus IV pethidine, Outcome 2 Pain score (1 hour after drug administration).

Review: Parenteral opioids for maternal pain management in labour

Comparison: 20 IV butorphanol versus IV pethidine

Outcome: 2 Pain score (1 hour after drug administration)

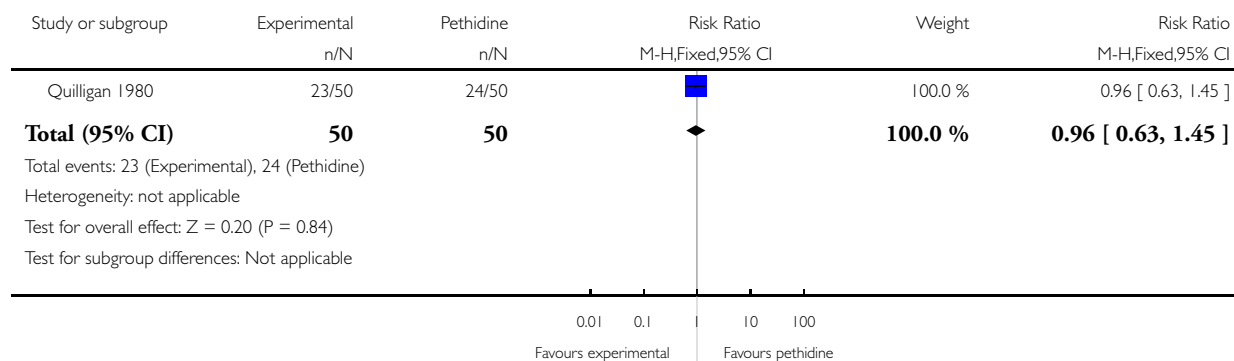


Analysis 20.3. Comparison 20 IV butorphanol versus IV pethidine, Outcome 3 Further analgesia (2nd dose) required.

Review: Parenteral opioids for maternal pain management in labour

Comparison: 20 IV butorphanol versus IV pethidine

Outcome: 3 Further analgesia (2nd dose) required

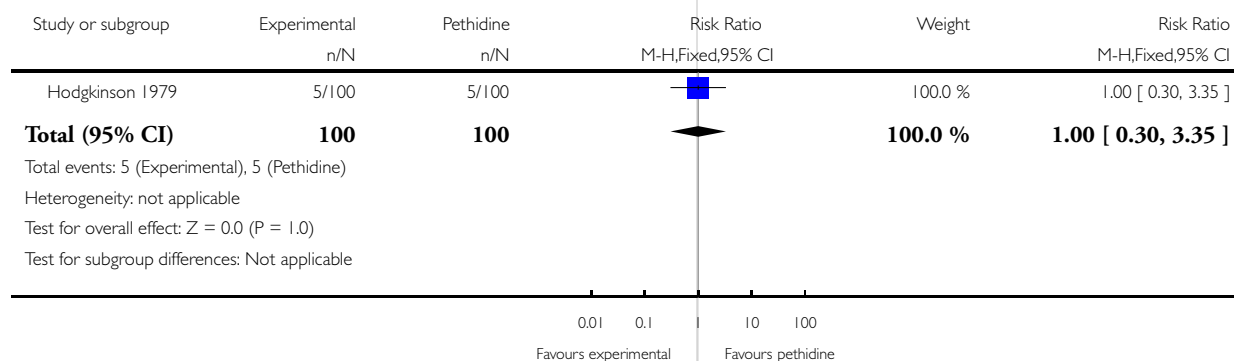


Analysis 20.4. Comparison 20 IV butorphanol versus IV pethidine, Outcome 4 Epidural.

Review: Parenteral opioids for maternal pain management in labour

Comparison: 20 IV butorphanol versus IV pethidine

Outcome: 4 Epidural

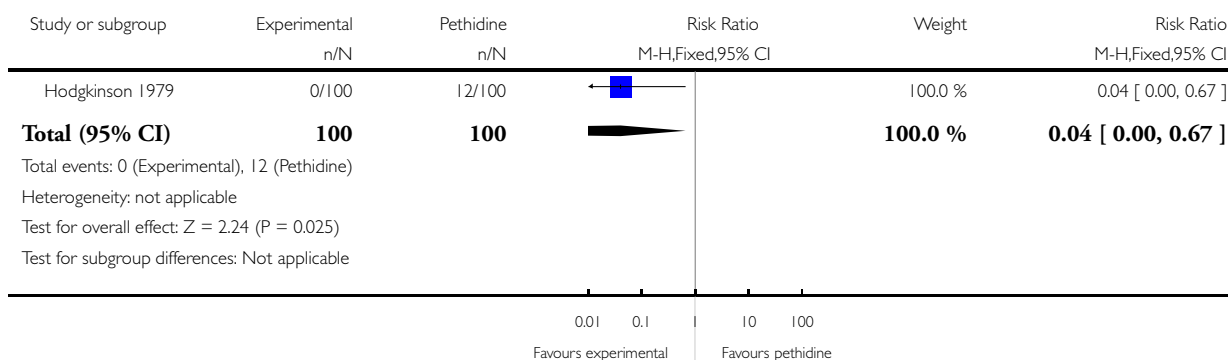


Analysis 20.5. Comparison 20 IV butorphanol versus IV pethidine, Outcome 5 Nausea and/or vomiting.

Review: Parenteral opioids for maternal pain management in labour

Comparison: 20 IV butorphanol versus IV pethidine

Outcome: 5 Nausea and/or vomiting

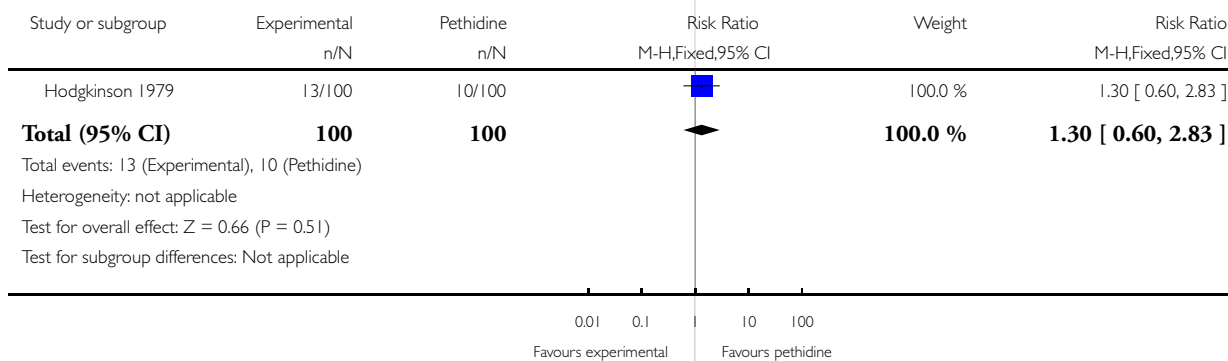


Analysis 20.6. Comparison 20 IV butorphanol versus IV pethidine, Outcome 6 Assisted vaginal delivery.

Review: Parenteral opioids for maternal pain management in labour

Comparison: 20 IV butorphanol versus IV pethidine

Outcome: 6 Assisted vaginal delivery

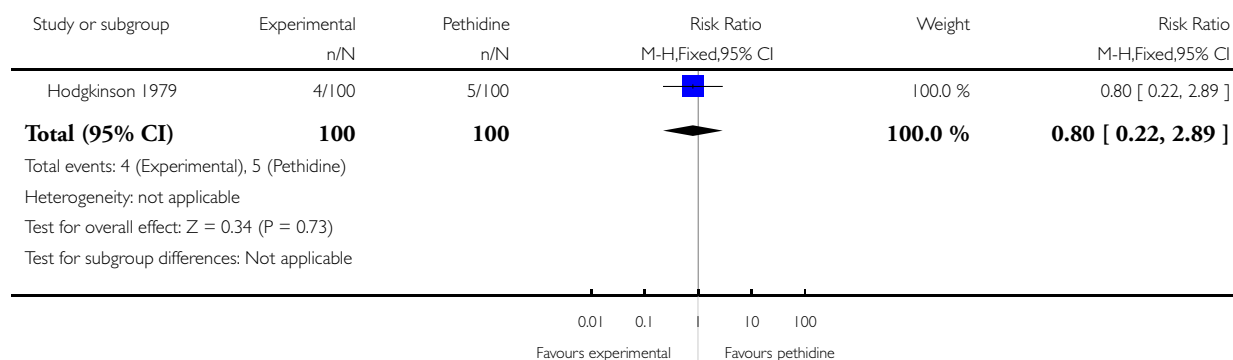


Analysis 20.7. Comparison 20 IV butorphanol versus IV pethidine, Outcome 7 Caesarean section.

Review: Parenteral opioids for maternal pain management in labour

Comparison: 20 IV butorphanol versus IV pethidine

Outcome: 7 Caesarean section

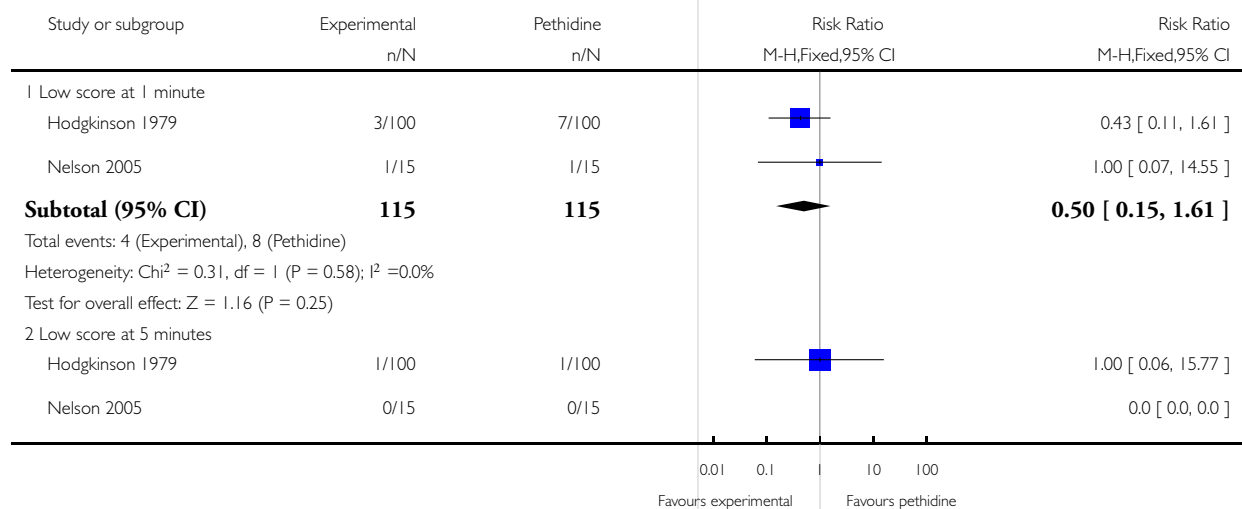


Analysis 20.8. Comparison 20 IV butorphanol versus IV pethidine, Outcome 8 Apgar score < 7 at 1 and 5 minutes.

Review: Parenteral opioids for maternal pain management in labour

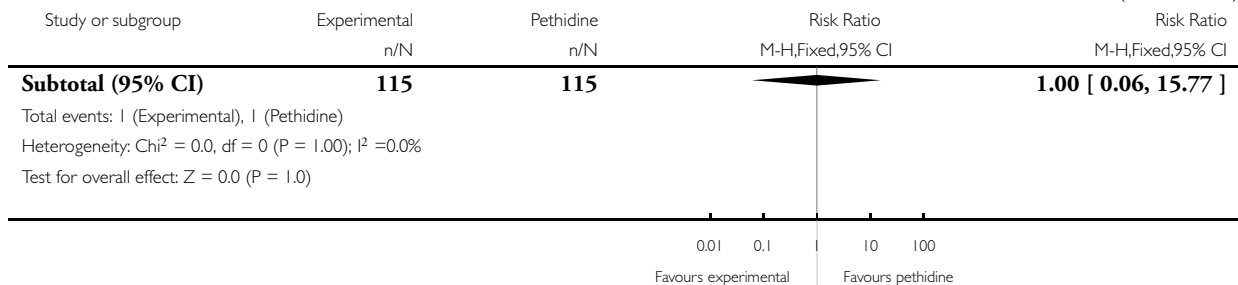
Comparison: 20 IV butorphanol versus IV pethidine

Outcome: 8 Apgar score < 7 at 1 and 5 minutes



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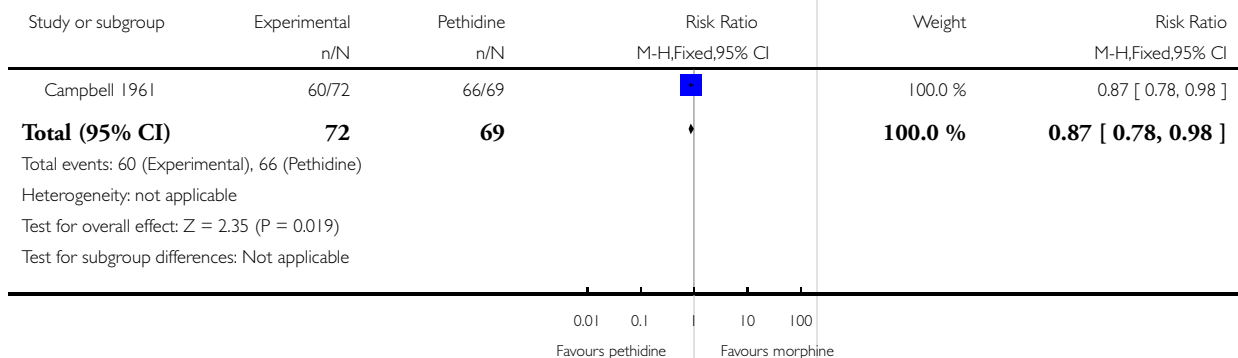


Analysis 21.1. Comparison 21 IV morphine versus IV pethidine, Outcome 1 Women satisfied with analgesia (assessed 3 days postpartum).

Review: Parenteral opioids for maternal pain management in labour

Comparison: 21 IV morphine versus IV pethidine

Outcome: 1 Women satisfied with analgesia (assessed 3 days postpartum)

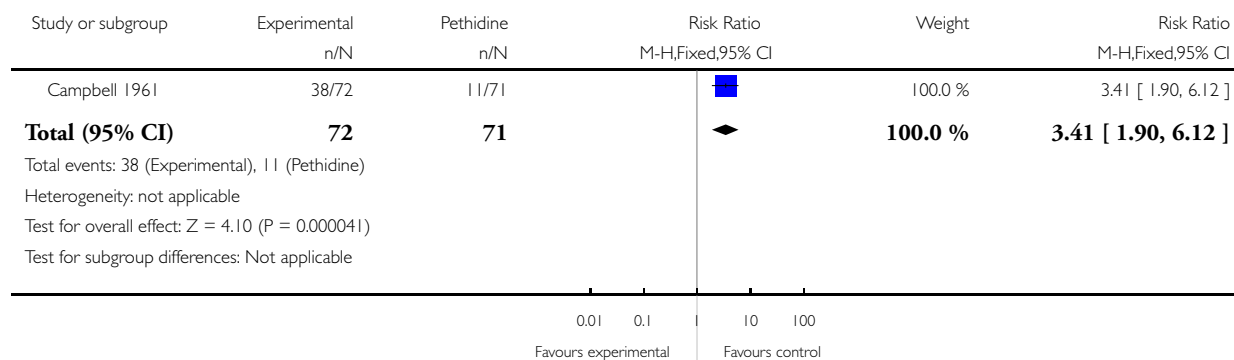


Analysis 21.2. Comparison 21 IV morphine versus IV pethidine, Outcome 2 Further dose of study analgesia required.

Review: Parenteral opioids for maternal pain management in labour

Comparison: 21 IV morphine versus IV pethidine

Outcome: 2 Further dose of study analgesia required

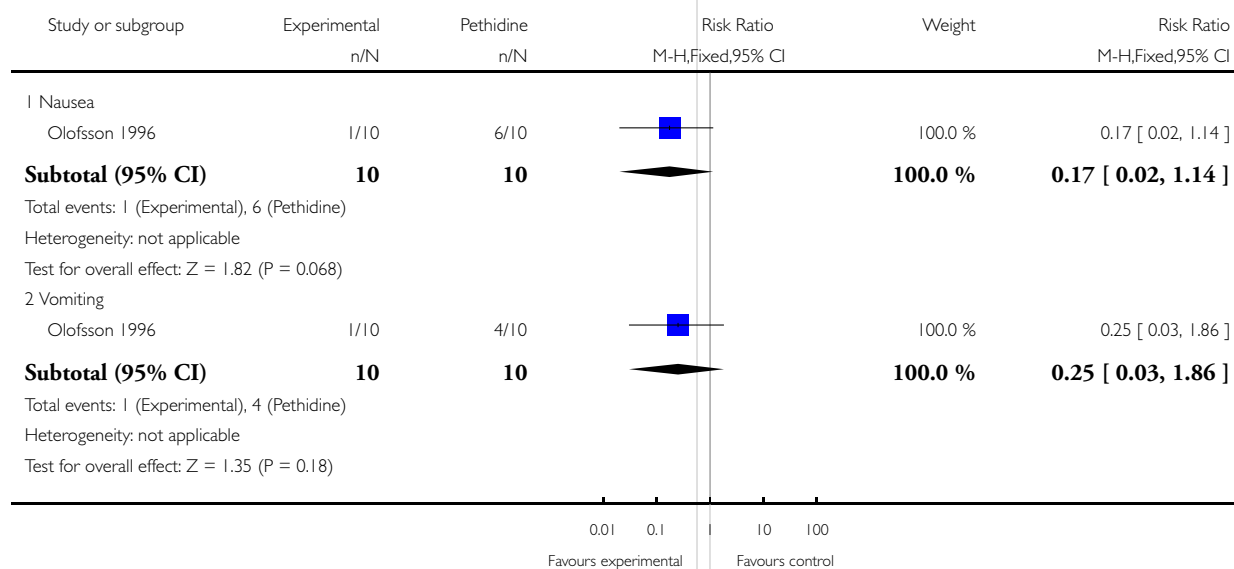


Analysis 21.3. Comparison 21 IV morphine versus IV pethidine, Outcome 3 Nausea and vomiting.

Review: Parenteral opioids for maternal pain management in labour

Comparison: 21 IV morphine versus IV pethidine

Outcome: 3 Nausea and vomiting



Analysis 21.4. Comparison 21 IV morphine versus IV pethidine, Outcome 4 Caesarean section.

Review: Parenteral opioids for maternal pain management in labour

Comparison: 21 IV morphine versus IV pethidine

Outcome: 4 Caesarean section

Study or subgroup	Experimental	Pethidine	Risk Ratio	
	n/N	n/N	M-H,Fixed,95% CI	Risk Ratio M-H,Fixed,95% CI
Olofsson 1996	0/10	0/10		0.0 [0.0, 0.0]
Total (95% CI)	10	10		0.0 [0.0, 0.0]
Total events: 0 (Experimental), 0 (Pethidine)				
Heterogeneity: not applicable				
Test for overall effect: Z = 0.0 (P < 0.00001)				
Test for subgroup differences: Not applicable				

Analysis 22.1. Comparison 22 IV nisentil versus IV pethidine, Outcome 1 Nausea and vomiting.

Review: Parenteral opioids for maternal pain management in labour

Comparison: 22 IV nisentil versus IV pethidine

Outcome: 1 Nausea and vomiting

Study or subgroup	Experimental	Pethidine	Risk Ratio		Weight	Risk Ratio
	n/N	n/N	M-H,Fixed,95% CI	M-H,Fixed,95% CI		
1 Nausea						
Gillam 1958	10/185	16/210		100.0 %	0.71 [0.33, 1.52]	
Subtotal (95% CI)	185	210		100.0 %	0.71 [0.33, 1.52]	
Total events: 10 (Experimental), 16 (Pethidine)						
Heterogeneity: not applicable						
Test for overall effect: Z = 0.88 (P = 0.38)						
2 Vomiting						
Gillam 1958 (1)	15/185	45/210		100.0 %	0.38 [0.22, 0.66]	
Subtotal (95% CI)	185	210		100.0 %	0.38 [0.22, 0.66]	
Total events: 15 (Experimental), 45 (Pethidine)						
(1) Both groups also received scopolamine						

(Continued . . .)

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Study or subgroup	Experimental n/N	Pethidine n/N	Risk Ratio M-H,Fixed,95% CI	Weight	Risk Ratio M-H,Fixed,95% CI
Heterogeneity: not applicable					
Test for overall effect: Z = 3.46 (P = 0.00053)					
0.01 0.1 10 100 Favours experimental Favours control					

(1) Both groups also received scopolamine

Analysis 22.2. Comparison 22 IV nisentil versus IV pethidine, Outcome 2 Babies requiring resuscitation/ventilatory support.

Review: Parenteral opioids for maternal pain management in labour

Comparison: 22 IV nisentil versus IV pethidine

Outcome: 2 Babies requiring resuscitation/ventilatory support

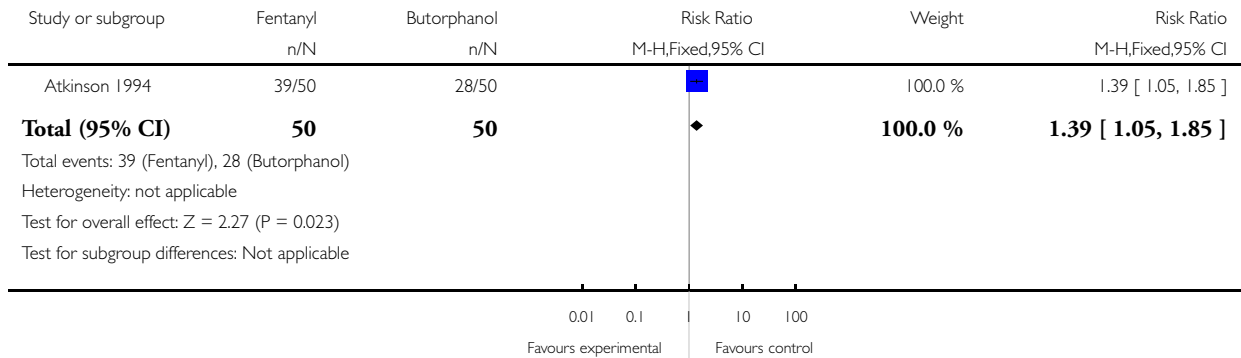
Study or subgroup	Experimental n/N	Pethidine n/N	Risk Ratio M-H,Fixed,95% CI	Weight	Risk Ratio M-H,Fixed,95% CI
Gillam 1958	14/185	8/210		100.0 %	1.99 [0.85, 4.63]
Total (95% CI)	185	210		100.0 %	1.99 [0.85, 4.63]
Total events: 14 (Experimental), 8 (Pethidine)					
Heterogeneity: not applicable					
Test for overall effect: Z = 1.59 (P = 0.11)					
Test for subgroup differences: Not applicable					
0.01 0.1 10 100 Favours experimental Favours pethidine					

Analysis 23.1. Comparison 23 IV fentanyl versus IV butorphanol, Outcome 1 Additional analgesia required (women requesting two or more doses).

Review: Parenteral opioids for maternal pain management in labour

Comparison: 23 IV fentanyl versus IV butorphanol

Outcome: 1 Additional analgesia required (women requesting two or more doses)

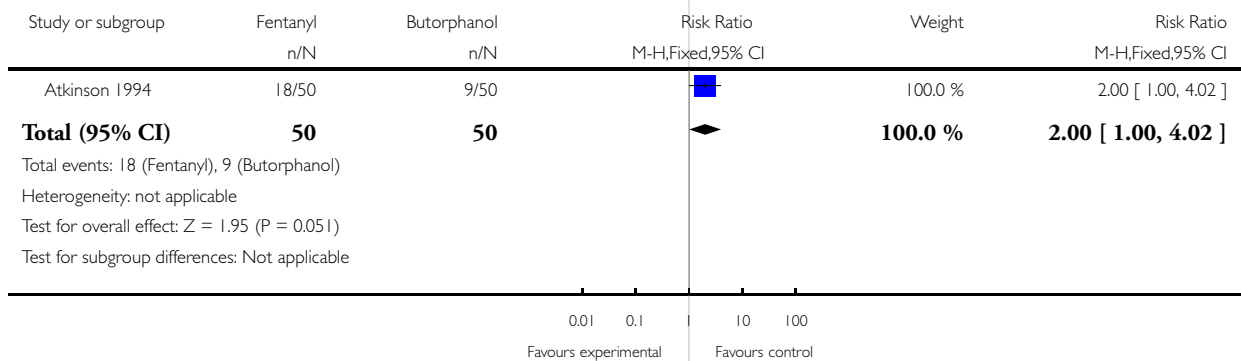


Analysis 23.2. Comparison 23 IV fentanyl versus IV butorphanol, Outcome 2 Epidural.

Review: Parenteral opioids for maternal pain management in labour

Comparison: 23 IV fentanyl versus IV butorphanol

Outcome: 2 Epidural

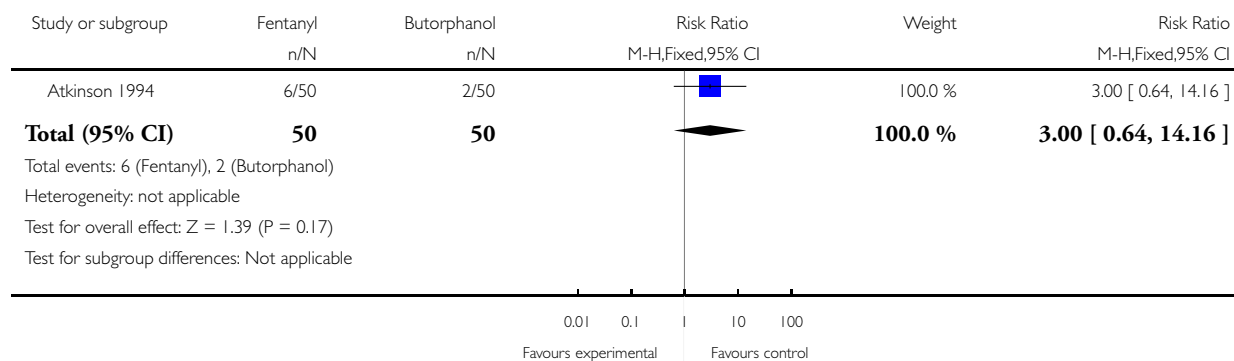


Analysis 23.3. Comparison 23 IV fentanyl versus IV butorphanol, Outcome 3 Maternal drowsiness (required tactile rousing).

Review: Parenteral opioids for maternal pain management in labour

Comparison: 23 IV fentanyl versus IV butorphanol

Outcome: 3 Maternal drowsiness (required tactile rousing)

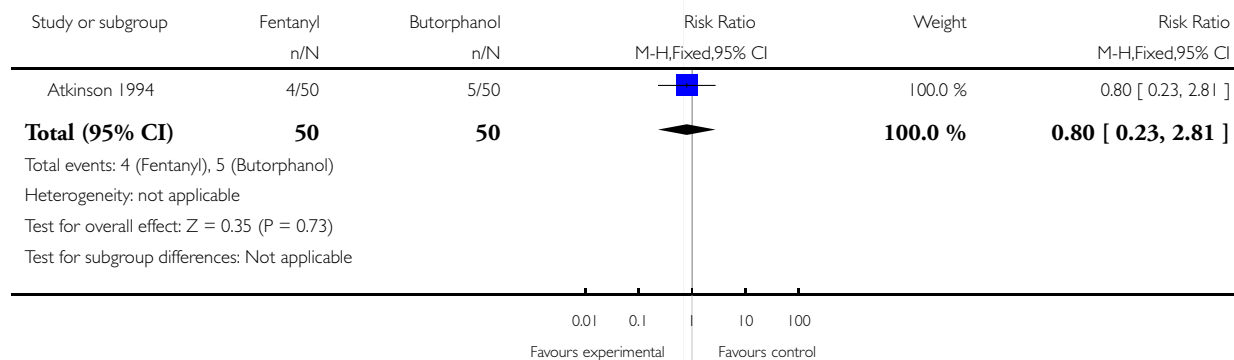


Analysis 23.4. Comparison 23 IV fentanyl versus IV butorphanol, Outcome 4 Caesarean section.

Review: Parenteral opioids for maternal pain management in labour

Comparison: 23 IV fentanyl versus IV butorphanol

Outcome: 4 Caesarean section

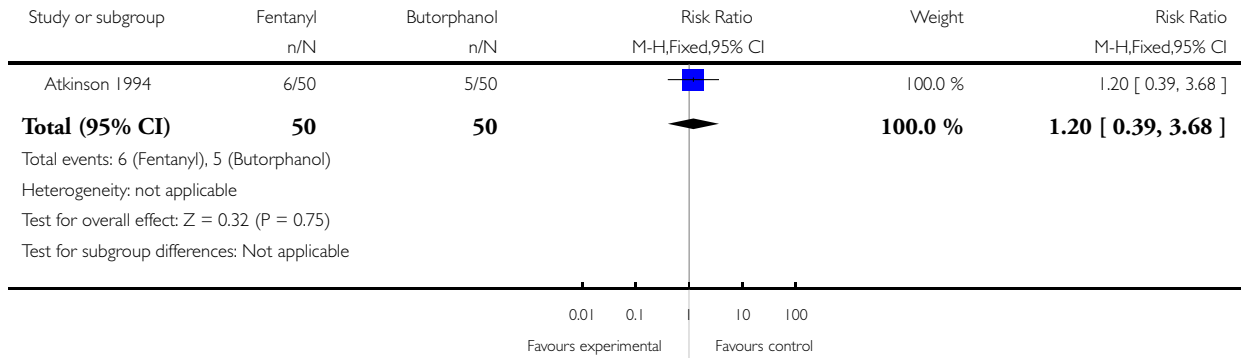


Analysis 23.5. Comparison 23 IV fentanyl versus IV butorphanol, Outcome 5 Apgar score < 7 at 5 minutes.

Review: Parenteral opioids for maternal pain management in labour

Comparison: 23 IV fentanyl versus IV butorphanol

Outcome: 5 Apgar score < 7 at 5 minutes

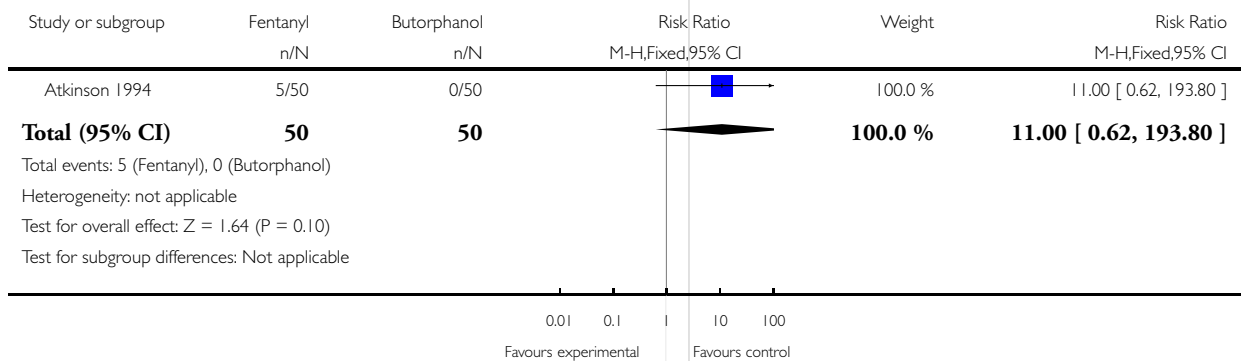


Analysis 23.6. Comparison 23 IV fentanyl versus IV butorphanol, Outcome 6 Babies requiring ventilatory support.

Review: Parenteral opioids for maternal pain management in labour

Comparison: 23 IV fentanyl versus IV butorphanol

Outcome: 6 Babies requiring ventilatory support

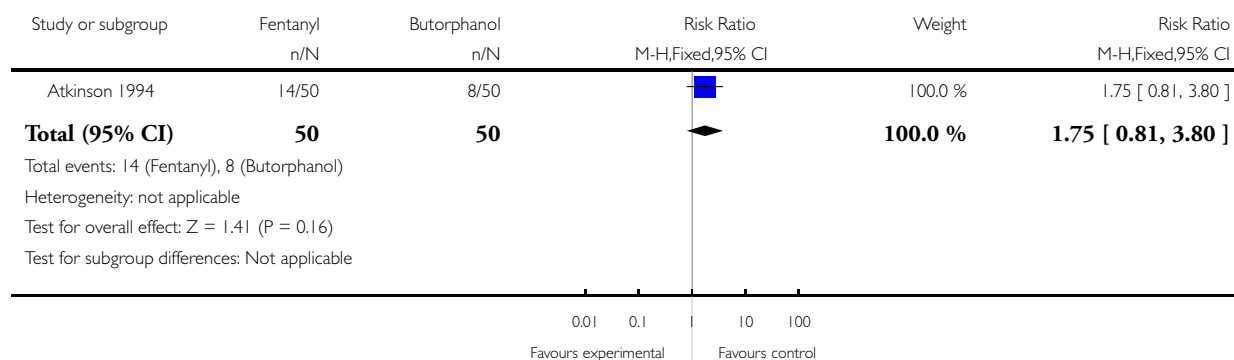


Analysis 23.7. Comparison 23 IV fentanyl versus IV butorphanol, Outcome 7 Naloxone required.

Review: Parenteral opioids for maternal pain management in labour

Comparison: 23 IV fentanyl versus IV butorphanol

Outcome: 7 Naloxone required

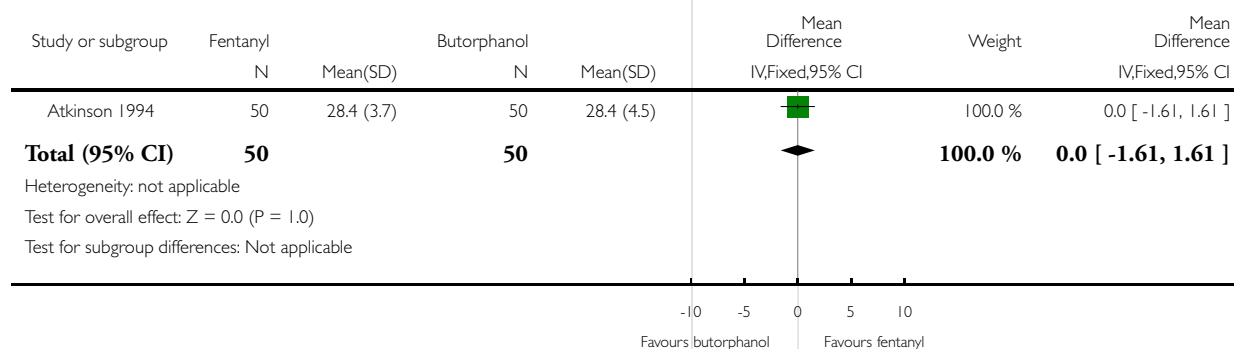


Analysis 23.8. Comparison 23 IV fentanyl versus IV butorphanol, Outcome 8 Neurobehavioural score at 2-4 hours.

Review: Parenteral opioids for maternal pain management in labour

Comparison: 23 IV fentanyl versus IV butorphanol

Outcome: 8 Neurobehavioural score at 2-4 hours

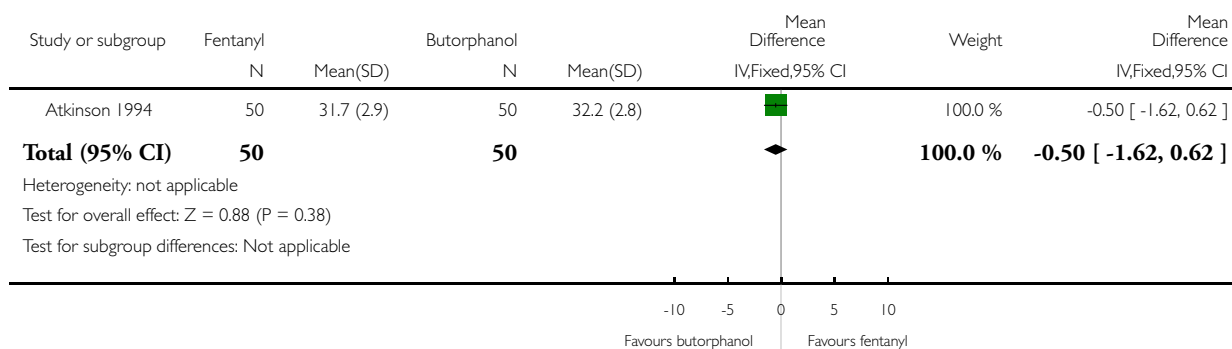


Analysis 23.9. Comparison 23 IV fentanyl versus IV butorphanol, Outcome 9 Neurobehavioural score at 24-36 hours.

Review: Parenteral opioids for maternal pain management in labour

Comparison: 23 IV fentanyl versus IV butorphanol

Outcome: 9 Neurobehavioural score at 24-36 hours

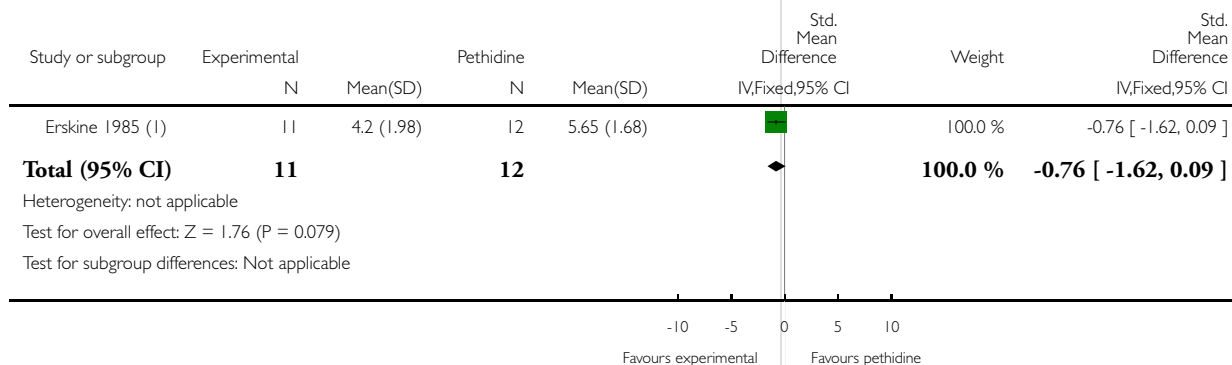


Analysis 24.1. Comparison 24 PCA pentazocine versus PCA pethidine, Outcome 1 Pain score in labour.

Review: Parenteral opioids for maternal pain management in labour

Comparison: 24 PCA pentazocine versus PCA pethidine

Outcome: 1 Pain score in labour



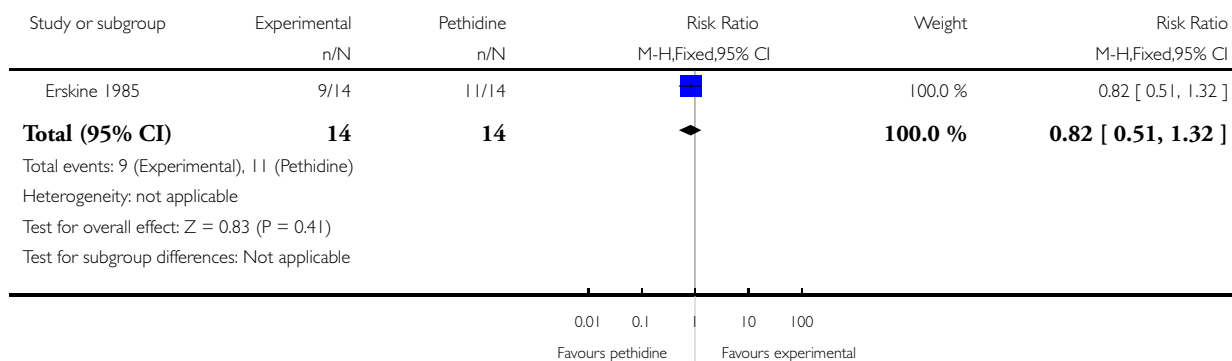
(1) Recorded just after delivery

Analysis 24.2. Comparison 24 PCA pentazocine versus PCA pethidine, Outcome 2 Pain relief rated as good one day after birth.

Review: Parenteral opioids for maternal pain management in labour

Comparison: 24 PCA pentazocine versus PCA pethidine

Outcome: 2 Pain relief rated as good one day after birth

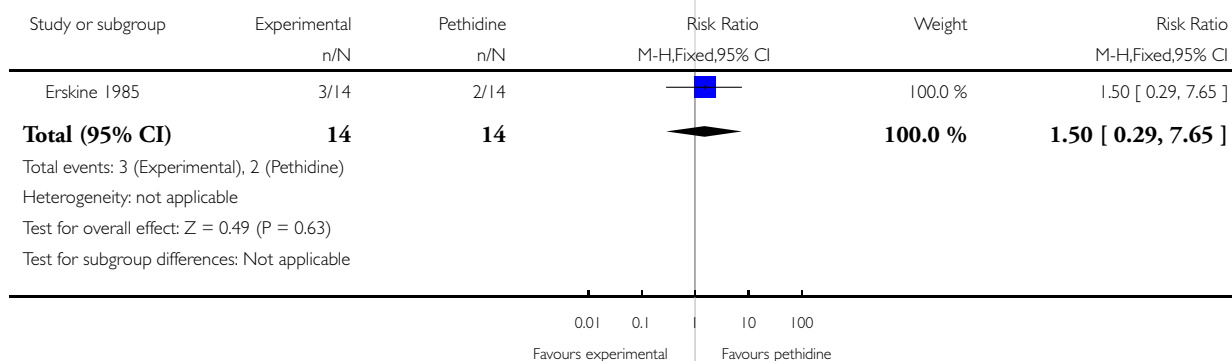


Analysis 24.3. Comparison 24 PCA pentazocine versus PCA pethidine, Outcome 3 Epidural.

Review: Parenteral opioids for maternal pain management in labour

Comparison: 24 PCA pentazocine versus PCA pethidine

Outcome: 3 Epidural

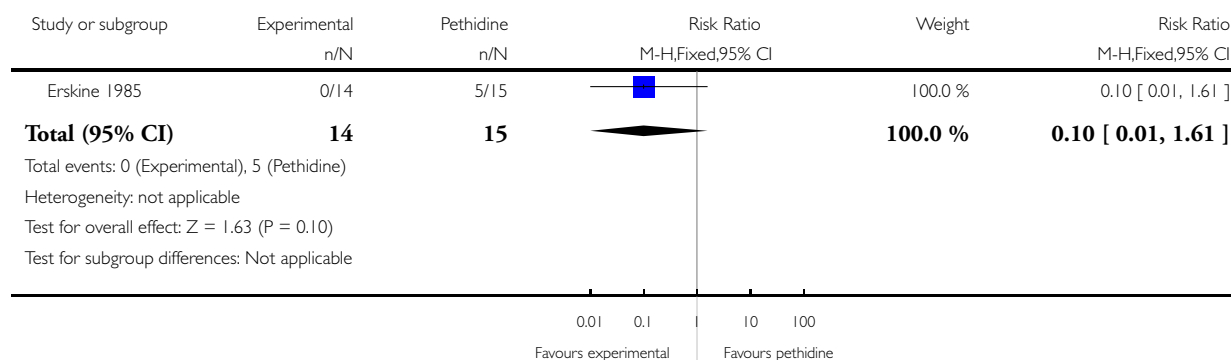


Analysis 24.4. Comparison 24 PCA pentazocine versus PCA pethidine, Outcome 4 Nausea and vomiting.

Review: Parenteral opioids for maternal pain management in labour

Comparison: 24 PCA pentazocine versus PCA pethidine

Outcome: 4 Nausea and vomiting

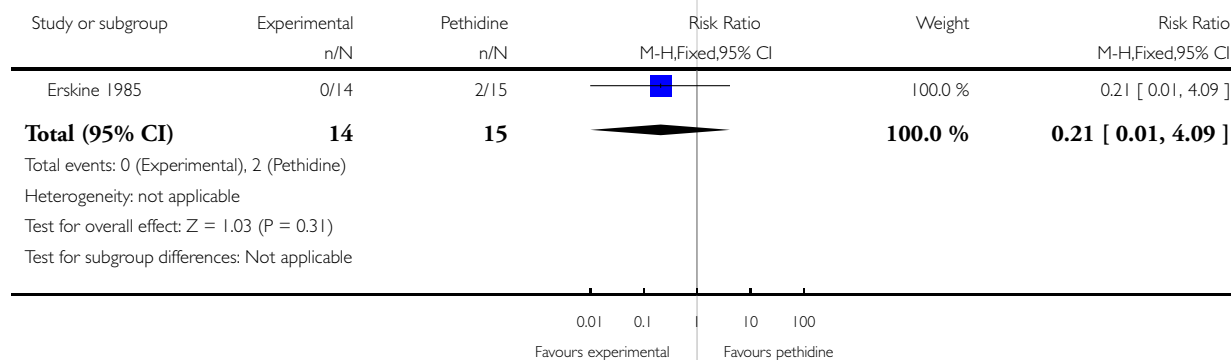


Analysis 24.5. Comparison 24 PCA pentazocine versus PCA pethidine, Outcome 5 Sedation.

Review: Parenteral opioids for maternal pain management in labour

Comparison: 24 PCA pentazocine versus PCA pethidine

Outcome: 5 Sedation

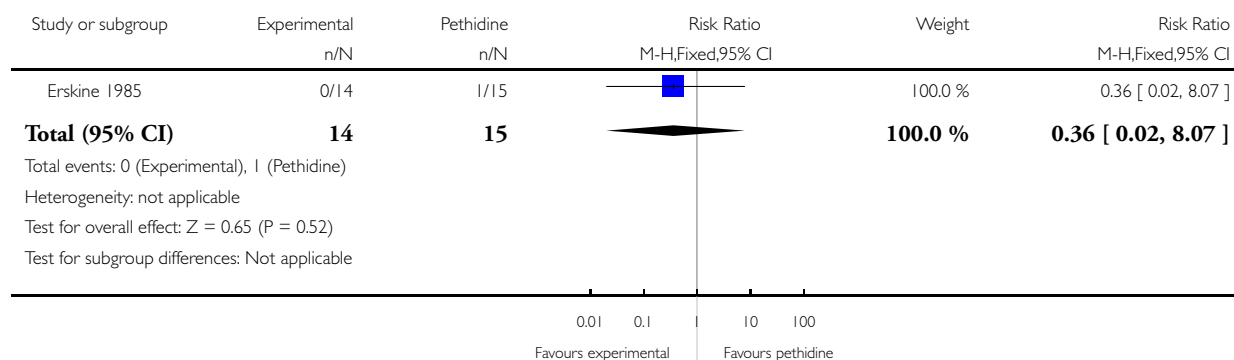


Analysis 24.6. Comparison 24 PCA pentazocine versus PCA pethidine, Outcome 6 Caesarean section.

Review: Parenteral opioids for maternal pain management in labour

Comparison: 24 PCA pentazocine versus PCA pethidine

Outcome: 6 Caesarean section

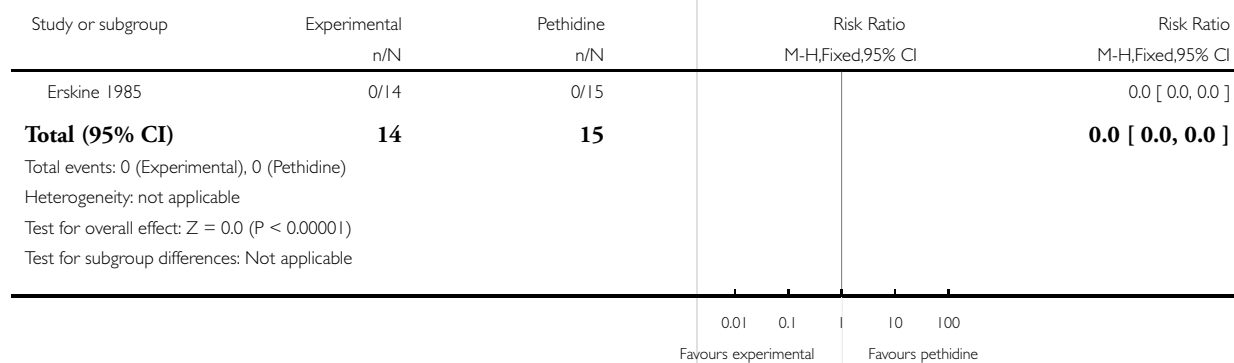


Analysis 24.7. Comparison 24 PCA pentazocine versus PCA pethidine, Outcome 7 Apgar score < 7 at 5 minutes.

Review: Parenteral opioids for maternal pain management in labour

Comparison: 24 PCA pentazocine versus PCA pethidine

Outcome: 7 Apgar score < 7 at 5 minutes

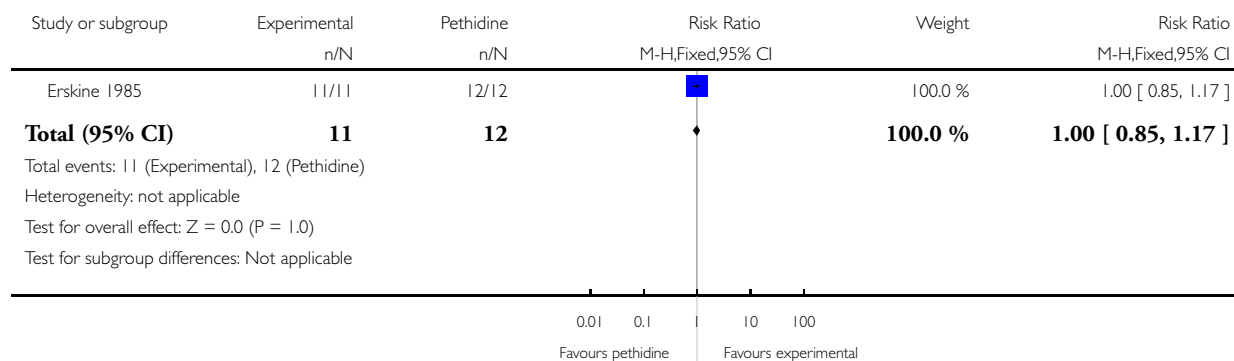


Analysis 24.8. Comparison 24 PCA pentazocine versus PCA pethidine, Outcome 8 Breastfeeding at discharge.

Review: Parenteral opioids for maternal pain management in labour

Comparison: 24 PCA pentazocine versus PCA pethidine

Outcome: 8 Breastfeeding at discharge

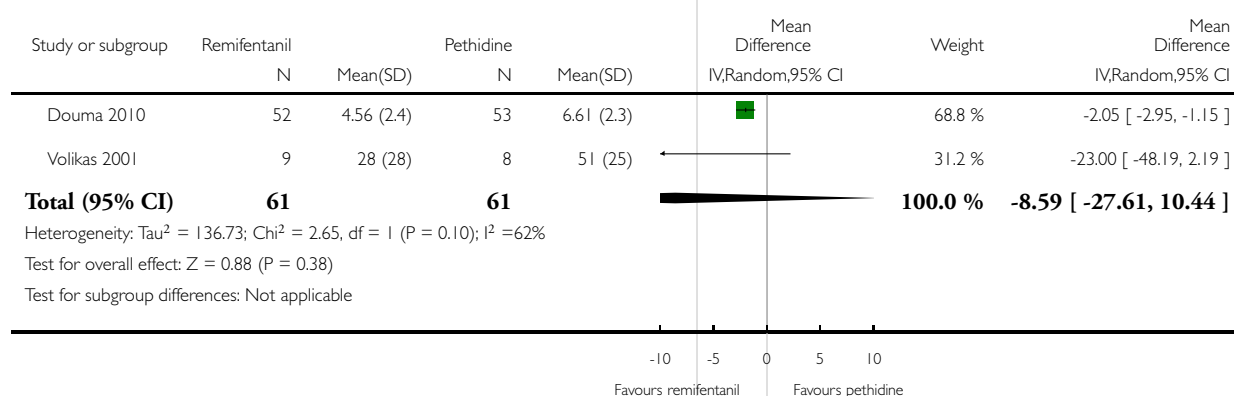


Analysis 25.1. Comparison 25 PCA remifentanil versus PCA pethidine, Outcome 1 Pain score in labour.

Review: Parenteral opioids for maternal pain management in labour

Comparison: 25 PCA remifentanil versus PCA pethidine

Outcome: 1 Pain score in labour

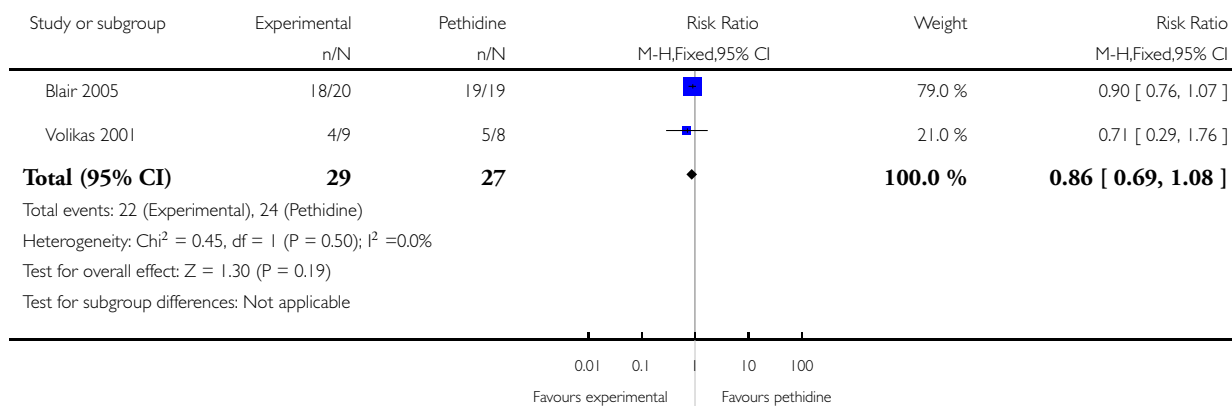


Analysis 25.2. Comparison 25 PCA remifentanil versus PCA pethidine, Outcome 2 Women receiving other analgesia (Entonox).

Review: Parenteral opioids for maternal pain management in labour

Comparison: 25 PCA remifentanil versus PCA pethidine

Outcome: 2 Women receiving other analgesia (Entonox)

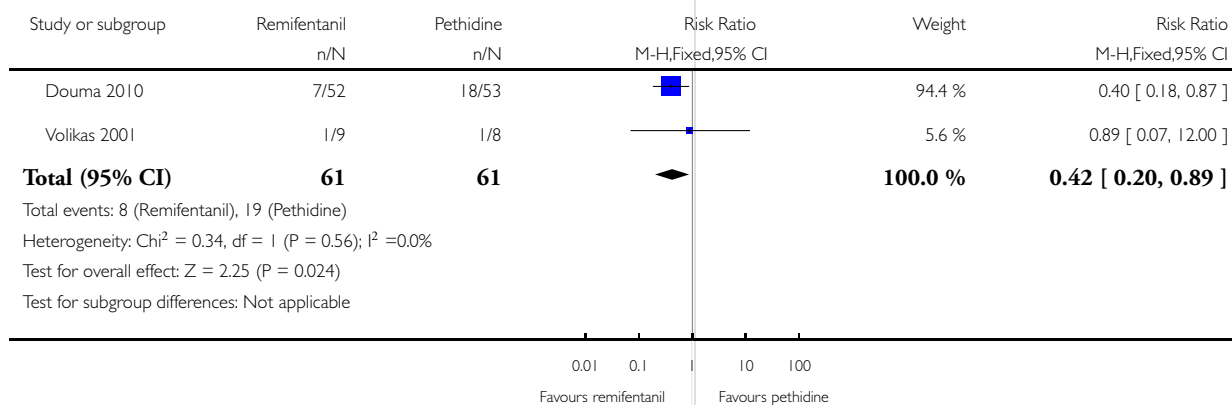


Analysis 25.3. Comparison 25 PCA remifentanil versus PCA pethidine, Outcome 3 Epidural.

Review: Parenteral opioids for maternal pain management in labour

Comparison: 25 PCA remifentanil versus PCA pethidine

Outcome: 3 Epidural

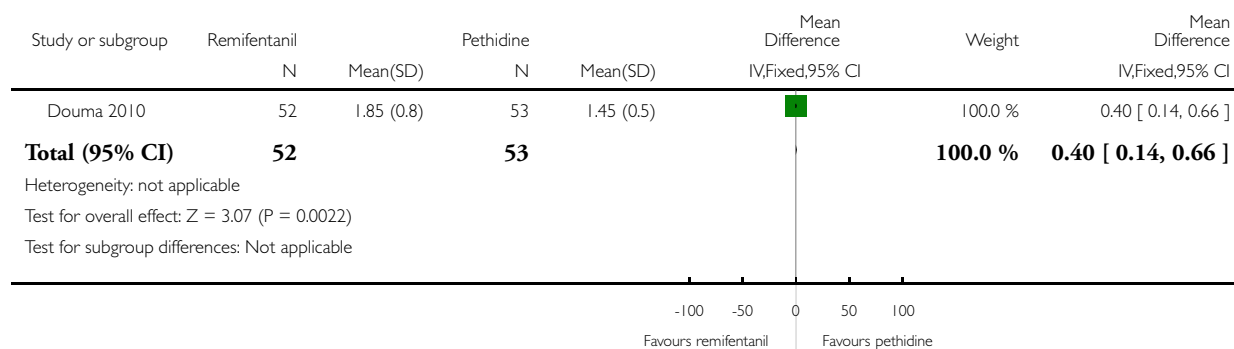


Analysis 25.4. Comparison 25 PCA remifentanil versus PCA pethidine, Outcome 4 Maternal sleepiness during labour.

Review: Parenteral opioids for maternal pain management in labour

Comparison: 25 PCA remifentanil versus PCA pethidine

Outcome: 4 Maternal sleepiness during labour

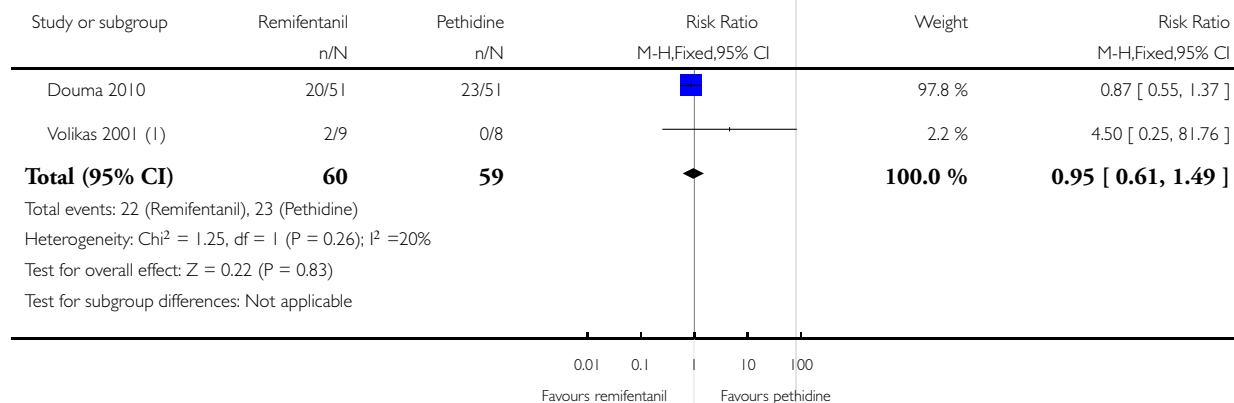


Analysis 25.5. Comparison 25 PCA remifentanil versus PCA pethidine, Outcome 5 Nausea and vomiting.

Review: Parenteral opioids for maternal pain management in labour

Comparison: 25 PCA remifentanil versus PCA pethidine

Outcome: 5 Nausea and vomiting

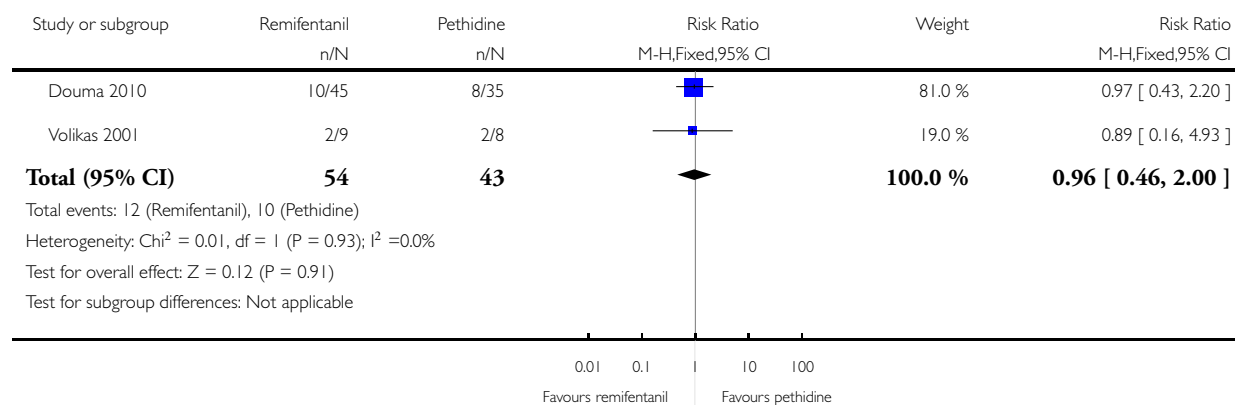


Analysis 25.6. Comparison 25 PCA remifentanil versus PCA pethidine, Outcome 6 Assisted vaginal birth.

Review: Parenteral opioids for maternal pain management in labour

Comparison: 25 PCA remifentanil versus PCA pethidine

Outcome: 6 Assisted vaginal birth

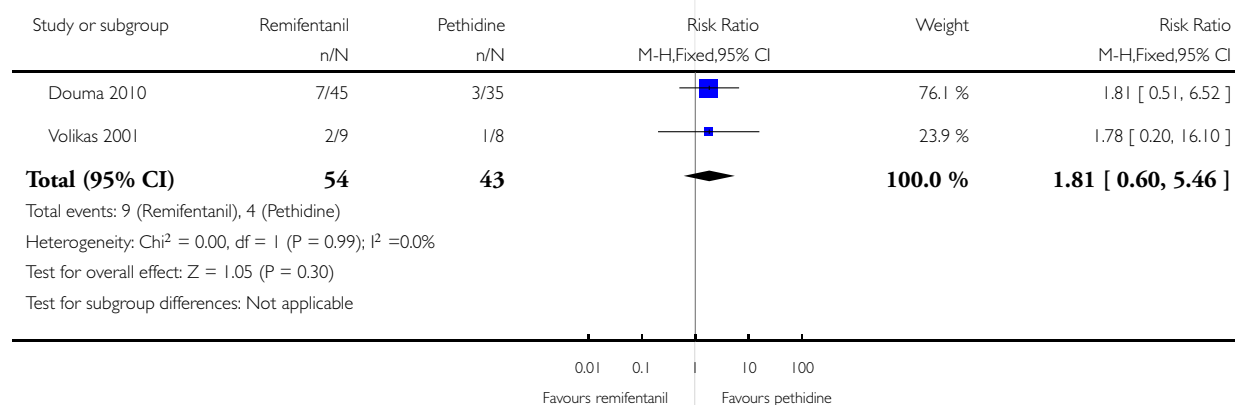


Analysis 25.7. Comparison 25 PCA remifentanil versus PCA pethidine, Outcome 7 Caesarean section.

Review: Parenteral opioids for maternal pain management in labour

Comparison: 25 PCA remifentanil versus PCA pethidine

Outcome: 7 Caesarean section

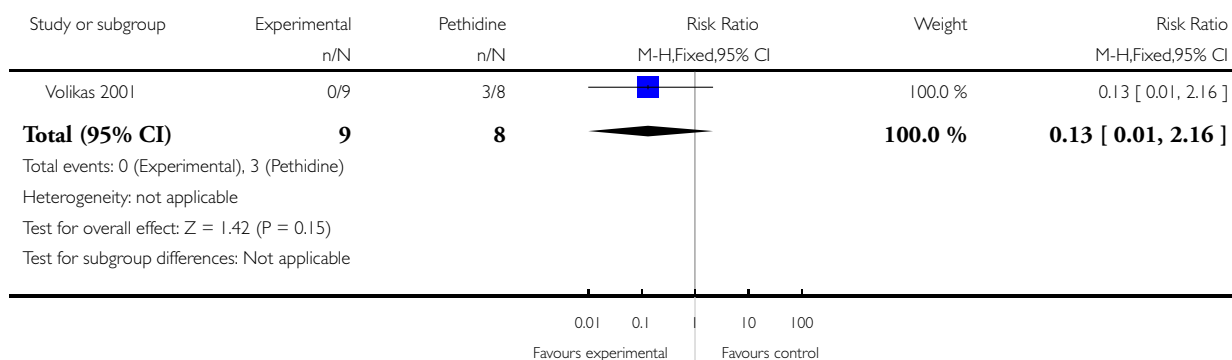


Analysis 25.8. Comparison 25 PCA remifentanil versus PCA pethidine, Outcome 8 Apgar score < 7 at 5 minutes.

Review: Parenteral opioids for maternal pain management in labour

Comparison: 25 PCA remifentanil versus PCA pethidine

Outcome: 8 Apgar score < 7 at 5 minutes

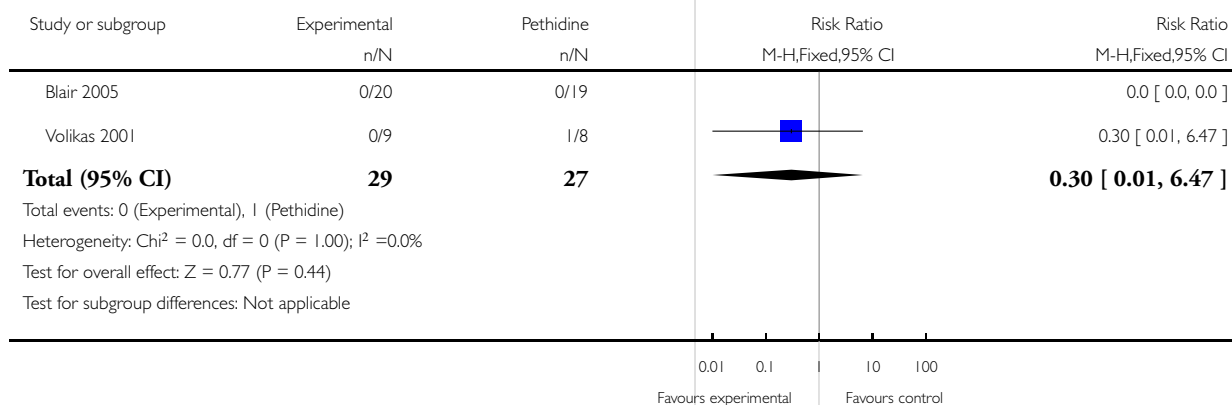


Analysis 25.9. Comparison 25 PCA remifentanil versus PCA pethidine, Outcome 9 Naloxone administered.

Review: Parenteral opioids for maternal pain management in labour

Comparison: 25 PCA remifentanil versus PCA pethidine

Outcome: 9 Naloxone administered

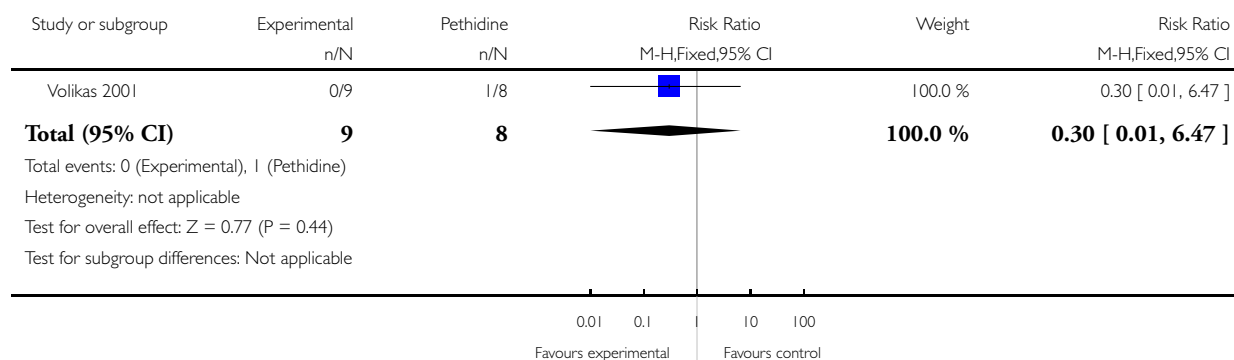


Analysis 25.10. Comparison 25 PCA remifentanil versus PCA pethidine, Outcome 10 Admission to NICU.

Review: Parenteral opioids for maternal pain management in labour

Comparison: 25 PCA remifentanil versus PCA pethidine

Outcome: 10 Admission to NICU

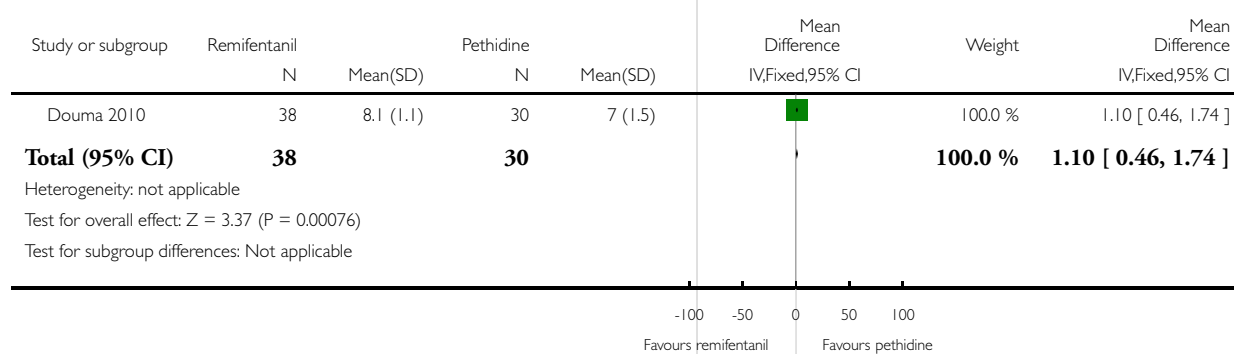


Analysis 25.11. Comparison 25 PCA remifentanil versus PCA pethidine, Outcome 11 Satisfaction with childbirth experience.

Review: Parenteral opioids for maternal pain management in labour

Comparison: 25 PCA remifentanil versus PCA pethidine

Outcome: 11 Satisfaction with childbirth experience

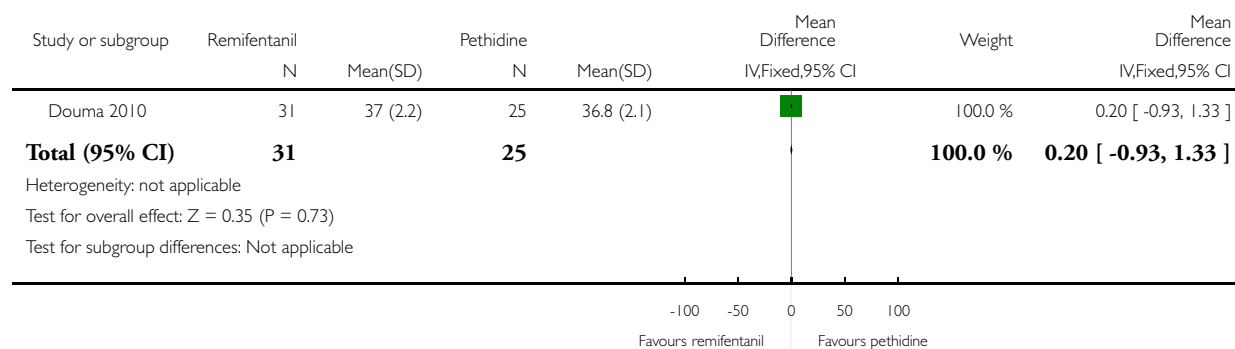


Analysis 25.12. Comparison 25 PCA remifentanil versus PCA pethidine, Outcome 12 Neurobehavioural score (15 minutes post delivery).

Review: Parenteral opioids for maternal pain management in labour

Comparison: 25 PCA remifentanil versus PCA pethidine

Outcome: 12 Neurobehavioural score (15 minutes post delivery)

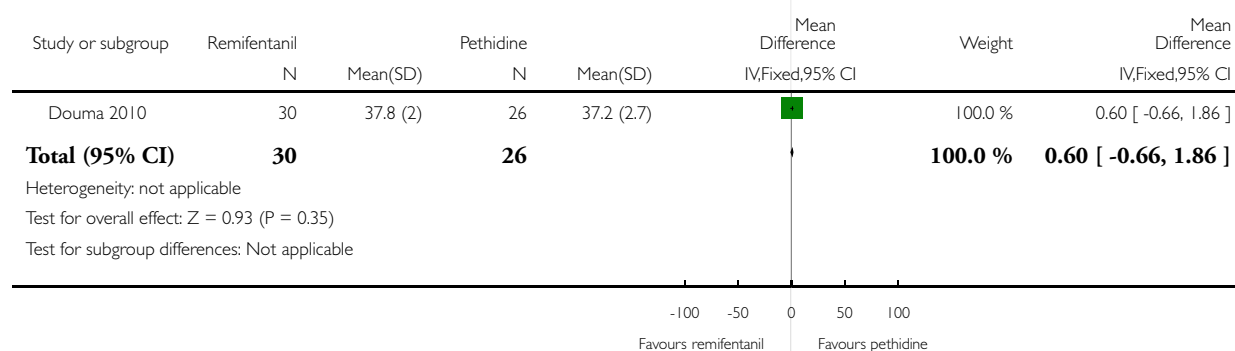


Analysis 25.13. Comparison 25 PCA remifentanil versus PCA pethidine, Outcome 13 Neurobehavioural score (2 hours post delivery).

Review: Parenteral opioids for maternal pain management in labour

Comparison: 25 PCA remifentanil versus PCA pethidine

Outcome: 13 Neurobehavioural score (2 hours post delivery)

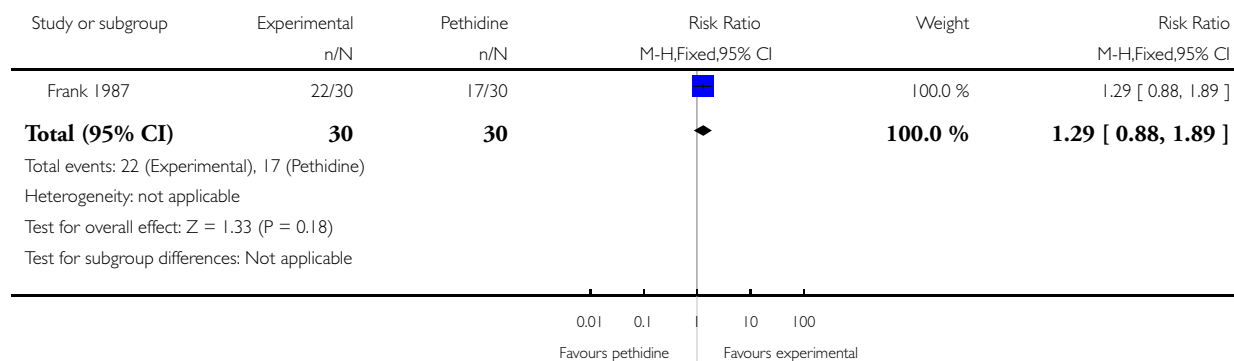


Analysis 26.1. Comparison 26 PCA nalbuphine versus PCA pethidine, Outcome 1 Pain relief in labour measured in the postnatal period (rated good or excellent).

Review: Parenteral opioids for maternal pain management in labour

Comparison: 26 PCA nalbuphine versus PCA pethidine

Outcome: 1 Pain relief in labour measured in the postnatal period (rated good or excellent)

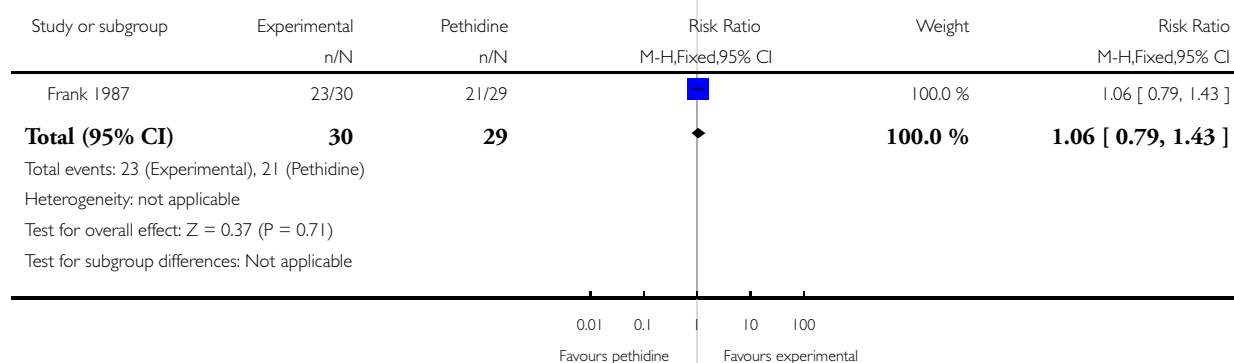


Analysis 26.2. Comparison 26 PCA nalbuphine versus PCA pethidine, Outcome 2 Would use the same pain relief again.

Review: Parenteral opioids for maternal pain management in labour

Comparison: 26 PCA nalbuphine versus PCA pethidine

Outcome: 2 Would use the same pain relief again

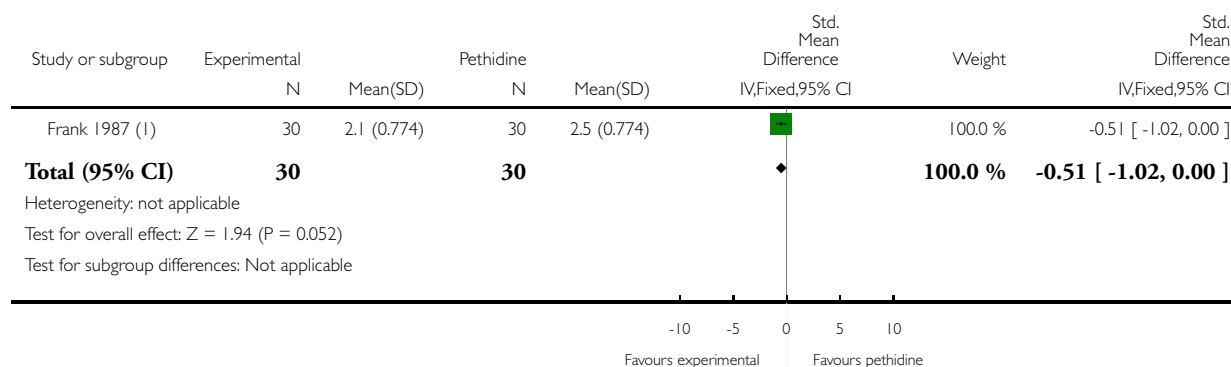


Analysis 26.3. Comparison 26 PCA nalbuphine versus PCA pethidine, Outcome 3 Pain score in labour.

Review: Parenteral opioids for maternal pain management in labour

Comparison: 26 PCA nalbuphine versus PCA pethidine

Outcome: 3 Pain score in labour



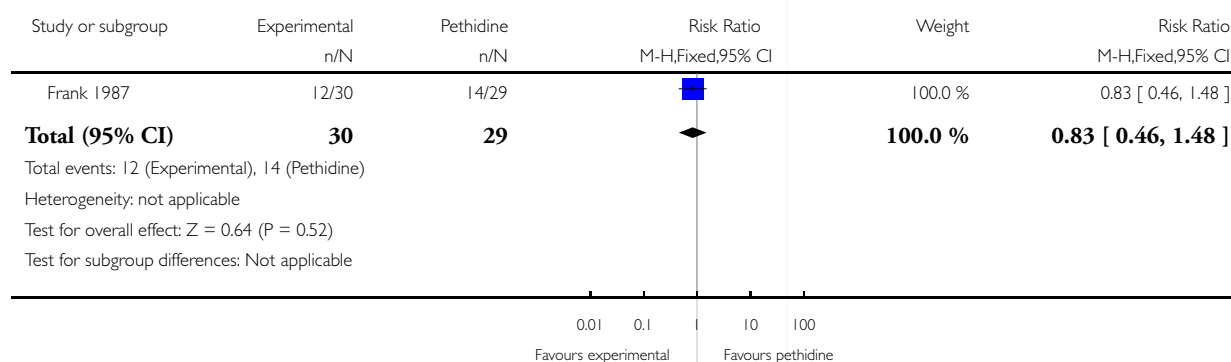
(1) SD estimated from P value 0.05

Analysis 26.4. Comparison 26 PCA nalbuphine versus PCA pethidine, Outcome 4 Women receiving other analgesia (Entonox).

Review: Parenteral opioids for maternal pain management in labour

Comparison: 26 PCA nalbuphine versus PCA pethidine

Outcome: 4 Women receiving other analgesia (Entonox)

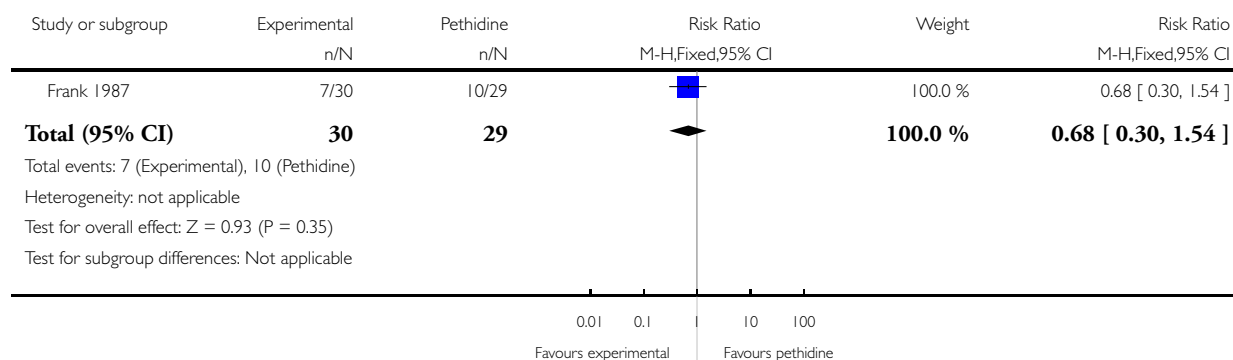


Analysis 26.5. Comparison 26 PCA nalbuphine versus PCA pethidine, Outcome 5 Nausea and vomiting.

Review: Parenteral opioids for maternal pain management in labour

Comparison: 26 PCA nalbuphine versus PCA pethidine

Outcome: 5 Nausea and vomiting

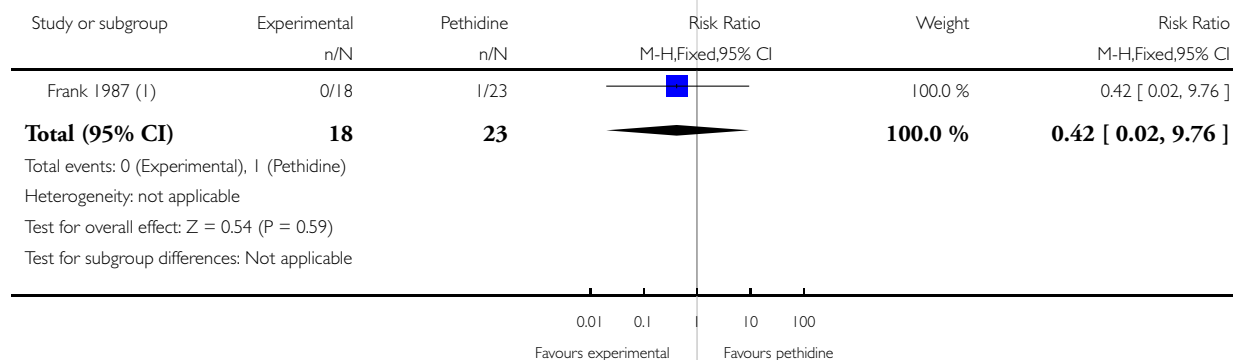


Analysis 26.6. Comparison 26 PCA nalbuphine versus PCA pethidine, Outcome 6 Apgar score < 7 at 5 minutes.

Review: Parenteral opioids for maternal pain management in labour

Comparison: 26 PCA nalbuphine versus PCA pethidine

Outcome: 6 Apgar score < 7 at 5 minutes



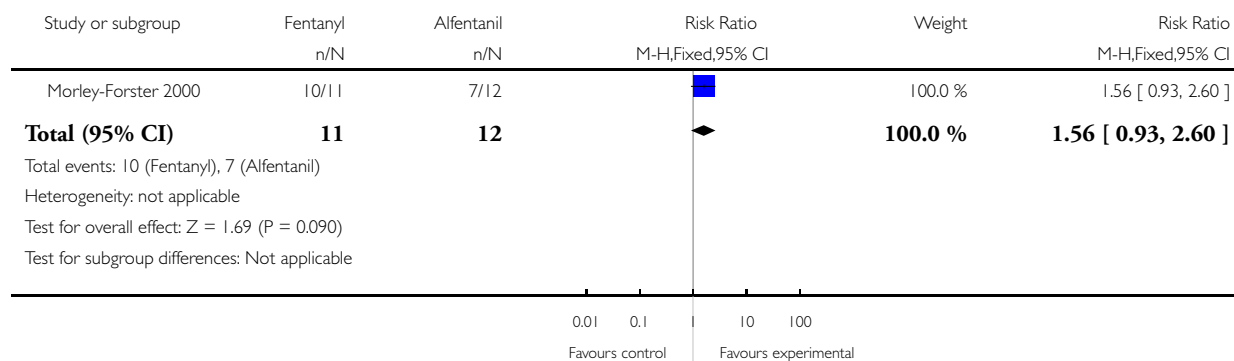
(1) Those babies delivered within 4 hrs of medication only

Analysis 27.1. Comparison 27 PCA fentanyl versus PCA alfentanil, Outcome 1 Pain relief described as adequate (recorded after delivery).

Review: Parenteral opioids for maternal pain management in labour

Comparison: 27 PCA fentanyl versus PCA alfentanil

Outcome: 1 Pain relief described as adequate (recorded after delivery)

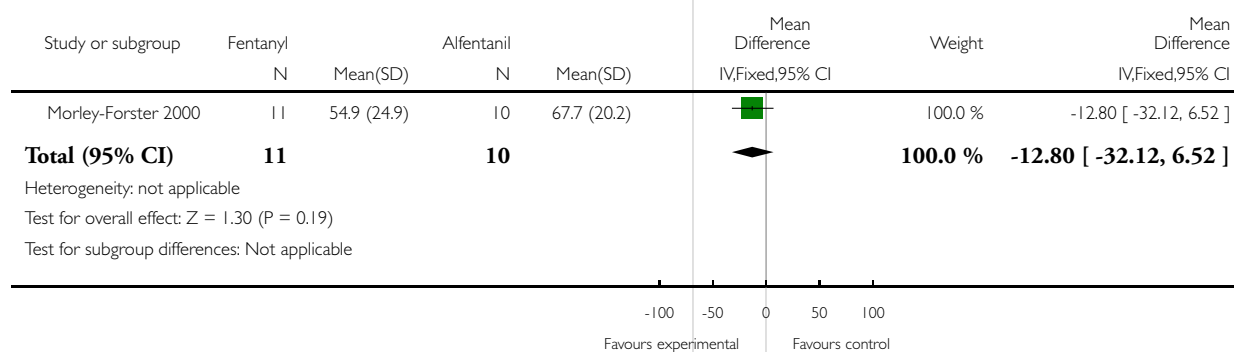


Analysis 27.2. Comparison 27 PCA fentanyl versus PCA alfentanil, Outcome 2 Pain score at 4-6 cm cervical dilatation.

Review: Parenteral opioids for maternal pain management in labour

Comparison: 27 PCA fentanyl versus PCA alfentanil

Outcome: 2 Pain score at 4-6 cm cervical dilatation

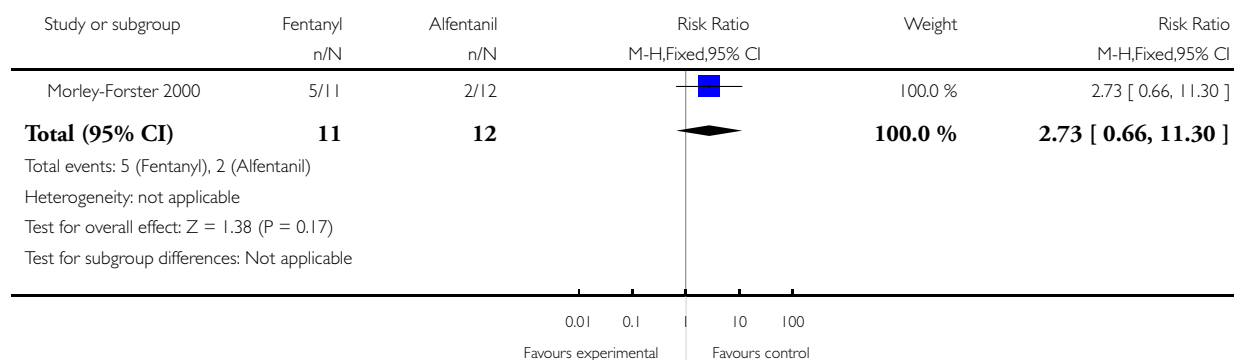


Analysis 27.3. Comparison 27 PCA fentanyl versus PCA alfentanil, Outcome 3 Nausea.

Review: Parenteral opioids for maternal pain management in labour

Comparison: 27 PCA fentanyl versus PCA alfentanil

Outcome: 3 Nausea

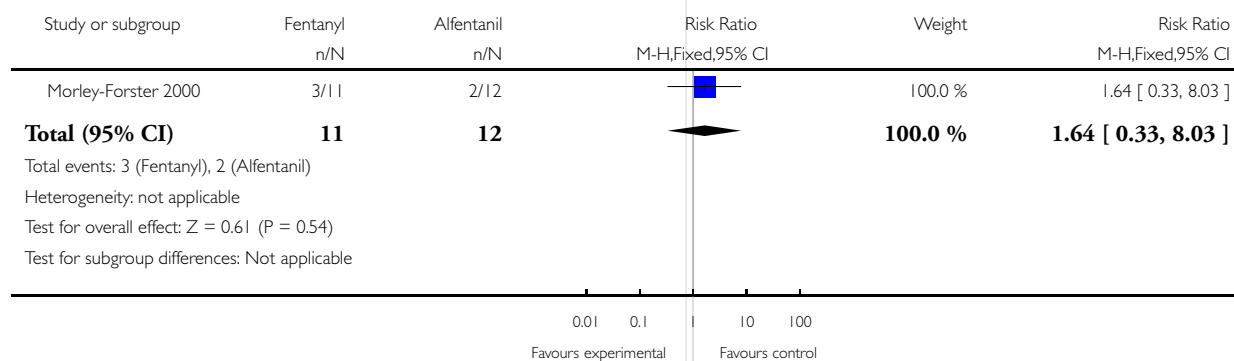


Analysis 27.4. Comparison 27 PCA fentanyl versus PCA alfentanil, Outcome 4 Caesarean section.

Review: Parenteral opioids for maternal pain management in labour

Comparison: 27 PCA fentanyl versus PCA alfentanil

Outcome: 4 Caesarean section

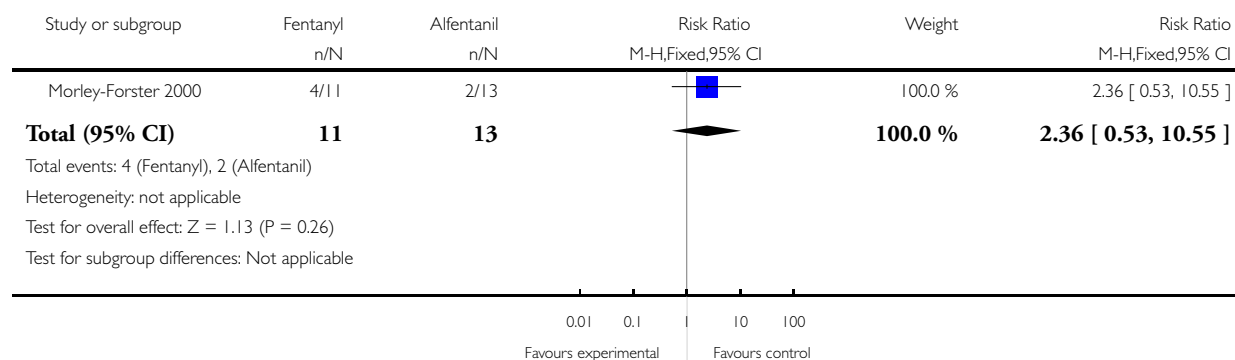


Analysis 27.5. Comparison 27 PCA fentanyl versus PCA alfentanil, Outcome 5 Naloxone required.

Review: Parenteral opioids for maternal pain management in labour

Comparison: 27 PCA fentanyl versus PCA alfentanil

Outcome: 5 Naloxone required

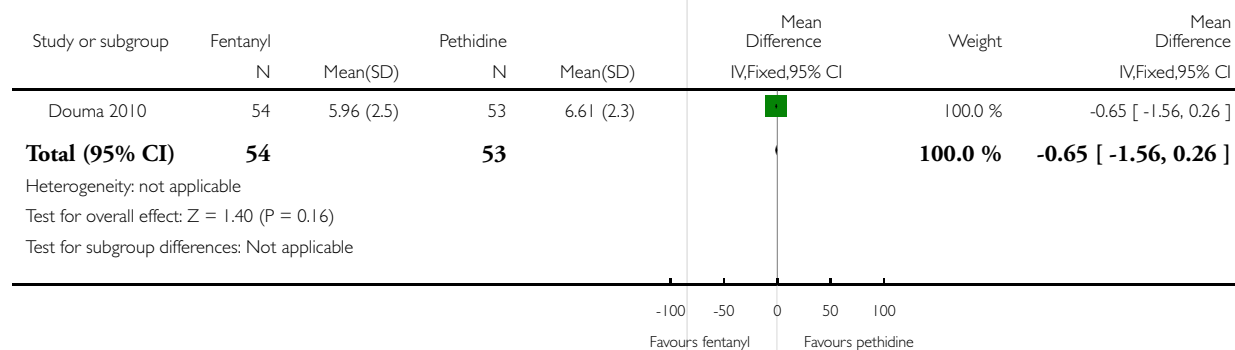


Analysis 28.1. Comparison 28 PCA fentanyl versus PCA pethidine, Outcome 1 Pain score in labour.

Review: Parenteral opioids for maternal pain management in labour

Comparison: 28 PCA fentanyl versus PCA pethidine

Outcome: 1 Pain score in labour

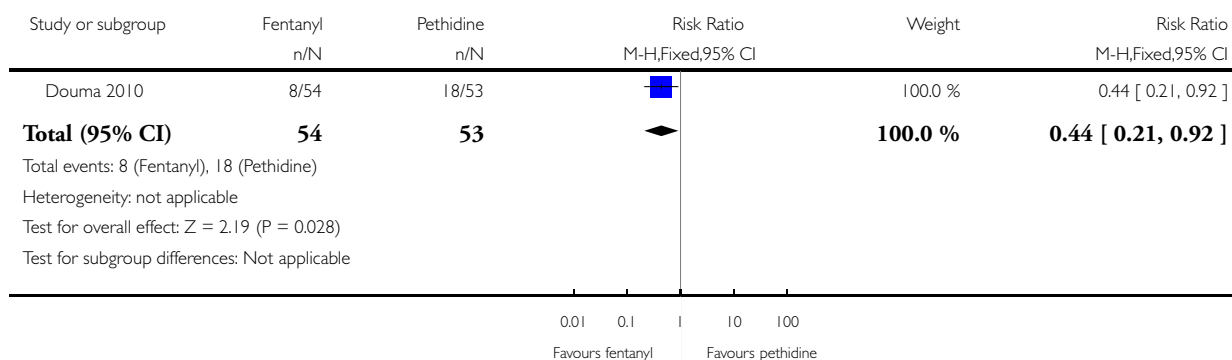


Analysis 28.2. Comparison 28 PCA fentanyl versus PCA pethidine, Outcome 2 Epidural.

Review: Parenteral opioids for maternal pain management in labour

Comparison: 28 PCA fentanyl versus PCA pethidine

Outcome: 2 Epidural

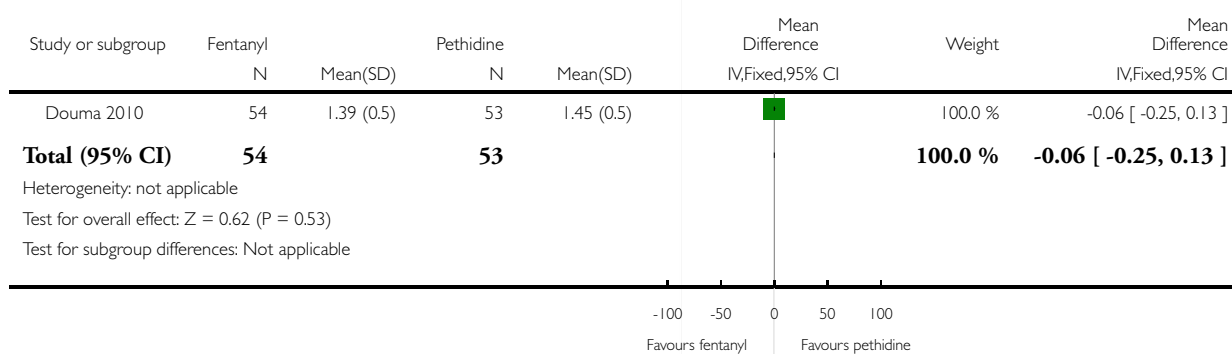


Analysis 28.3. Comparison 28 PCA fentanyl versus PCA pethidine, Outcome 3 Maternal sleepiness during labour.

Review: Parenteral opioids for maternal pain management in labour

Comparison: 28 PCA fentanyl versus PCA pethidine

Outcome: 3 Maternal sleepiness during labour

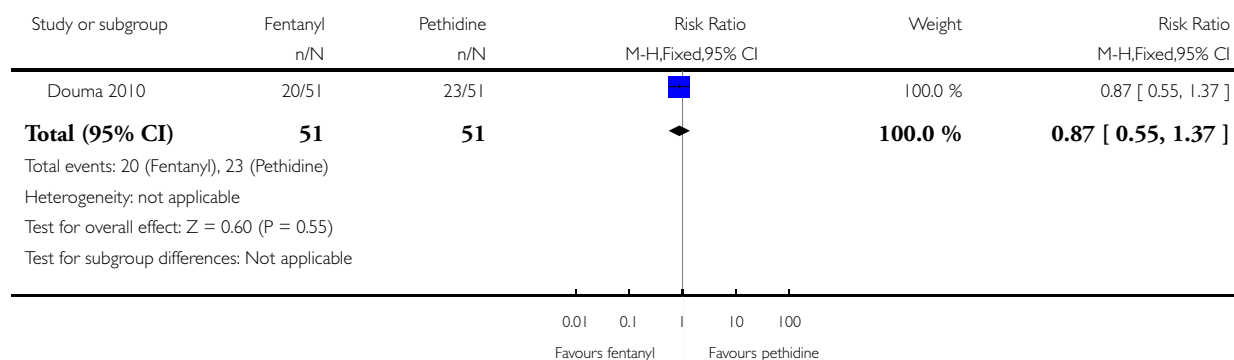


Analysis 28.4. Comparison 28 PCA fentanyl versus PCA pethidine, Outcome 4 Nausea and vomiting.

Review: Parenteral opioids for maternal pain management in labour

Comparison: 28 PCA fentanyl versus PCA pethidine

Outcome: 4 Nausea and vomiting

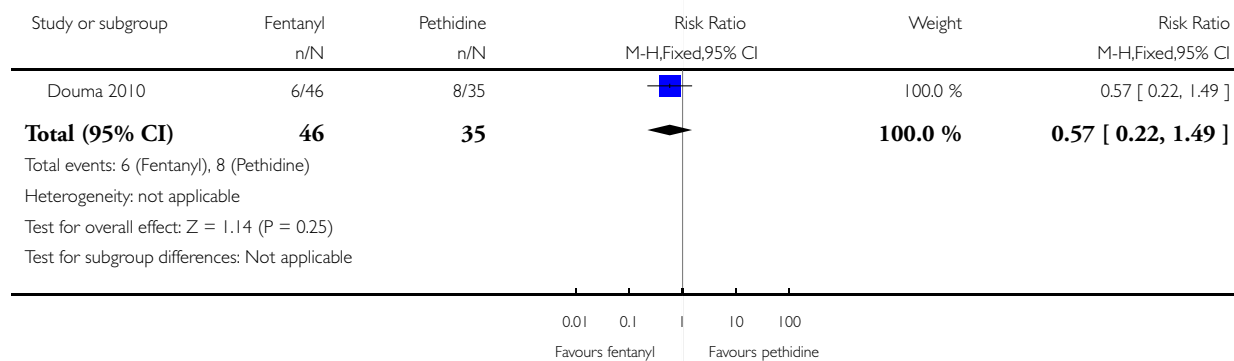


Analysis 28.5. Comparison 28 PCA fentanyl versus PCA pethidine, Outcome 5 Assisted vaginal birth.

Review: Parenteral opioids for maternal pain management in labour

Comparison: 28 PCA fentanyl versus PCA pethidine

Outcome: 5 Assisted vaginal birth

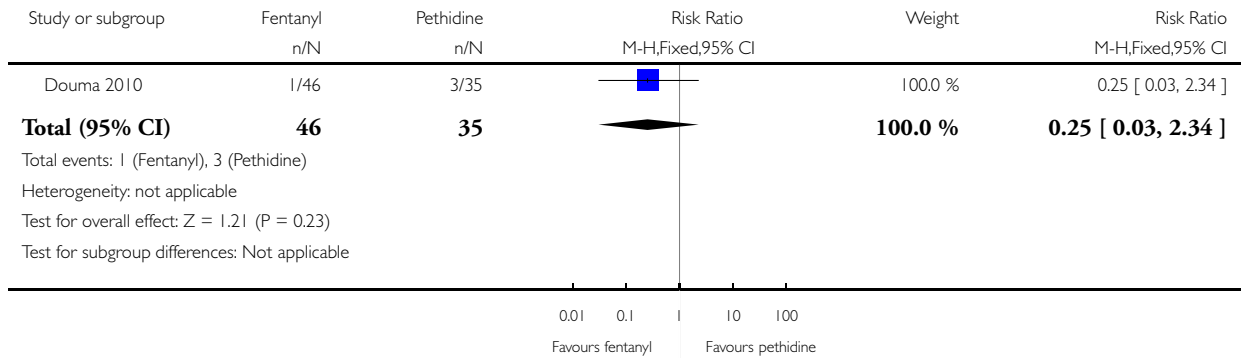


Analysis 28.6. Comparison 28 PCA fentanyl versus PCA pethidine, Outcome 6 Caesarean section.

Review: Parenteral opioids for maternal pain management in labour

Comparison: 28 PCA fentanyl versus PCA pethidine

Outcome: 6 Caesarean section

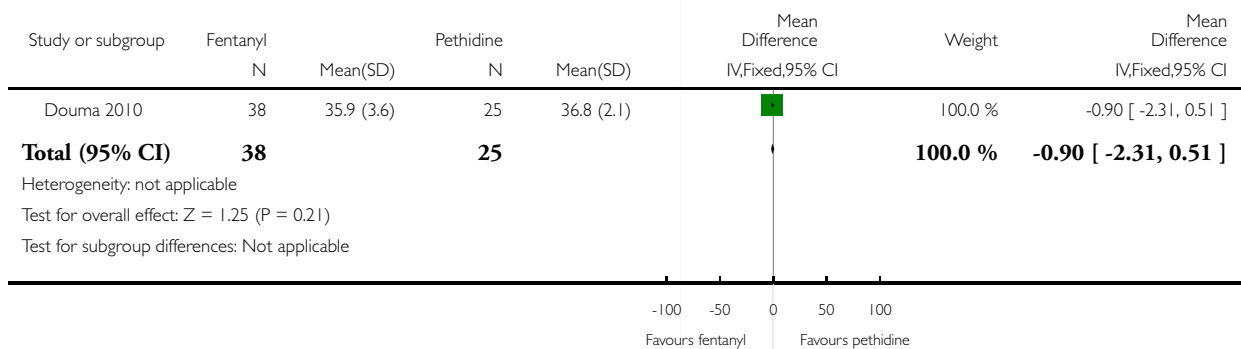


Analysis 28.7. Comparison 28 PCA fentanyl versus PCA pethidine, Outcome 7 Neurobehavioural score (15 minutes post delivery).

Review: Parenteral opioids for maternal pain management in labour

Comparison: 28 PCA fentanyl versus PCA pethidine

Outcome: 7 Neurobehavioural score (15 minutes post delivery)

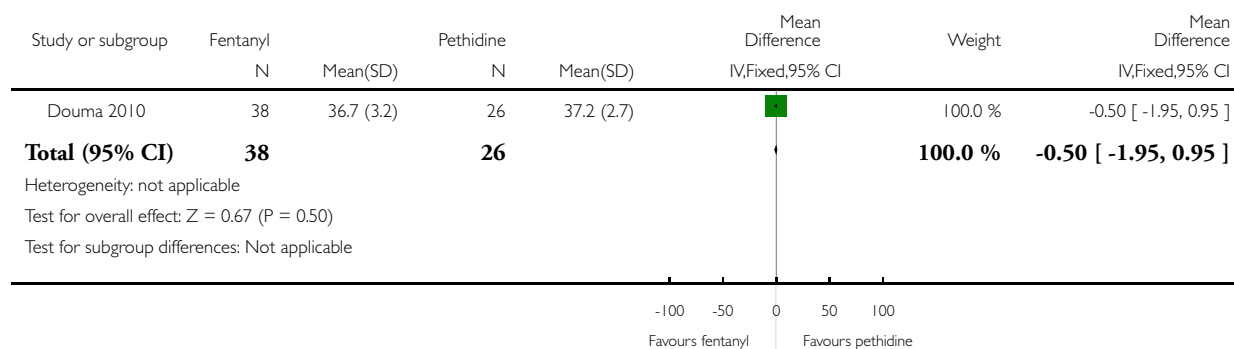


Analysis 28.8. Comparison 28 PCA fentanyl versus PCA pethidine, Outcome 8 Neurobehavioural score (2 hours post delivery).

Review: Parenteral opioids for maternal pain management in labour

Comparison: 28 PCA fentanyl versus PCA pethidine

Outcome: 8 Neurobehavioural score (2 hours post delivery)

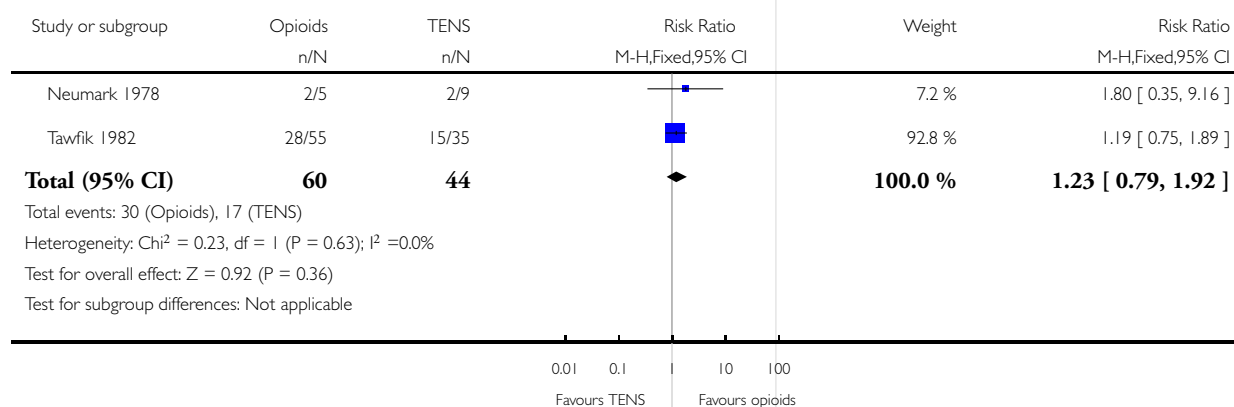


Analysis 29.1. Comparison 29 Opioids versus TENS, Outcome 1 Maternal satisfaction with analgesia measured post delivery (rated as good).

Review: Parenteral opioids for maternal pain management in labour

Comparison: 29 Opioids versus TENS

Outcome: 1 Maternal satisfaction with analgesia measured post delivery (rated as good)

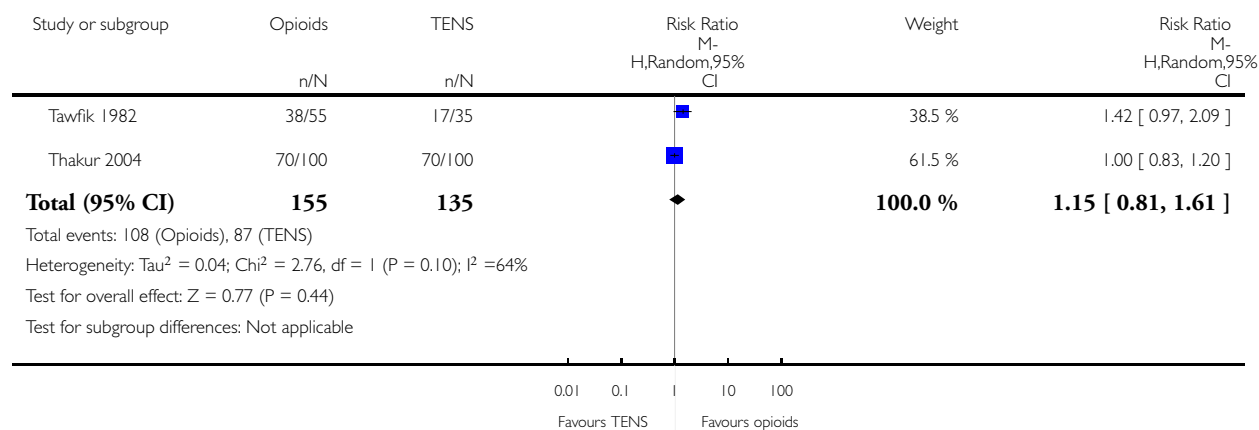


Analysis 29.2. Comparison 29 Opioids versus TENS, Outcome 2 Maternal pain score measured during labour.

Review: Parenteral opioids for maternal pain management in labour

Comparison: 29 Opioids versus TENS

Outcome: 2 Maternal pain score measured during labour

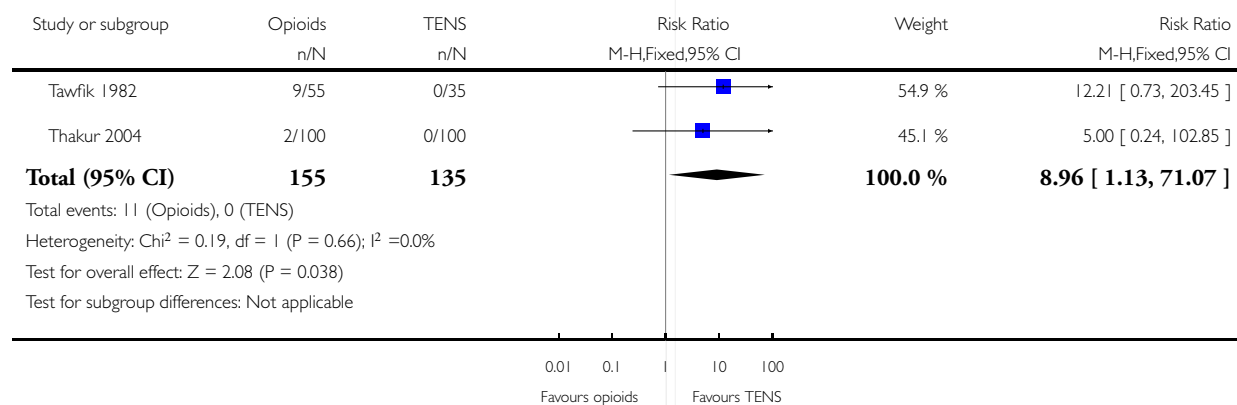


Analysis 29.3. Comparison 29 Opioids versus TENS, Outcome 3 Drowsiness.

Review: Parenteral opioids for maternal pain management in labour

Comparison: 29 Opioids versus TENS

Outcome: 3 Drowsiness

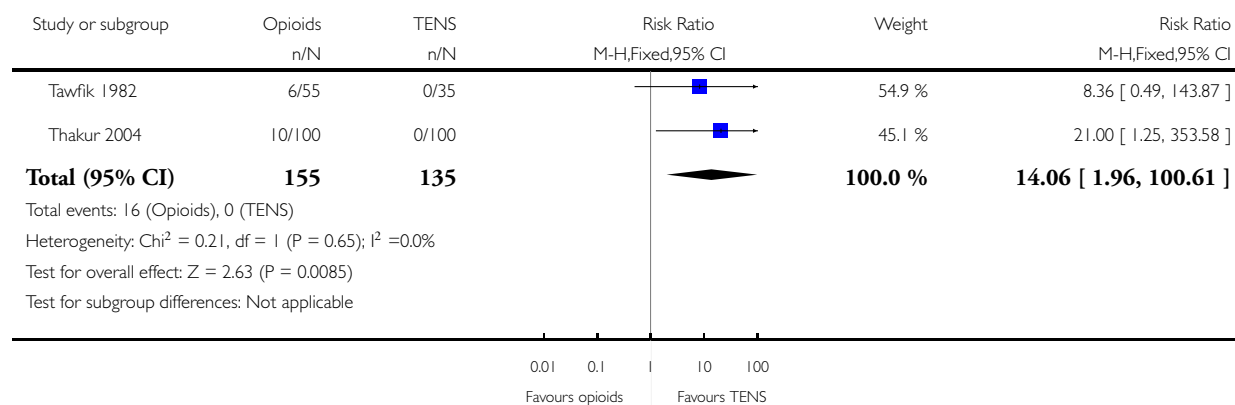


Analysis 29.4. Comparison 29 Opioids versus TENS, Outcome 4 Nausea and vomiting.

Review: Parenteral opioids for maternal pain management in labour

Comparison: 29 Opioids versus TENS

Outcome: 4 Nausea and vomiting

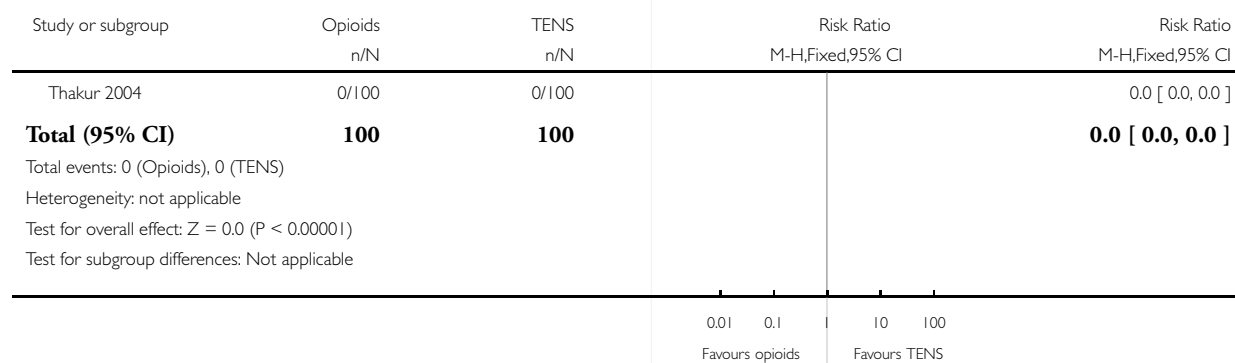


Analysis 29.5. Comparison 29 Opioids versus TENS, Outcome 5 Caesarean section.

Review: Parenteral opioids for maternal pain management in labour

Comparison: 29 Opioids versus TENS

Outcome: 5 Caesarean section

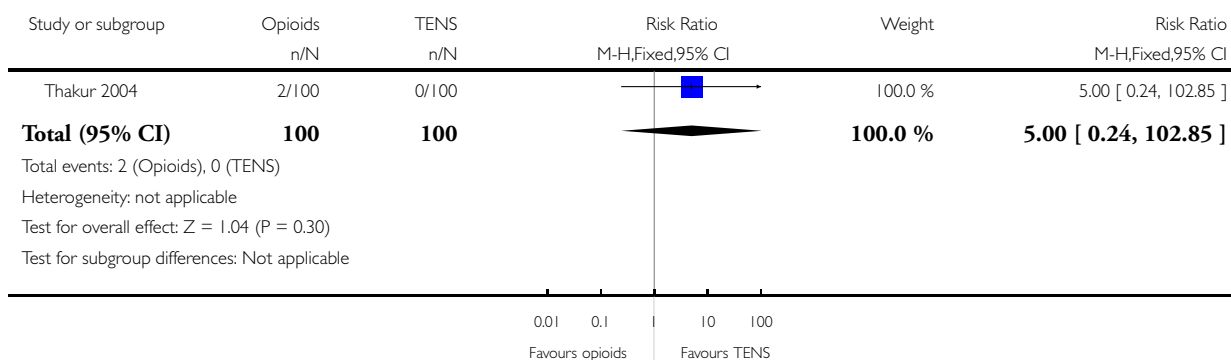


Analysis 29.6. Comparison 29 Opioids versus TENS, Outcome 6 Assisted vaginal birth.

Review: Parenteral opioids for maternal pain management in labour

Comparison: 29 Opioids versus TENS

Outcome: 6 Assisted vaginal birth

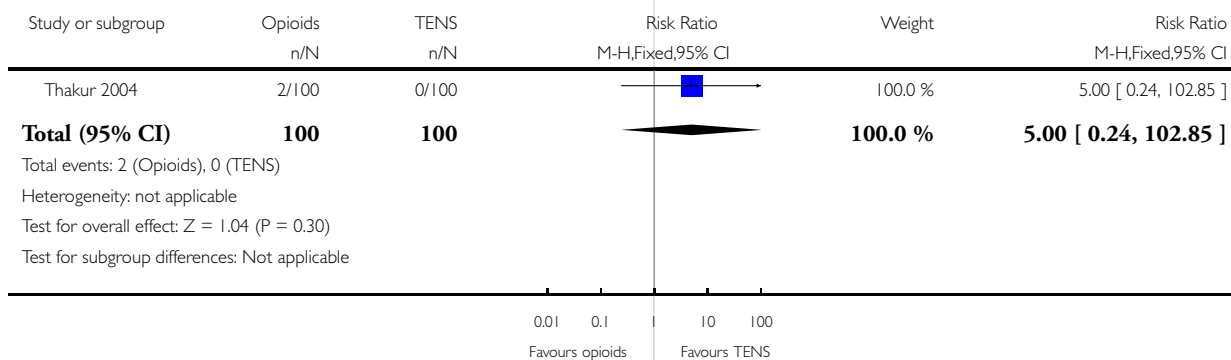


Analysis 29.7. Comparison 29 Opioids versus TENS, Outcome 7 Fetal distress.

Review: Parenteral opioids for maternal pain management in labour

Comparison: 29 Opioids versus TENS

Outcome: 7 Fetal distress



WHAT'S NEW

Last assessed as up-to-date: 6 July 2011.

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 .

HISTORY

Protocol first published: Issue 4, 2008

Review first published: Issue 9, 2010

CONTRIBUTIONS OF AUTHORS

Roz Ullman and Therese Dowswell drafted the protocol. Roz Ullman, Lesley Smith, Ethel Burns and Therese Dowswell assessed studies for eligibility, carried out data extraction and analysis, and drafted the text of the review. Rintaro Mori carried out data extraction and commented on drafts.

DECLARATIONS OF INTEREST

None known.

SOURCES OF SUPPORT

Internal sources

- (TD) The University of Liverpool, UK.

External sources

- (TD) National Institute for Health Research, UK.
NIHR NHS Cochrane Collaboration Programme Grant Scheme award for NHS-prioritised centrally-managed, pregnancy and childbirth systematic reviews:CPGS02

DIFFERENCES BETWEEN PROTOCOL AND REVIEW

The [Background](#) section of the review has been updated and amended since publication of the protocol. Two new review authors that joined the team at the review stage (L Smith and E Burns) considered that it was important to make these amendments.

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.

This review is one of a series of reviews to be included in an overview of reviews examining methods of pain management in labour (in development). It has been updated to follow the generic protocol developed in 2011 for reviews contributing to the overview ([Jones 2011a](#)), as a result of which we have added a new comparison (opioids versus TENS).

INDEX TERMS

Medical Subject Headings (MeSH)

Analgesia, Obstetrical [*methods]; Analgesics, Opioid [*administration & dosage; adverse effects]; Injections, Intramuscular; Injections, Intravenous; Labor Pain [*drug therapy]; Randomized Controlled Trials as Topic

MeSH check words

Female; Humans; Pregnancy