Authors' objectives
To determine the safety and effectiveness of parenteral opioids for pain relief in labour.

Searching
The Cochrane Pregnancy and Childbirth Group's Specialised Register, the Cochrane Controlled Trials Register, the Cochrane Database of Systematic Reviews, and another obstetric anaesthesia register (see Other Publications of Related Interest no.1) were searched. The reference lists of the retrieved articles were also examined.

Study selection
Study designs of evaluations included in the review
Eligible studies were restricted to randomised controlled trials (RCTs) with a low or moderate risk of allocation concealment bias and attrition rates of less than 25%.

Specific interventions included in the review
The inclusion criteria were not defined a priori in terms of the interventions. Opioids that were never or were no longer used in the context of pain relief were excluded; namely, intramuscular oxymorphone, phenazocine, anileridine, benzethidine and furethine. However, trials examining the intravenous administration of these drugs were eligible. Controversions involving currently used drugs were eligible. The pharmacological agents included were pethidine, tramadol, meptazinol, diamorphine, pentazocine, nalbuphine, butorphanol, morphine and fentanyl. Administration was by intravenous, intramuscular and patient-controlled methods. Epidural analgesia and active and placebo paracervical block were also included. The co-drugs included diazepam, lorazepam, promethazine, metoclopramide and placebo.

Participants included in the review
Other than women in labour, the inclusion criteria were not defined a priori in terms of the participants.

Outcomes assessed in the review
The primary outcomes were the mother's dissatisfaction with pain relief 1 or 2 hours after administration, and neonatal resuscitation (as defined by the trial authors).

The secondary maternal outcomes included: maternal visual analogue score 1 to 2 hours after administration; use of any further analgesia during labour (other than epidural); nausea, vomiting, and use of anti-emetics; drowsiness or sleepiness, and catheterisation in labour; oxytocin augmentation; mother unable to participate in the labour; time from randomisation or first dose to delivery; rates of Caesarean section and instrumental delivery; the mother's dissatisfaction with the birth experience; and the mother's dissatisfaction with labour pain relief after birth.

The secondary neonatal outcomes included: administration of naloxone; Apgar score less than 7 at 5 minutes; death of the baby or admission to transitional, special, or intensive care; feeding problems; and problems with mother-baby interaction.

How were decisions on the relevance of primary studies made?
The authors do not state how the papers were selected for the review, or how many of the reviewers performed the selection.

Assessment of study quality
Validity was assessed using the allocation concealment criteria recommended in the Cochrane Collaboration Handbook (see Other Publications of Related Interest no.2). One author assessed the validity of the papers and discussed concerns or unclear issues with a second author.
Data extraction
One author extracted the data and discussed concerns or unclear issues with a second author. The data extracted included details of the interventions and the number of women in the treatment and control groups. The data analysis in the original studies should have been conducted on an intention to treat basis. When this was not the case, the data were reanalysed where possible. Data that could not be analysed on an intention to treat basis were excluded.

Methods of synthesis
How were the studies combined?
The studies were grouped according to the treatments compared and, initially, a narrative synthesis was undertaken. The studies were also combined in a meta-analysis where the data were available. For dichotomous data, the pooled relative risk and 95% confidence interval (CI) was calculated using a fixed-effect model. For continuous data, the weighted mean differences and 95% CI were estimated.

How were differences between studies investigated?
Differences between the studies were discussed in the text of the review and statistical heterogeneity was assessed.

Results of the review
Forty-eight RCTs with more than 9,800 women were included.

The methodological flaws of the trials included post-randomisation exclusions and underpowered trials. There was a lack of consistency in the methods used to report the outcomes, making synthesis difficult. Intramuscular pethidine versus placebo (1 double-blind RCT involving 224 women).

Women were significantly more dissatisfied with placebo, compared with pethidine, both during labour (83% versus 71%; p=0.04) and after labour (54% versus 25%; p=0.00004).

Intramuscular opioid versus an alternative intramuscular opioid (20 RCTs involving 3,188 women, of which 17 were double-blind RCTs).

Maternal pain relief was similar among the different opioids. Meptazinol was the most common alternative. There was no convincing evidence that the alternatives were better than pethidine. Dissatisfaction with pain relief varied widely among studies (27 to 87%), as did maternal side-effects. Few trials assessed neonatal outcomes, and those that did reported no differences in substantive neonatal outcomes.

Intramuscular opioid versus an alternative dose of the same intramuscular opioid (3 double-blind RCTs involving 273 women).

Higher doses of tramadol (100 versus 50 mg) and pethidine (80 versus 40 mg) were associated with improved pain relief. There was no difference between 1 and 2 mg butorphanol. The side-effects were also similar. The data on neonatal outcomes were lacking.

Intravenous versus intramuscular pethidine (1 unblinded RCT involving 39 women). Women in the intravenous group received significantly more pethidine and reported significantly lower labour pain than the intramuscular group in this small trial. Neonatal outcomes were reported to be similar between the treatment groups, but seven women who had Caesarean sections were excluded from this analysis.

Intravenous versus a different intramuscular opioid (8 RCTs involving 772 women).

Five different opioids were compared with pethidine, resulting in limited data for each comparison. There was no convincing evidence of any differences between the different opioids.

Intravenous versus a different mode of administration of the same opioid (2 RCTs involving 141 women).
The data were limited and neonatal outcomes were not reported. There were no differences in the study outcomes between patient-controlled opioids and intermittent bolus for either pethidine or fentanyl.

Parenteral opioids versus epidural analgesia (11 RCTs involving 3,320 women).

All of the five RCTs that measured pain relief reported improved pain relief and satisfaction with pain relief for epidural, compared with intravenous butorphanol, pethidine and fentanyl. There was significant heterogeneity (p<0.0014) among the studies for the duration of first and second stages of labour and rates of oxytocin augmentation. Labour-related outcomes favoured epidural. The neonatal outcomes were similar between the treatment groups.

Intramuscular pethidine versus paracervical block (1 double-blind RCT involving 117 women).

There was a significant difference in pain relief favouring paracervical block up to 60 minutes, but not thereafter.

Parenteral opioids and co-drugs versus parenteral opioids. Benzodiazepine as a co-drug (2 RCTs involving 432 women): one RCT provided data on nausea and vomiting. The other RCT reported significantly better pain relief with intramuscular pethidine plus oral lorazepam, compared with pethidine alone (weighted mean difference -22.00, 95% CI: -37.5, -6.50), and decreased dissatisfaction with labour pain relief (0% versus 45%; p=0.005). Sedation was significantly increased in the co-drug group (45% versus 10%; p=0.04), while nausea and vomiting were similar.

Tranquilisers and anti-emetics (phenothiazines) as a co-drug (2 double-blind RCTs involving 992 women): the results from studies examining promethazine were conflicting.

Authors' conclusions
Pethidine is the most commonly used opioid worldwide. It has the benefits of familiarity and low cost, although there are considerable concerns about its analgesic effectiveness and about its potential maternal, foetal and neonatal side-effects. There is currently no convincing evidence to show that alternative opioids are better.

CRD commentary
The aims were stated and the inclusion criteria were defined in terms of the study design and interventions. The inclusion criteria were not defined a priori in terms of the participants or outcomes. The literature search was reasonable: several relevant sources were searched with an emphasis on trials registered with the Cochrane Collaboration. However, the keywords used were not reported and it was not stated whether any language restrictions were applied. In addition, the methods used to select the studies were not described.

The quality of the included studies was assessed using predefined criteria. Eligible studies were restricted to those with a low or moderate risk of bias and attrition rates of less than 25%. Details of the included trials are available on a website (www.maternitywise.org/prof/pain/). One author extracted the data and assessed validity but the results were not checked by a second reviewer. Few studies compared identical treatments. The data were grouped by treatment comparisons and combined predominantly in the narrative, which was appropriate. When the data were combined, statistical heterogeneity was assessed and reported. The numerous outcomes reported in the review reflect the many secondary outcomes considered by the authors to be eligible.

The limited evidence identified and presented in the review does appear to support the authors' conclusions.

Implications of the review for practice and research
Practice: The authors state that if a woman opts for parenteral opioids, no specific opioids or mode of administration can be recommended given the limited data available. They also state that women should be provided with all the available information, preferably before labour, and make an informed choice.

Research: The authors state that well-designed and adequately powered trials are required to compare pethidine with the main alternatives (diamorphine and newer opioids such as fentanyl), and to compare opioids with pharmacologic methods (other than epidural) and non-pharmacologic methods. They further state that studies should address...
substantive outcomes for mothers and babies, and should evaluate outcomes using validated tools. Qualitative research is also required to identify factors that influence the women’s expectations, choices and birth experiences.

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