National Institute for Health and Care Excellence

Draft for consultation

Caesarean birth

[F] Evidence review for opioids for pain relief after caesarean birth

NICE guideline CG132 (update)

Evidence review

October 2020

Draft for Consultation

This evidence review was developed by the National Guideline Alliance which is a part of the Royal College of Obstetricians and Gynaecologists

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Opioids for pain relief

Review question

Are opioids safe and effective for pain management after caesarean birth?

Introduction

The previous NICE guideline recommended 'patient-controlled analgesia (PCA) using opioid analgesics should be offered after caesarean birth (CB) because it improves pain relief.' However, this recommendation was withdrawn in August 2019 because of safety concerns, particularly regarding the use of patient-controlled opioids in women who have received intrathecal opioids, and changes in practice in the UK. These changes include greater use of neuraxial opioids, widespread use of transverse (rather than midline) incisions which are associated with less pain and use of local anaesthetic blocks in the transverse abdominus plane in those requiring a general anaesthetic. There is also a reluctance to restrict women's mobility and ability to look after her baby with the use of an intravenous PCA.

A number of women will obtain adequate analgesia with non-opioid medicines following caesarean birth, and the aim of this review is to identify the role of opioids in pain management following caesarean birth.

Summary of the protocol

Please see Table 1 for a summary of the Population, Intervention, Comparison and Outcome (PICO) characteristics of this review.

Table 1: Summary of the protocol (PICO table)

Population	All women who have had a caesarean birth: • include any of the different modes of anaesthesia (general anaesthesia/epidural anaesthesia/spinal anaesthesia) • include any type of caesarean birth (emergency or planned)
Intervention	• **Choice of opioid**: ○ Morphine ○ Diamorphine ○ Weak opioids – codeine, dihydrocodeine ○ Fentanyl ○ Pethidine (also known as meperidine) ○ Oxycodone ○ Tramadol • **Route of administration**: ○ Oral ○ Intravenous –patient controlled analgesia (PCA) or non-PCA ○ Intramuscular ○ Intranasal ○ Transdermal
Comparison	• Each of the interventions outlined above • No pain control • Placebo
Outcomes	**Critical outcomes:** • Pain scores • Clinically significant respiratory depression (pooled outcome)

Important outcomes

- Establishment of breastfeeding
- Women's satisfaction with treatment/health-related quality of life
- Nausea and vomiting
- Constipation
- Pruritus

Relevant time frame for all interventions and outcomes is the first 48 hours after a caesarean birth

PCA: patient-controlled analgesia

For further details, see the review protocol in appendix A.

Methods and process

This evidence review was developed using the methods and process described in Developing NICE guidelines: the manual (2014). Methods specific to this review question are described in the review protocol in appendix A.

Declarations of interest were recorded according to NICE's 2014 conflicts of interest policy until 31 March 2018. From 1 April 2018, declarations of interest were recorded according to NICE's 2018 conflicts of interest policy. Those interests declared until April 2018 were reclassified according to NICE's 2018 conflicts of interest policy (see Register of Interests).

Clinical evidence

Included studies

Eleven randomised controlled trials (RCTs) were included in this review. Three studies assessed women who had all received general anaesthesia (GA) (Demirel 2014, Saracoglu 2010, Saracoglu 2012), 1 study included 10% of women who had general anaesthesia (Yost 2004), and the remaining 7 studies assessed women who had spinal/regional anaesthesia for caesarean birth (<5% GA) (Davis 2006, Ffrench-O'Carroll 2019, Makela 2019, Niklasson 2015, Sammour 2011, Snell 2006, Yefet 2017).

None of the included studies used transverse abdominis plane (TAP) block.

Comparisons were grouped into:

(1) pharmacological interventions (where different drugs were used)

(2) mode of delivery (where the same drug was used, but using different methods of administration, for example oral, intramuscular (IM), intravenous (IV) or IV PCA)

(3) complex interventions (where both the drug and method were compared).

None of the included studies reported on clinically significant respiratory depression (CSRD) as defined in our protocol (need for: airway intervention, pharmacological therapy such as centrally acting respiratory stimulants or opioid antagonists, oxygen therapy due to a low respiratory rate or hypoxia, or other intervention due to excessive sedation).

See the literature search strategy in appendix B and study selection flow chart in appendix C.

Excluded studies

Studies not included in this review with reasons for their exclusions are provided in appendix K.

1 Summary of clinical studies included in the evidence review

2 A summary of the studies that were included in this review are presented in Table 2.

3 **Table 2: Summary of included studies**

Study	Population	Comparison	Outcomes	Comments
Davis 2006 RCT USA	N=93; oral analgesia N=46; PCA N=47	IV PCA morphine continuous infusion of 1 mg/hr versus Oral oxycodone-acetaminophen (5/325 mg), 1-2 tablets per 4 hours	• Pain • Nausea • Vomiting • Pruritus	• Spinal anaesthesia • Analgesia post CB
Demirel 2014 RCT Turkey	N=40; 20 per group	IV PCA versus IV continuous	• Pain • Satisfaction • Nausea	• General anaesthesia • Analgesia post CB • Tramadol in both groups
Ffrench-O'Carroll 2019 RCT Ireland	N=68; Oxycodone N=35; tapentadol N=33	Oral tapentadol 50mg versus Oral oxycodone controlled release 10mg	• Pain • Satisfaction • Nausea • Vomiting • Constipation • Pruritus	• Spinal anaesthesia • Analgesia 12-hours post CB
Makela 2019 RCT Finland	N=270; PCA N=133; oral analgesia N=137	IV PCA versus Oral	• Pain • Satisfaction • Nausea • Vomiting	• Spinal anaesthesia • Unclear when analgesia administered • Oxycodone in both groups
Niklasson 2015 RCT Sweden	Randomised: N=80; 40 per group Analysed: oxycodone n=38; morphine/codeine n=39	IV nurse-administered morphine 10mg versus oral oxycodone long acting 10mg	• Pain (at rest)	• Spinal anaesthesia • Analgesia post CB
Sammour 2011 RCT Israel	120; 30 to each group only 2 groups relevant to this review (N=60)	oral - fixed intervals versus oral - on request	• Pain	• Spinal anaesthesia • Analgesia 2-hours post CB • Oral tramadol 100mg
Saracoglu 2010 RCT Turkey	N=60; 30 per group	IV PCA fentanyl versus IV PCA tramadol	• Pain	• General anaesthesia • Analgesia post CB
Saracoglu 2012 RCT Turkey	N=60; 30 per group	IV PCA fentanyl versus IV PCA tramadol	• Pain	• General anaesthesia • Analgesia post CB
Snell 2006	N=66	oral morphine versus	• Pain • Nausea	• Subarachnoid (spinal) anaesthesia

Study	Population	Comparison	Outcomes	Comments
RCT UK	groups 2 and 3 only; midwife-oral N=33, midwife-oral+IM N=33	IM morphine	• Vomiting • Satisfaction	• Analgesia immediately post CB • Both groups received oral co-dydramol and diclofenac • Midwife-administered (fixed or on request)
Yefet 2017 RCT Israel	Randomised N=214: 108 to fixed time interval group, 106 to on-demand group Analysed: N=200; 100 per group	oral - fixed intervals versus oral - on request	• Pain • Satisfaction	• Spinal anaesthesia • Analgesia post CB, arrival on maternity ward • Oral tramadol, paracetamol and diclofenac
Yost 2004 RCT (cluster) USA	N=2644 allocated; IM meperidine N=306; PCA meperidine N=319; IM morphine N=322; PCA morphine N=309	IM meperidine versus IM morphine versus IV PCA meperidine versus IV PCA morphine	• Pain • Satisfaction • Breastfeeding	• 4-arm trial • Regional anaesthesia (90%); GA 10% • Analgesia on postpartum ward; up to 24hrs post CB

CB: caesarean birth; GA: general anaesthetic; N: number of women; RCT: randomised controlled trial; IM: intramuscular; IV: intravenous; PCA: patient-controlled analgesia

See the full evidence tables in appendix D and the forest plots in appendix E.

Quality assessment of clinical outcomes included in the evidence review

See the clinical evidence profiles (GRADE tables) in appendix F.

Economic evidence

Included studies

A systematic review of the economic literature was conducted but no economic studies were identified which were applicable to this review question.

See the literature search strategy in appendix B.

Economic model

No economic modelling was undertaken for this review because the committee agreed that the opioids reviewed are not expensive and that any recommendations on their use were unlikely to have a significant resource impact. It was not considered a high priority for economic analysis in the previous guideline and no economic model was developed.

Evidence statements

When subgroups have been assessed, these statements are presented as bullet points below the main comparison

PHARMACOLOGICAL INTERVENTIONS

Comparison 1. Oxycodone (oral) versus tapentadol (oral)

Critical outcomes

Pain scores

- Moderate quality evidence from 1 RCT (N=68) shows no difference between oxycodone and tapentadol in pain relief at 36 hours or 48 hours.

Clinically significant respiratory distress

- No evidence was available for this outcome.

Important outcomes

Breastfeeding

- No evidence was available for this outcome.

Women's satisfaction/HRQoL

- Moderate quality evidence from 1 RCT (N=68) shows no difference between oxycodone and tapentadol in satisfaction at 36 hours or 48 hours.

Nausea and vomiting

- Low quality evidence from 1 RCT (N=68) shows no difference between oxycodone and tapentadol in nausea or vomiting.

Constipation

- Moderate quality evidence from 1 RCT (N=68) shows no difference between oxycodone and tapentadol in constipation at 48 hours.

Pruritus

- Moderate quality evidence from 1 RCT (N=68) shows no difference between oxycodone and tapentadol in pruritus (itching).

Comparison 2. Fentanyl (IV PCA) versus tramadol (IV PCA)

Critical outcomes

Pain scores

- Low quality evidence from 2 RCTs (N=120) shows no difference between fentanyl and tramadol in pain at 1 hour, 2 hours, 8 hours, and 12 hours.
- Moderate quality evidence from 2 RCTs (N=120) shows no difference between fentanyl and tramadol in pain at 4 hours and 24 hours.

Clinically significant respiratory distress

- No evidence was available for this outcome.

Important outcomes

Breastfeeding

- No evidence was available for this outcome.

Women's satisfaction/HRQoL

- No evidence was available for this outcome.

Nausea and vomiting

- No evidence was available for this outcome.

Constipation

- No evidence was available for this outcome.

Pruritus

- No evidence was available for this outcome.

Comparison 3. Morphine (IM or IV PCA) versus meperidine (IM or IV PCA)

Critical outcomes

Pain scores

- Very low quality evidence from 1 RCT (N=1256) shows a clinically important difference: lower incidence of moderate/severe pain (>4/10) in the morphine group compared to the meperidine group.

Clinically significant respiratory distress

- No evidence was available for this outcome.

Important outcomes

Breastfeeding

- Very low quality evidence from 1 RCT (N=1256) shows no difference in establishment of breastfeeding between morphine and meperidine groups.
- Very low quality evidence from 1 RCT (N=1256) shows a clinically important difference: lower incidence of discontinuation of breastfeeding in the morphine group compared to meperidine group.

Women's satisfaction/HRQoL

- Very low quality evidence from 1 RCT (N=1256) shows no difference in number of women who were satisfied or strongly satisfied between morphine and meperidine groups.

Nausea and vomiting

- No evidence was available for this outcome.

Constipation

- No evidence was available for this outcome.

Pruritus

- No evidence was available for this outcome.

MODE OF DELIVERY

Comparison 4. IV PCA versus continuous infusion (tramadol in both arms)

Critical outcomes

Pain scores

- Very low quality evidence from 1 RCT (N=40) shows no difference in pain scores between IV PCA and IV continuous infusion of pain relief at 1 hour, 2 hours, 4 hours, 8 hours, 16 hours, and 24 hours.

Clinically significant respiratory distress

- No evidence was available for this outcome.

Important outcomes

Breastfeeding

- No evidence was available for this outcome.

Women's satisfaction/HRQoL

- Very low quality evidence from 1 RCT (N=40) shows no difference between IV PCA and IV continuous infusion of pain relief in number of women who were satisfied or very satisfied.

Nausea and vomiting

- Very low quality evidence from 1 RCT (N=40) shows no difference between IV PCA and IV continuous infusion of pain relief in number of women who had nausea at 1 hour, 2 hours, 4 hours, 8 hours, 16 hours, and 24 hours.

Constipation

- No evidence was available for this outcome.

Pruritus

- No evidence was available for this outcome.

Comparison 5. IV PCA versus oral (oxycodone in both arms)

Critical outcomes

Pain scores

- Very low quality evidence from 1 RCT shows no difference in incidence of severe pain (>7/10) at rest between IV PCA and oral groups at 2 hours (N=243), 4 hours (N=249), 8 hours (N=241).
- Low quality evidence from 1 RCT (N=217) shows a clinically important difference: higher incidence of severe pain (>7/10) at rest in the IV PCA group compared to the oral group at 24 hours.

Clinically significant respiratory distress

- No evidence was available for this outcome.

Important outcomes

Breastfeeding

- No evidence was available for this outcome.

Women's satisfaction/HRQoL

- Very low quality evidence from 1 RCT shows no difference in dissatisfaction (NRS<3/10) between IV PCA and oral analgesia groups at 2 hours (N=233), 4 hours (N=230), 8 hours (N=235), and 24 hours (N=211).

Nausea and vomiting

- Low quality evidence from 1 RCT (N=246) shows a clinically important difference: higher incidence of women reporting nausea at 4 hours in the IV PCA group compared to the oral group.
- Very low quality evidence from 1 RCT shows no difference between IV PCA and oral analgesia groups for nausea at 8 hours (N=241), 24 hours (N=215)
- Very low quality evidence from 1 RCT (N=214) shows no difference between IV PCA and oral analgesia groups for vomiting at 4 hours.
- Low quality evidence from 1 RCT (N=216) shows a clinically important difference: higher incidence of women reporting vomiting at 8 hours in the IV PCA group compared to the oral group.
- Very low quality evidence from 1 RCT (N=191) shows a clinically important difference: higher incidence of women reporting vomiting at 24 hours in the IV PCA group compared to the oral group.

Constipation

- No evidence was available for this outcome.

Pruritus

- No evidence was available for this outcome.

Comparison 6. IV PCA versus intramuscular (IM) (meperidine or morphine)

Critical outcomes

Pain scores

- Very low quality evidence from 1 RCT (N=1256) shows a clinically important difference: lower incidence of moderate/severe pain (>4/10) in the IV PCA group compared to the IM group.

Clinically significant respiratory distress

- No evidence was available for this outcome.

Important outcomes

Breastfeeding

- Very low quality evidence from 1 RCT (N=1256) showed no difference in establishment or discontinuation of breastfeeding between IV PCA and IM analgesia.

Women's satisfaction/HRQoL

- Very low quality evidence from 1 RCT (N=1256) showed no difference between IV PCA and IM analgesia in the number of women satisfied or strongly satisfied.

Nausea and vomiting

- No evidence was available for this outcome.

Constipation

- No evidence was available for this outcome.

Pruritus

- No evidence was available for this outcome.

Comparison 7. Oral fixed timing versus oral on-demand (tramadol in both arms)

Critical outcomes

Pain scores

- Very low quality evidence from 2 RCTs (N=260) showed no difference in pain at 6 hours and 24 hours between oral fixed timing and on-demand analgesia.
- Moderate quality evidence from 2 RCTs (N=260) showed a clinically important difference: pain at 12 hours was lower in the fixed timing group compared to the on-demand analgesia group.
- Moderate quality evidence from 1 RCT (N=200) showed a clinically important difference: pain at 18 hours, 30 hours, 36 hours, and 42 hours was lower in the fixed timing group compared to the on-demand analgesia group.
- Low quality evidence from 1 RCT (N=200) showed no difference in pain at 48 hours between oral fixed timing and on-demand analgesia.

Clinically significant respiratory distress

- No evidence was available for this outcome.

Important outcomes

Breastfeeding

- No evidence was available for this outcome.

Women's satisfaction/HRQoL

- Low quality evidence from 1 RCT (N=60) showed a clinically important difference: higher levels of satisfaction in the oral fixed timing group compared to the on-demand analgesia group.

Nausea and vomiting

- No evidence was available for this outcome.

Constipation

- No evidence was available for this outcome.

Pruritus

- No evidence was available for this outcome.

Comparison 8. Oral versus IM (morphine in both arms)

Critical outcomes

Pain scores

- Very low quality evidence from 1 RCT (N=66) showed no differences in pain on day 1 or day 2 between oral and IM analgesia.

Clinically significant respiratory distress

- No evidence was available for this outcome.

Important outcomes

Breastfeeding

- No evidence was available for this outcome.

Women's satisfaction/HRQoL

- Very low quality evidence from 1 RCT (N=66) showed no differences in the level of satisfaction (>7/10) between oral and intramuscular analgesia.

Nausea and vomiting

- Very low quality evidence from 1 RCT (N=66) showed no differences in nausea on day 1 or day 2 between oral and intramuscular analgesia.
- Very low quality evidence from 1 RCT (N=66) showed no differences in vomiting on day 1 or day 2 between oral and intramuscular analgesia.

Constipation

- No evidence was available for this outcome.

Pruritus

- No evidence was available for this outcome.

COMPLEX (MULTIPLE) INTERVENTIONS

Comparison 9. IV morphine versus oral oxycodone

Critical outcomes

Pain scores

- Very low quality evidence from 2 RCTs (N=170) showed a clinically important difference: higher pain scores at 6 hours in the IV morphine group compared to the oral oxycodone group.
  - Low quality evidence from 1 RCT (N=77) showed a clinically important difference: higher pain scores at 6 hours in the IV nurse administered morphine group compared to the oral oxycodone group.
  - Low quality evidence from 1 RCT (N=93) showed a clinically important difference: higher pain scores at 6 hours in the IV PCA morphine group compared to the oral oxycodone group.
- Very low quality evidence from 2 RCTs (N=170) showed a clinically important difference: higher pain scores at 24 hours in the IV morphine group compared to the oral oxycodone group.

  - Low quality evidence from 1 RCT (N=77) showed no differences in pain scores at 24 hours between the IV nurse-administered morphine group and the oral oxycodone group.
  - Low quality evidence from 1 RCT (N=93) showed a clinically important difference: higher pain scores at 24 hours in the IV PCA morphine group versus the oral oxycodone group.
- Low quality evidence from 1 RCT (N=77) showed a clinically important difference: higher pain scores at 48 hours in the IV nurse-administered morphine group compared to the oral oxycodone group.

Clinically significant respiratory distress

- No evidence was available for this outcome.

Important outcomes

Breastfeeding

- No evidence was available for this outcome.

Women's satisfaction/HRQoL

- No evidence was available for this outcome.

Nausea and vomiting

- Moderate quality evidence from 1 RCT (N=93) showed a clinically important difference: increased incidence of nausea at 6 hours in the IV PCA morphine group compared to the oral oxycodone group.
- Low quality evidence from 1 RCT (N=93) showed no differences in nausea at 24 hours between IV PCA morphine group and oral oxycodone group.

Constipation

- No evidence was available for this outcome.

Pruritus

- Low quality evidence from 1 RCT (N=93) showed no differences in pruritus at 6 hours between IV PCA morphine group and oral oxycodone group
- Moderate quality evidence from 1 RCT (N=93) showed no differences in pruritus at 24 hours between IV PCA morphine group and oral oxycodone group.

Comparison 10. IV PCA meperidine versus IM morphine

Critical outcomes

Pain scores

- Very low quality evidence from 1 RCT (N=641) showed a clinically important difference: higher incidence of moderate/severe pain (>4/10) in the IV PCA meperidine group compared to the IM morphine group.

Clinically significant respiratory distress

- No evidence was available for this outcome.

Important outcomes

Breastfeeding

- Very low quality evidence from 1 RCT (N=641) showed no differences in establishment and discontinuation of breastfeeding between IV PCA meperidine and IM morphine groups.

Women's satisfaction/HRQoL

- Very low quality evidence from 1 RCT (N=641) showed no differences in women who were satisfied or strongly satisfied between IV PCA meperidine and IM morphine groups.

Nausea and vomiting

- No evidence was available for this outcome.

Constipation

- No evidence was available for this outcome.

Pruritus

- No evidence was available for this outcome.

Comparison 11. IV PCA morphine versus IM meperidine

Critical outcomes

Pain scores

- Very low quality evidence from 1 RCT (N=615) showed a clinically important difference: lower incidence of moderate/severe pain (>4/10) in the IV PCA morphine compared to the IM meperidine group.

Clinically significant respiratory distress

- No evidence was available for this outcome.

Important outcomes

Breastfeeding

- Very low quality evidence from 1 RCT (N=615) showed no differences in establishment of breastfeeding between IV PCA morphine and IM meperidine group.
- Very low quality evidence from 1 RCT (N=615) showed a clinically important difference: lower incidence of discontinuation of breastfeeding in IV PCA morphine group compared to IM meperidine group.

Women's satisfaction/HRQoL

- Very low quality evidence from 1 RCT (N=615) showed no differences in women who were satisfied or strongly satisfied between IV PCA morphine and IM (meperidine) group.

Nausea and vomiting

- No evidence was available for this outcome.

Constipation

- No evidence was available for this outcome.

Pruritus

- No evidence was available for this outcome.

The committee's discussion of the evidence

Interpreting the evidence

The outcomes that matter most

As the aim of the review was to ensure women had safe and effective opioid analgesia after CB, pain was selected by the committee as a critical outcome. Opioids may cause respiratory depression and therefore clinically significant respiratory depression (CSRD) was also prioritised as a critical outcome. None of the included studies reported on CSRD as defined within the protocol.

As opioids may impact on the baby, establishment of breastfeeding was selected as an important outcome, as women may have concerns about breastfeeding if they are taking medicines, or poor pain control may reduce the likelihood of successful breastfeeding. Other potential adverse effects of opioids for the mother include constipation, nausea and vomiting and pruritus so these were selected as important outcomes. Satisfaction with treatment or quality of life was also selected as an important outcome as effective analgesia should allow a woman to have a positive birth experience and care for her baby in the period after CB.

The quality of the evidence

The quality of evidence for this review was assessed using GRADE.

Evidence varied from very low to moderate quality. Quality was largely downgraded for imprecision (wide confidence intervals), and unclear or high risk of bias across multiple domains (blinding of participants/personnel, and outcomes). In addition, studies typically had a small sample size, and were downgraded for imprecision. Pain was reported as an outcome for all comparisons, but adverse events such as impact on breast-feeding, constipation, and pruritus were less commonly reported.

Benefits and harms

The committee discussed the available evidence and noted that the vast majority of evidence came from women who underwent CB with spinal/regional anaesthesia, with limited data for women who required a general anaesthetic for the procedure. The committee noted that this was a reasonable reflection of current practice, as general anaesthesia is used in a very small number of women (less than 5%). They also noted that since approximately 1999, an opioid (normally diamorphine) has been used intrathecally, in addition to a local anaesthetic, and this provides women with a degree of analgesia for the first 12 to 24 hours after surgery. In comparison, women who have a general anaesthetic do not receive such analgesia and so require a different approach to post-operative pain control. Consequently, the committee decided to make separate recommendations regarding post-operative opioid analgesia for women who had a spinal/regional anaesthesia and those who have had general anaesthesia.

<u>Opioid analgesia for women who have had a spinal/epidural anaesthesia:</u>

The committee noted that (in studies which used spinal anaesthesia) morphine was more effective than pethidine (also known as meperidine) for pain relief and had less impact on breastfeeding. Oral oxycodone was more effective than IV morphine or IV oxycodone at reducing the incidence of moderate and severe pain, with less nausea and vomiting. However, the committee discussed that the FDA and American Academy of Paediatrics advise that oxycodone (as well as codeine and tramadol) increases the risk of neonatal sedation and respiratory depression, and that oral morphine or the less commonly-used hydromorphone may be suitable alternatives. In addition, the MHRA has issued a warning advising that codeine should not be taken by breastfeeding mothers. The committee noted that codeine and tramadol can be particularly problematic in up to 28% of women who are

CYP2D6 ultra-rapid metabolisers and who convert these drugs to morphine rapidly, leading to high morphine levels in their breast milk.

As the committee were keen to promote breastfeeding where possible, and not cause undue barriers to initiation and continuation of breastfeeding, they agreed that any medicine that was recommended for postoperative analgesia should be safe for breastfeeding mothers, and so recommended oral morphine, with IV/IM morphine to be used when oral administration was not possible, for example due to nausea or vomiting.

Opioid analgesia for women who have had a general anaesthesia

There was paucity of evidence regarding post-operative analgesia for women who had general anaesthesia. The limited comparisons (IV PCA tramadol compared to IV continuous infusion tramadol, and IV PCA fentanyl compared to IV PCA tramadol) showed no differences for the outcomes of interest. However, the committee felt it was important to provide separate guidance on post-operative analgesia for these women as the recovery pathway is different compared to the post-spinal/regional cohort. The committee discussed the pain experienced by women who have had CB with general anaesthesia, agreeing that these women often experience more severe pain in comparison to the spinal anaesthesia cohort, and are likely to need 'rescue analgesia' with the use of IV opioids, especially following extubation. The committee therefore recommended that intravenous morphine administered using PCA could be considered for these women. In women who did not need or did not wish to have PCA morphine, oral morphine could be used as an alternative.

Non-opioid analgesia and analgesia while breastfeeding (all women)

The committee had not reviewed the evidence for non-opioid analgesia, but they used their knowledge and expertise to amend the recommendations from the previous guideline, as the previous recommendations were very brief and did not provide options for women with different levels of pain. In accordance with current practice, the committee agreed to continue to recommend the use of non-steroidal anti-inflammatory drugs (NSAIDS) (unless contraindicated, for example due to inflammatory bowel disease, gastric ulcer or pre-eclampsia) and paracetamol alongside the opioid analgesic as part of a multi-modal approach to pain management after caesarean.

The committee discussed the differing mechanisms of action of the analgesics and the fact that paracetamol, NSAIDs and opioids may act on different types of pain. Thus, a multi-modal approach, utilising paracetamol, NSAIDS and opioids would provide the most effective and satisfactory level of relief/pain management, and reduce the need for high doses of opioids. This was also reflected in the available evidence, as included studies also used NSAIDS and/or paracetamol as a standard treatment in both groups, where the comparison of interest was the opioid or method of opioid administration. The committee agreed that the ideal approach was a gradual step-down from NSAIDs and/or paracetamol plus opioids to NSAIDs and/or paracetamol alone, and that this should be done as soon as possible, provided that there is adequate pain management. The committee also recognised that 15-30% of women do not require any opioid analgesia post-operatively, and NSAIDs and/or paracetamol may be sufficient.

In reviewing the evidence for a dosing schedule, the committee agreed that a fixed dosing schedule is preferable (extrapolated from the evidence with oral tramadol) in ongoing pain management, with higher levels of satisfaction from the women, compared to the provision of analgesia only when requested by the woman. The committee agreed that regular administration would be preferable to maintain a continuous level of pain relief, and easier to manage on a recovery ward.

The committee discussed some other options for women who did not need morphine, but whose pain could not be controlled on NSAIDs and paracetamol, or where NSAIDs were contraindicated and paracetamol alone was not effective. In this scenario, the committee

agreed that the use of a weak opioid-paracetamol combination such as co-dydramol would be suitable, as it can be used while breastfeeding, and may also be used as a discharge medicine.

The committee also discussed that in some women who experienced more severe pain, more potent analgesics such as oral tramadol or oral oxycodone may need to be used. However, the committee was aware that there may be associated risks to the baby in women who are breastfeeding, and that these medicines should therefore be used for the shortest possible time and at the lowest effective dose if no other analgesics have provided adequate pain control. In such cases, the risks to the baby should be discussed with the woman before initiation of tramadol or oxycodone. The committee raised further concerns regarding the use of oxycodone post-operatively due to the highly addictive nature of the drug, which could lead to community management issues if women are discharged with oxycodone, or feel the need to access it for insufficient pain management later on. The committee agreed that pain is usually, and understandably, most severe in the first 24 hours post-operatively, and falls rapidly in the first 72 hours. Consequently, they specified that only a short course of tramadol/oxycodone should be used, though due to lack of data on this, they did not define the time period or dosage, and decided that the treating clinician should manage on a case by case basis. The committee were aware that there were general recommendations in the BNF on the use of opioids in breastfeeding women and so included these as part of their recommendations.

As already discussed above, the committee recommended not using codeine due to the MHRA alert over the use of codeine in breastfeeding women due to the risk to the baby. The committee also noted the importance of advising women that some over the counter medicines, which could be bought by the woman or her support network, contain codeine, and these should not be used while breastfeeding.

Cost effectiveness and resource use

In general, the committee considered that their recommendations did not represent a significant departure from current practice. Furthermore, with the availability of generic (not brand-name) drugs, the committee assessed the recommendations as having a negligible impact compared to current resource use and cost. They thought that there might be some small savings resulting from reductions in the use of IV PCA for pain management following caesarean birth and the preference given to oral morphine over other opioid analgesics.

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Appendices

Appendix A – Review protocol

Review protocol for review question: Are opioids safe and effective for pain management after caesarean birth?

Table 3: Review protocol for opioids as pain relief

Field (based on PRISMA-P)	Content
Actual review question	Are opioids safe and effective for pain management after caesarean birth (CB)?
Type of review question	Intervention
Objective of the review	To identify how opioids should be used for analgesia after CB, to ensure adequate pain management but minimize adverse effects. Background: The current guideline has recommended 'Patient-controlled analgesia using opioid analgesics should be offered after CB because it improves pain relief.' However, this recommendation has now been withdrawn as there is concern over the use of PCA routinely, including in patients who have received intrathecal opioids. PCA may, however, have a role in women who have had a CB under GA.
Eligibility criteria – **population**/disease/condition/issue/domain	All women who have had a caesarean birth: • include any of the different modes of anaesthesia (general anaesthesia/epidural anaesthesia/spinal anaesthesia) • include any type of caesarean birth (emergency or planned)

Field (based on PRISMA-P)	Content
Eligibility criteria – **intervention**(s)/exposure(s)/prognostic factor(s)	• Choice of opioid: ○ Morphine ○ Diamorphine ○ Weak opioids – codeine, dihydrocodeine ○ Fentanyl ○ Pethidine (also known as meperidine) ○ Oxycodone ○ Tramadol • Route of administration: ○ Oral ○ Intravenous – PCA (patient controlled analgesia) or non-PCA ○ Intramuscular ○ Intranasal ○ Transdermal Data on opioids administered through the epidural (either as a single bolus, given by an anaesthetist, or as patient controlled epidural analgesia) are not relevant for this review and should be excluded.
Eligibility criteria – **comparator(s)**/control or reference (gold) standard	• Each of the interventions outlined above compared to another • No pain control • Placebo
Outcomes and prioritisation	**Critical outcomes:** • Pain scores • Clinically significant respiratory depression (CSRD) (pooled outcome) defined as one or more of the following: - need for airway intervention - need for pharmacological therapy (centrally acting respiratory stimulants or opioid antagonists)

Field (based on PRISMA-P)	Content
	- need for oxygen therapy due to a low respiratory rate or hypoxia - need for other intervention due to excessive sedation **Important outcomes** • Establishment of breastfeeding • Women's satisfaction with treatment/HRQoL • Nausea and vomiting • Constipation • Pruritus Relevant time frame for all interventions and outcomes is the first 48 hours after a caesarean birth. Data after this time point will not be included in the review.
Eligibility criteria – **study design**	Only published full text papers • Systematic reviews/meta-analyses of RCTs • RCTs
Other inclusion **exclusion criteria**	Exclude conference abstracts Exclude studies from non-OECD countries Exclude studies where all women have additional morbidities such as pre-eclampsia or post-operative morbidities such as sepsis, PPH, APH.
Proposed stratified, sensitivity/**sub-group analysis**, or meta-regression	**Subgroup analyses:** • Different opioids (strong opioids [e.g. morphine, diamorphine] versus weak opioids [e.g. oxycodone dihydrocodeine]) • Routes of administration (PCA vs other routes) • Method of anaesthesia for caesarean birth (general, epidural, intrathecal, +/- TAP blocks)
Selection process – duplicate screening/selection/analysis	Duplicate screening/selection/analysis will not be undertaken for this review as this question was not prioritised for it. Included and excluded studies will be cross checked with the committee and with published systematic reviews when available.

Field (based on PRISMA-P)	Content
Data management (software)	If pairwise meta-analyses are undertaken, they will be performed using Cochrane Review Manager (RevMan5). 'GRADE' will be used to assess the quality of evidence for each outcome. STAR will be used for bibliographies/citations and study sifting. Microsoft Word will be used for data extraction and quality assessment/critical appraisal
Information sources – databases and dates	Sources to be searched: Medline, Medline In-Process, CCTR, CDSR, DARE, HTA and Embase. Limits (e.g. date, study design): Study design limited to Systematic Reviews and RCTs. Apply standard animal/non-English language filters. A date limit will be applied to this review to include studies from 1999 onwards. Techniques for obstetric anaesthesia are markedly different now (since 1999) - this will have a large impact on post-operative pain and analgesia requirements, and means that earlier studies are not relevant to modern obstetrics. Supplementary search techniques: No supplementary search techniques will be used.
Identify if an update	Yes, this is an update of a question reviewed for the 2004 Caesarean section guideline (and not updated as part of the previous update in 2011).
Author contacts	Developer: National Guideline Alliance NGA-enquiries@RCOG.ORG.UK
Highlight if amendment to previous protocol	For details please see section 4.5 of Developing NICE guidelines: the manual
Search strategy – for one database	For details please see appendix B

Field (based on PRISMA-P)	Content
Data collection process – forms/duplicate	A standardised evidence table format will be used, and published as appendix D (clinical evidence tables) or H (economic evidence tables).
Data items – define all variables to be collected	For details please see evidence tables in appendix D (clinical evidence tables) or H (economic evidence tables).
Methods for assessing bias at outcome/study level	Appraisal of methodological quality: The methodological quality of each study will be assessed using an appropriate checklist: • ROBIS for systematic reviews • Cochrane risk of bias tool for randomised studies For details please see section 6.2 of Developing NICE guidelines: the manual The risk of bias across all available evidence will evaluated for each outcome using an adaptation of the 'Grading of Recommendations Assessment, Development and Evaluation (GRADE) toolbox' developed by the international GRADE working group http://www.gradeworkinggroup.org/
Criteria for quantitative synthesis	For details please see section 6.4 of Developing NICE guidelines: the manual
Methods for quantitative analysis – combining studies and exploring (in)consistency	Synthesis of data: Meta-analysis will be conducted where appropriate using Review Manager. <u>Minimum important differences</u> For all outcomes, default values will be used of: 0.8 and 1.25 times the relative risk for dichotomous outcomes; 0.5 times control group SD at baseline for continuous outcomes, unless more appropriate values are identified by the guideline committee or in the literature.

Field (based on PRISMA-P)	Content
Meta-bias assessment – publication bias, selective reporting bias	For details please see section 6.2 of Developing NICE guidelines: the manual.
Confidence in cumulative evidence	For details please see sections 6.4 and 9.1 of Developing NICE guidelines: the manual
Rationale/context – what is known	For details please see the introduction to the evidence review
Describe contributions of authors and guarantor	A multidisciplinary committee developed the guideline. The committee was convened by the NGA and chaired by Sarah Fishburn in line with section 3 of Developing NICE guidelines: the manual. Staff from the NGA undertook systematic literature searches, appraised the evidence, conducted meta-analysis and cost-effectiveness analysis where appropriate, and drafted the guideline in collaboration with the committee. For details please see the methods chapter of the full guideline.
Sources of funding/support	The NGA is funded by NICE and hosted by the Royal College of Obstetricians and Gynaecologists
Name of sponsor	The NGA is funded by NICE and hosted by the Royal College of Obstetricians and Gynaecologists
Roles of sponsor	NICE funds the NGA to develop guidelines for the NHS in England.
PROSPERO registration number	Not registered with PROSPERO

CDSR: Cochrane Database of Systematic Reviews; CENTRAL: Cochrane Central Register of Controlled Trials; DARE: Database of Abstracts of Reviews of Effects; GRADE: Grading of Recommendations Assessment, Development and Evaluation; HTA: Health Technology Assessment; NGA: National Guideline Alliance; NHS: National health service; NICE: National Institute for Health and Care Excellence; RCT: randomised controlled trial; RoB: risk of bias; SD: standard deviation

Appendix B – Literature search strategies

Literature search strategies for review question: Are opioids safe and effective for pain management after caesarean birth?

Review question search strategies

Databases: Medline; Medline EPub Ahead of Print; and Medline In-Process & Other Non-Indexed Citations

Date of last search: 11/12/2019

#	Searches
1	META-ANALYSIS/
2	META-ANALYSIS AS TOPIC/
3	(meta analy* or metanaly* or metaanaly*).ti,ab.
4	((systematic* or evidence*) adj2 (review* or overview*)).ti,ab.
5	(reference list* or bibliograph* or hand search* or manual search* or relevant journals).ab.
6	(search strategy or search criteria or systematic search or study selection or data extraction).ab.
7	(search* adj4 literature).ab.
8	(medline or pubmed or cochrane or embase or psychlit or psyclit or psychinfo or psycinfo or cinahl or science citation index or bids or cancerlit).ab.
9	cochrane.jw.
10	or/1-9
11	randomized controlled trial.pt.
12	controlled clinical trial.pt.
13	pragmatic clinical trial.pt.
14	randomi#ed.ab.
15	placebo.ab.
16	randomly.ab.
17	CLINICAL TRIALS AS TOPIC/
18	trial.ti.
19	or/11-18
20	exp CESAREAN SECTION/ and (POSTOPERATIVE PERIOD/ or POSTOPERATIVE CARE/)
21	((post or follow$ or after$) adj5 (c?esar#an$ or c section$ or csection$ or (deliver$ adj3 abdom$))).ti,ab.
22	or/20-21
23	exp NARCOTICS/
24	(opiod? or opiate? or morphine or diamorphine or codeine or dihydrocodeine or fentanyl or pethidine or meperidine or oxycodone or tramadol or alfentanil or alphaprodine or buprenorphine or butorphanol or dextromoramide or dextropropoxyphene or dihydromorphine or ethylmorphine or etorphine or heroin or hydrocodone or hydromorphone or levorphanol or meptazinol or methadone or opium or oxymorphone or pentazocine or phenazocine or phenoperidine or pirinitramide or promedol or sufentanil or thebaine or tilidine or diphenoxylate or enkephalin or ethylketocyclazocine or methadyl acetate or nalbuphine or remifentanil or tapentadol).ti,ab.
25	or/23-24
26	22 and 25
27	limit 26 to english language
28	limit 27 to yr="1999 -Current"
29	LETTER/
30	EDITORIAL/
31	NEWS/
32	exp HISTORICAL ARTICLE/
33	ANECDOTES AS TOPIC/
34	COMMENT/
35	CASE REPORT/
36	(letter or comment*).ti.
37	or/29-36
38	RANDOMIZED CONTROLLED TRIAL/ or random*.ti,ab.
39	37 not 38
40	ANIMALS/ not HUMANS/
41	exp ANIMALS, LABORATORY/
42	exp ANIMAL EXPERIMENTATION/
43	exp MODELS, ANIMAL/
44	exp RODENTIA/
45	(rat or rats or mouse or mice).ti.
46	or/39-45
47	28 not 46

#	Searches
48	10 and 47
49	19 and 47
50	or/48-49

Databases: Embase; and Embase Classic

Date of last search: 11/12/2019

#	Searches
1	SYSTEMATIC REVIEW/
2	META-ANALYSIS/
3	(meta analy* or metanaly* or metaanaly*).ti,ab.
4	((systematic or evidence) adj2 (review* or overview*)).ti,ab.
5	(reference list* or bibliograph* or hand search* or manual search* or relevant journals).ab.
6	(search strategy or search criteria or systematic search or study selection or data extraction).ab.
7	(search* adj4 literature).ab.
8	(medline or pubmed or cochrane or embase or psychlit or psyclit or psychinfo or psycinfo or cinahl or science citation index or bids or cancerlit).ab.
9	((pool* or combined) adj2 (data or trials or studies or results)).ab.
10	cochrane.jw.
11	or/1-10
12	random*.ti,ab.
13	factorial*.ti,ab.
14	(crossover* or cross over*).ti,ab.
15	((doubl* or singl*) adj blind*).ti,ab.
16	(assign* or allocat* or volunteer* or placebo*).ti,ab.
17	CROSSOVER PROCEDURE/
18	SINGLE BLIND PROCEDURE/
19	RANDOMIZED CONTROLLED TRIAL/
20	DOUBLE BLIND PROCEDURE/
21	or/12-20
22	exp CESAREAN SECTION/ and (POSTOPERATIVE PERIOD/ or POSTOPERATIVE CARE/)
23	((post or follow$ or after$) adj5 (c?esar#an$ or c section$ or csection$ or (deliver$ adj3 abdom$))).ti,ab.
24	or/22-23
25	exp NARCOTIC AGENT/
26	exp NARCOTIC ANALGESIC AGENT/
27	(opiod? or opiate? or morphine or diamorphine or codeine or dihydrocodeine or fentanyl or pethidine or meperidine or oxycodone or tramadol or alfentanil or alphaprodine or buprenorphine or butorphanol or dextromoramide or dextropropoxyphene or dihydromorphine or ethylmorphine or etorphine or heroin or hydrocodone or hydromorphone or levorphanol or meptazinol or methadone or opium or oxymorphone or pentazocine or phenazocine or phenoperidine or pirinitramide or promedol or sufentanil or thebaine or tilidine or diphenoxylate or enkephalin or ethylketocyclazocine or methadyl acetate or nalbuphine or remifentanil or tapentadol).ti,ab.
28	or/25-27
29	24 and 28
30	limit 29 to english language
31	limit 30 to yr="1999 -Current"
32	letter.pt. or LETTER/
33	note.pt.
34	editorial.pt.
35	CASE REPORT/ or CASE STUDY/
36	(letter or comment*).ti.
37	or/32-36
38	RANDOMIZED CONTROLLED TRIAL/ or random*.ti,ab.
39	37 not 38
40	ANIMAL/ not HUMAN/
41	NONHUMAN/
42	exp ANIMAL EXPERIMENT/
43	exp EXPERIMENTAL ANIMAL/
44	ANIMAL MODEL/
45	exp RODENT/
46	(rat or rats or mouse or mice).ti.
47	or/39-46
48	31 not 47
49	11 and 48
50	21 and 48
51	or/49-50

Databases: Cochrane Central Register of Controlled Trials; and Cochrane Database of Systematic Reviews

Date of last search: 11/12/2019

#	Searches
#1	[mh "CESAREAN SECTION"] and ([mh ^"POSTOPERATIVE PERIOD"] or [mh ^"POSTOPERATIVE CARE"])
#2	((post or follow* or after*) near/5 (cesar#an* or caesar#an* or "c section*" or csection* or (deliver* near/3 abdom*))):ti,ab
#3	#1 or #2
#4	[mh NARCOTICS]
#5	(opiod* or opiate* or morphine or diamorphine or codeine or dihydrocodeine or fentanyl or pethidine or meperidine or oxycodone or tramadol or alfentanil or alphaprodine or buprenorphine or butorphanol or dextromoramide or dextropropoxyphene or dihydromorphine or ethylmorphine or etorphine or heroin or hydrocodone or hydromorphone or levorphanol or meptazinol or methadone or opium or oxymorphone or pentazocine or phenazocine or phenoperidine or pirinitramide or promedol or sufentanil or thebaine or tilidine or diphenoxylate or enkephalin or ethylketocyclazocine or "methadyl acetate" or nalbuphine or remifentanil or tapentadol):ti,ab
#6	#4 or #5
#7	#3 and #6
#8	#3 and #6 with Cochrane Library publication date Between Jan 1999 and Dec 2019, in Cochrane Reviews
#9	#3 and #6 with Publication Year from 1999 to 2019, in Trials

Databases: Database of Abstracts of Reviews of Effects

Date of last search: 11/12/2019

#	Searches
1	MeSH DESCRIPTOR CESAREAN SECTION EXPLODE ALL TREES IN DARE
2	MeSH DESCRIPTOR POSTOPERATIVE PERIOD IN DARE
3	MeSH DESCRIPTOR POSTOPERATIVE CARE IN DARE
4	#2 OR #3
5	#1 AND #4
6	((((post or follow* or after*) NEAR5 (cesarean* OR caesarean* OR "c section*" OR csection*)))) and ((Systematic review:ZDT and Bibliographic:ZPS) OR (Systematic review:ZDT and Abstract:ZPS))
7	#5 OR #6
8	MeSH DESCRIPTOR NARCOTICS EXPLODE ALL TREES IN DARE
9	((opiod* or opiate* or morphine or diamorphine or codeine or dihydrocodeine or fentanyl or pethidine or meperidine or oxycodone or tramadol or alfentanil or alphaprodine or buprenorphine or butorphanol or dextromoramide or dextropropoxyphene or dihydromorphine or ethylmorphine or etorphine or heroin or hydrocodone or hydromorphone or levorphanol or meptazinol or methadone or opium or oxymorphone or pentazocine or phenazocine or phenoperidine or pirinitramide or promedol or sufentanil or thebaine or tilidine or diphenoxylate or enkephalin or ethylketocyclazocine or "methadyl acetate" or nalbuphine or remifentanil or tapentadol)) and ((Systematic review:ZDT and Bibliographic:ZPS) OR (Systematic review:ZDT and Abstract:ZPS))
10	#8 OR #9
11	#7 AND #10

Databases: Health Technology Assessment

Date of last search: 11/12/2019

#	Searches
1	MeSH DESCRIPTOR CESAREAN SECTION EXPLODE ALL TREES IN HTA
2	MeSH DESCRIPTOR POSTOPERATIVE PERIOD IN HTA
3	MeSH DESCRIPTOR POSTOPERATIVE CARE IN HTA
4	#2 OR #3
5	#1 AND #4
6	(((post or follow* or after*) NEAR5 (cesarean* OR caesarean* OR "c section*" OR csection*))) IN HTA
7	#5 OR #6
8	MeSH DESCRIPTOR NARCOTICS EXPLODE ALL TREES IN HTA
9	(opiod* or opiate* or morphine or diamorphine or codeine or dihydrocodeine or fentanyl or pethidine or meperidine or oxycodone or tramadol or alfentanil or alphaprodine or buprenorphine or butorphanol or dextromoramide or dextropropoxyphene or dihydromorphine or ethylmorphine or etorphine or heroin or hydrocodone or hydromorphone or levorphanol or meptazinol or methadone or opium or oxymorphone or pentazocine or phenazocine or phenoperidine or pirinitramide or promedol or sufentanil or thebaine or tilidine or diphenoxylate or enkephalin or ethylketocyclazocine or "methadyl acetate" or nalbuphine or remifentanil or tapentadol) IN HTA
10	#8 OR #9
11	#7 AND #10

Health economics search strategies

Databases: Medline; Medline EPub Ahead of Print; and Medline In-Process & Other Non-Indexed Citations

Date of last search: 16/12/2019

#	Searches
1	ECONOMICS/
2	VALUE OF LIFE/
3	exp "COSTS AND COST ANALYSIS"/
4	exp ECONOMICS, HOSPITAL/
5	exp ECONOMICS, MEDICAL/
6	exp RESOURCE ALLOCATION/
7	ECONOMICS, NURSING/
8	ECONOMICS, PHARMACEUTICAL/
9	exp "FEES AND CHARGES"/
10	exp BUDGETS/
11	budget*.ti,ab.
12	cost*.ti,ab.
13	(economic* or pharmaco?economic*).ti,ab.
14	(price* or pricing*).ti,ab.
15	(financ* or fee or fees or expenditure* or saving*).ti,ab.
16	(value adj2 (money or monetary)).ti,ab.
17	resourc* allocat*.ti,ab.
18	(fund or funds or funding* or funded).ti,ab.
19	(ration or rations or rationing* or rationed).ti,ab.
20	ec.fs.
21	or/1-20
22	exp CESAREAN SECTION/ and (POSTOPERATIVE PERIOD/ or POSTOPERATIVE CARE/)
23	((post or follow$ or after$) adj5 (c?esar#an$ or c section$ or csection$ or (deliver$ adj3 abdom$))).ti,ab.
24	or/22-23
25	exp NARCOTICS/
26	(opiod? or opiate? or morphine or diamorphine or codeine or dihydrocodeine or fentanyl or pethidine or meperidine or oxycodone or tramadol or alfentanil or alphaprodine or buprenorphine or butorphanol or dextromoramide or dextropropoxyphene or dihydromorphine or ethylmorphine or etorphine or heroin or hydrocodone or hydromorphone or levorphanol or meptazinol or methadone or opium or oxymorphone or pentazocine or phenazocine or phenoperidine or pirinitramide or promedol or sufentanil or thebaine or tilidine or diphenoxylate or enkephalin or ethylketocyclazocine or methadyl acetate or nalbuphine or remifentanil or tapentadol).ti,ab.
27	or/25-26
28	24 and 27
29	limit 28 to english language
30	limit 29 to yr="1999 -Current"
31	LETTER/
32	EDITORIAL/
33	NEWS/
34	exp HISTORICAL ARTICLE/
35	ANECDOTES AS TOPIC/
36	COMMENT/
37	CASE REPORT/
38	(letter or comment*).ti.
39	or/31-38
40	RANDOMIZED CONTROLLED TRIAL/ or random*.ti,ab.
41	39 not 40
42	ANIMALS/ not HUMANS/
43	exp ANIMALS, LABORATORY/
44	exp ANIMAL EXPERIMENTATION/
45	exp MODELS, ANIMAL/
46	exp RODENTIA/
47	(rat or rats or mouse or mice).ti.
48	or/41-47
49	30 not 48
50	21 and 49

Databases: Embase; and Embase Classic

Date of last search: 16/12/2019

#	Searches
1	HEALTH ECONOMICS/
2	exp ECONOMIC EVALUATION/
3	exp HEALTH CARE COST/
4	exp FEE/
5	BUDGET/
6	FUNDING/
7	RESOURCE ALLOCATION/
8	budget*.ti,ab.
9	cost*.ti,ab.
10	(economic* or pharmaco?economic*).ti,ab.
11	(price* or pricing*).ti,ab.
12	(financ* or fee or fees or expenditure* or saving*).ti,ab.
13	(value adj2 (money or monetary)).ti,ab.
14	resourc* allocat*.ti,ab.
15	(fund or funds or funding* or funded).ti,ab.
16	(ration or rations or rationing* or rationed).ti,ab.
17	or/1-16
18	exp CESAREAN SECTION/ and (POSTOPERATIVE PERIOD/ or POSTOPERATIVE CARE/)
19	((post or follow$ or after$) adj5 (c?esar#an$ or c section$ or csection$ or (deliver$ adj3 abdom$))).ti,ab.
20	or/18-19
21	exp NARCOTIC AGENT/
22	exp NARCOTIC ANALGESIC AGENT/
23	(opiod? or opiate? or morphine or diamorphine or codeine or dihydrocodeine or fentanyl or pethidine or meperidine or oxycodone or tramadol or alfentanil or alphaprodine or buprenorphine or butorphanol or dextromoramide or dextropropoxyphene or dihydromorphine or ethylmorphine or etorphine or heroin or hydrocodone or hydromorphone or levorphanol or meptazinol or methadone or opium or oxymorphone or pentazocine or phenazocine or phenoperidine or pirinitramide or promedol or sufentanil or thebaine or tilidine or diphenoxylate or enkephalin or ethylketocyclazocine or methadyl acetate or nalbuphine or remifentanil or tapentadol).ti,ab.
24	or/21-23
25	20 and 24
26	limit 25 to english language
27	limit 26 to yr="1999 -Current"
28	letter.pt. or LETTER/
29	note.pt.
30	editorial.pt.
31	CASE REPORT/ or CASE STUDY/
32	(letter or comment*).ti.
33	or/28-32
34	RANDOMIZED CONTROLLED TRIAL/ or random*.ti,ab.
35	33 not 34
36	ANIMAL/ not HUMAN/
37	NONHUMAN/
38	exp ANIMAL EXPERIMENT/
39	exp EXPERIMENTAL ANIMAL/
40	ANIMAL MODEL/
41	exp RODENT/
42	(rat or rats or mouse or mice).ti.
43	or/35-42
44	27 not 43
45	17 and 44

Database: Cochrane Central Register of Controlled Trials

Date of last search: 16/12/2019

#	Searches
#1	MeSH descriptor: [Economics] this term only
#2	MeSH descriptor: [Value of Life] this term only
#3	MeSH descriptor: [Costs and Cost Analysis] explode all trees
#4	MeSH descriptor: [Economics, Hospital] explode all trees
#5	MeSH descriptor: [Economics, Medical] explode all trees
#6	MeSH descriptor: [Resource Allocation] explode all trees
#7	MeSH descriptor: [Economics, Nursing] this term only
#8	MeSH descriptor: [Economics, Pharmaceutical] this term only
#9	MeSH descriptor: [Fees and Charges] explode all trees
#10	MeSH descriptor: [Budgets] explode all trees
#11	budget*:ti,ab
#12	cost*:ti,ab
#13	(economic* or pharmaco?economic*):ti,ab

#	Searches
#14	(price* or pricing*):ti,ab
#15	(financ* or fee or fees or expenditure* or saving*):ti,ab
#16	(value near/2 (money or monetary)):ti,ab
#17	resourc* allocat*:ti,ab
#18	(fund or funds or funding* or funded):ti,ab
#19	(ration or rations or rationing* or rationed) .ti,ab.
#20	#1 or #2 or #3 or #4 or #5 or #6 or #7 or #8 or #9 or #10 or #11 or #12 or #13 or #14 or #15 or #16 or #17 or #18 or #19
#21	[mh "CESAREAN SECTION"] and ([mh ^"POSTOPERATIVE PERIOD"] or [mh ^"POSTOPERATIVE CARE"])
#22	((post or follow* or after*) near/5 (cesar#an* or caesar#an* or "c section*" or csection* or (deliver* near/3 abdom*))):ti,ab
#23	#21 or #22
#24	[mh NARCOTICS]
#25	(opiod* or opiate* or morphine or diamorphine or codeine or dihydrocodeine or fentanyl or pethidine or meperidine or oxycodone or tramadol or alfentanil or alphaprodine or buprenorphine or butorphanol or dextromoramide or dextropropoxyphene or dihydromorphine or ethylmorphine or etorphine or heroin or hydrocodone or hydromorphone or levorphanol or meptazinol or methadone or opium or oxymorphone or pentazocine or phenazocine or phenoperidine or pirinitramide or promedol or sufentanil or thebaine or tilidine or diphenoxylate or enkephalin or ethylketocyclazocine or "methadyl acetate" or nalbuphine or remifentanil or tapentadol):ti,ab
#26	#24 or #25
#27	#23 and #26
#28	#23 and #26 with Publication Year from 1999 to 2019, in Trials
#29	#20 and #28

Databases: NHS Economic Evaluation Database

Date of last search: 16/12/2019

#	Searches
1	MeSH DESCRIPTOR CESAREAN SECTION EXPLODE ALL TREES IN NHSEED
2	MeSH DESCRIPTOR POSTOPERATIVE PERIOD IN NHSEED
3	MeSH DESCRIPTOR POSTOPERATIVE CARE IN NHSEED
4	#2 OR #3
5	#1 AND #4
6	(((post or follow* or after*) NEAR5 (cesarean* OR caesarean* OR "c section*" OR csection*))) IN NHSEED
7	#5 OR #6
8	MeSH DESCRIPTOR NARCOTICS EXPLODE ALL TREES IN NHSEED
9	(opiod* or opiate* or morphine or diamorphine or codeine or dihydrocodeine or fentanyl or pethidine or meperidine or oxycodone or tramadol or alfentanil or alphaprodine or buprenorphine or butorphanol or dextromoramide or dextropropoxyphene or dihydromorphine or ethylmorphine or etorphine or heroin or hydrocodone or hydromorphone or levorphanol or meptazinol or methadone or opium or oxymorphone or pentazocine or phenazocine or phenoperidine or pirinitramide or promedol or sufentanil or thebaine or tilidine or diphenoxylate or enkephalin or ethylketocyclazocine or "methadyl acetate" or nalbuphine or remifentanil or tapentadol) IN NHSEED
10	#8 OR #9
11	#7 AND #10

Databases: Health Technology Assessment

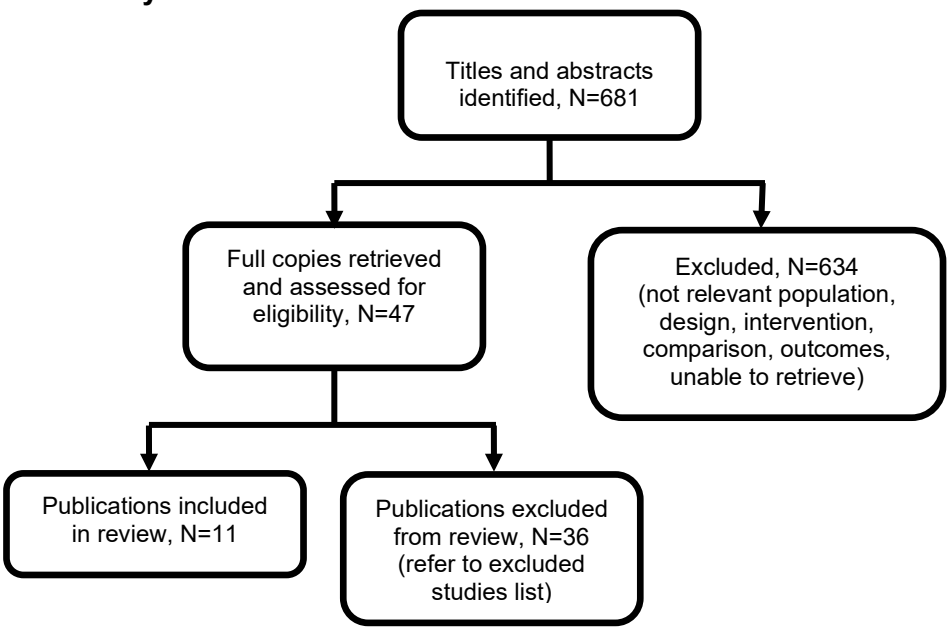
Date of last search: 16/12/2019

#	Searches
1	MeSH DESCRIPTOR CESAREAN SECTION EXPLODE ALL TREES IN HTA
2	MeSH DESCRIPTOR POSTOPERATIVE PERIOD IN HTA
3	MeSH DESCRIPTOR POSTOPERATIVE CARE IN HTA
4	#2 OR #3
5	#1 AND #4
6	(((post or follow* or after*) NEAR5 (cesarean* OR caesarean* OR "c section*" OR csection*))) IN HTA
7	#5 OR #6
8	MeSH DESCRIPTOR NARCOTICS EXPLODE ALL TREES IN HTA
9	(opiod* or opiate* or morphine or diamorphine or codeine or dihydrocodeine or fentanyl or pethidine or meperidine or oxycodone or tramadol or alfentanil or alphaprodine or buprenorphine or butorphanol or dextromoramide or dextropropoxyphene or dihydromorphine or ethylmorphine or etorphine or heroin or hydrocodone or hydromorphone or levorphanol or meptazinol or methadone or opium or oxymorphone or pentazocine or phenazocine or phenoperidine or pirinitramide or promedol or sufentanil or thebaine or tilidine or diphenoxylate or enkephalin or ethylketocyclazocine or "methadyl acetate" or nalbuphine or remifentanil or tapentadol) IN HTA
10	#8 OR #9
11	#7 AND #10

Appendix C – Clinical evidence study selection

Clinical study selection for review question: Are opioids safe and effective for pain management after caesarean birth?

Figure 1: Study selection flow chart



Appendix D – Clinical evidence tables

Clinical evidence tables for review question: Are opioids safe and effective for pain management after caesarean birth?

Table 4: Clinical evidence tables for opioids as pain relief

<table>
<tr><th>Study details</th><th>Participants</th><th>Interventions</th><th>Methods</th><th>Outcomes and Results</th><th>Comments</th></tr>
<tr>
<td>Full citation

Davis, Kathryn M., Esposito, Matthew A., Meyer, Bruce A., Oral analgesia compared with intravenous patient-controlled analgesia for pain after cesarean delivery: a randomized controlled trial, American Journal of Obstetrics and Gynecology, 194, 967-71, 2006

Ref Id

1160487</td>
<td>Sample size
N=93; oral analgesia N=46; PCA N=47

Characteristics
<table>
<tr><td></td><td>oral analgesia</td><td>PCA</td></tr>
<tr><td>N</td><td>46</td><td>47</td></tr>
<tr><td>age (yrs)</td><td>31.9 SD 4.5</td><td>31.5 SD 4.7</td></tr>
<tr><td>GA (wks)</td><td>38.5 SD 2.3</td><td>39.0 SD 1.9</td></tr>
</table>
Inclusion criteria
All patients aged >=18 years in Labor and Delivery for planned cesarean delivery

Exclusion criteria

• unplanned cesarean delivery;
• a known allergy/hypersensitivity to morphine, oxycodone, or acetaminophen;
• treatment with magnesium sulfate;</td>
<td>Interventions
PCA: patients received an intravenous PCA device with preservative-free morphine sulfate, with a continuous infusion of 1 mg/hr. An additional 1-mg dose was administered on patient demand, with a lockout interval of 6 minutes. After 12 hours, the PCA was discontinued, and oral analgesia was begun with oxycodone-acetaminophen (5/325 mg), with 1 to 2 tablets permitted every 4 hours as needed for pain.
Oral: 2 tablets of oxycodone-acetaminophen immediately after</td>
<td>Details
Spinal anesthesia was administered with bupivacaine (Marcaine) and fentanyl in the operating room, and cesarean delivery was performed in a standard fashion without injecting local anesthetic into the incision. No long-acting intrathecal narcotics were administered. All patients had Pfannenstiel incisions. Patients in both groups received ketorolac, 30 mg intravenously immediately after surgery, followed by 15 mg intravenously every 6 hours, for 24 hours after the</td>
<td>Results
Pain scores: VAS 0-10 (0 no pain, 10 worst pain)
<table>
<tr><td>PAIN</td><td>oral N=46</td><td>PCA N=47</td></tr>
<tr><td>6hrs</td><td>3.2 SD 1.8</td><td>4.1 SD 2.5</td></tr>
<tr><td>24hrs</td><td>2.9 SD 1.7</td><td>4.1 SD 2.1</td></tr>
</table>
Nausea and vomiting. VAS 0-10
<table>
<tr><td>NAUSEA</td><td>oral</td><td>PCA</td></tr>
<tr><td>6 hrs</td><td>0.2 SD 0.9</td><td>2.0 SD 3.4</td></tr>
<tr><td>24 hrs</td><td>1.0 SD 2.3</td><td>0.3 SD 0.8</td></tr>
</table>
Pruritus. VAS 0-10
<table>
<tr><td>PRURITUS</td><td>oral</td><td>PCA</td></tr>
<tr><td>6 hrs</td><td>0.9 SD 1.9</td><td>1.7 SD 2.5</td></tr>
<tr><td>24 hrs</td><td>1.0 SD 2.3</td><td>1.1 SD 1.8</td></tr>
</table>
</td>
<td>Limitations
RoB
Selection bias (Random sequence generation) LOW
Selection Bias (Allocation concealment) LOW
Performance bias (Blinding of participants and personnel) HIGH (cannot blind to allocation)
Detection bias (Blinding of outcomes) UNCLEAR (no information regarding collection of outcome data)
Attrition bias (incomplete outcome data) LOW
Reporting bias (selective reporting) UNCLEAR (no protocol available)
Other biases NONE IDENTIFIED</td>
</tr>
</table>

Study details	Participants	Interventions	Methods	Outcomes and Results	Comments
Country/ies where the study was carried out USA **Study type** RCT **Aim of the study** determine whether oral analgesia with oxycodone-acetaminophen or a patient-controlled analgesia device with morphine provides superior analgesia after cesarean birth **Study dates** November 2004 to May 2005	• the chronic use of narcotics or substance abuse; • the use of general anesthesia; • a history of a pain syndrome.	completion of the cesarean delivery. For 12 hours after the procedure, 2 tablets of oxycodone-acetaminophen were administered at fixed intervals every 3 hours. After 12 hours, 1 to 2 tablets were permitted every 4 hours as needed for pain, for a maximum of 12 tablets in 24 hours. After the 24-hour study period, patients continued to receive oral oxycodone-acetaminophen and ibuprofen. All were discharged with these oral agents.	procedure. Standing orders for all patients also allowed promethazine, 25 mg intramuscularly every 4 hours as needed for nausea. Crossover between groups was permitted. At patient request, rescue analgesia for breakthrough pain was administered with intramuscular meperidine (50 mg), as frequently as every 4 hours. Intramuscular dosing was provided because not all patients had functional intravenous lines.		**Other information**

<table>
<tr><th>Study details</th><th>Participants</th><th>Interventions</th><th>Methods</th><th>Outcomes and Results</th><th>Comments</th></tr>
<tr><td>Source of funding
Not reported</td><td></td><td></td><td></td><td></td><td></td></tr>
<tr><td>Full citation

Demirel, Ismail, Ozer, Ayse Belin, Atilgan, Remzi, Kavak, Burcin Salih, Unlu, Serap, Bayar, Mustafa Kemal, Sapmaz, Ekrem, Comparison of patient-controlled analgesia versus continuous infusion of tramadol in post-cesarean section pain management, The journal of obstetrics and gynaecology research, 40, 392-8, 2014

Ref Id</td><td>Sample size
N=40; 20 per group

Characteristics
<table><tr><td></td><td>PCA</td><td>continuous</td></tr><tr><td>age (yrs)</td><td>31.85 ± 5.18</td><td>28.40 ± 6.48</td></tr><tr><td>surgery duration (min)</td><td>54.75 ± 16.42</td><td>50.25 ± 15.24</td></tr></table>
Inclusion criteria
pregnant woman aged 20–40 in ASA 1&2 scheduling elective cesarean section and refusing
regional anesthesia

Exclusion criteria
not able to handle the PCA device,
cardiovascular or psychiatric disorders,
known allergy to the study drug
borderline lung function tests
refused treatment</td><td>Interventions
IV PCA group, n = 20: received i.v. tramadol prepared as a solution of 5 mg in 100 mL normal saline, through a PCA device (CADD-Legacy PCA pump) at a 5 mg/h basal rate, a 20 mg bolus injection, and PCA with a 30-min lockout interval and a 4-h limit of 150 mg through a PCA device (CADD-Legacy PCA pump).
Continuous IV infusion group, n = 20: were administrated a solution of tramadol, 400 mg in
100 mL normal saline as a continuous i.v. infusion at the rate of 12 mg/h (with additional tramadol, 20 mg, if</td><td>Details
No patient received preoperative medication. Following anesthesia induction with thiopental sodium (Pental; 4 mg/kg) and succinylcholine (Lysthenon; 1 mg/kg) and orotracheal intubation, anesthesia maintenance was achieved with 50:50% oxygen and nitrous oxide with sevoflurane (1%). Additionally, vecuronium (Norcuron; 0.03 mg/kg) was given as needed for muscle relaxation, as well as fentanyl, 1 µg/kg i.v., following delivery. Patients in both groups were given an infusion of tramadol, 100 mg in 15 min, before the end of surgery.</td><td>Results
PAIN on a scale from 0 = total absence of pain to 10 = most intolerable pain imaginable
<table><tr><td>PAIN VAS median [range]</td><td>PCA n=20</td><td>continuous n=20</td></tr><tr><td>PACU</td><td>5 [3-7]</td><td>5 [3-8]</td></tr><tr><td>1 hr</td><td>3 [2-5]</td><td>4 [2-7]</td></tr><tr><td>2 hr</td><td>3 [2-4]</td><td>3 [1-5]</td></tr><tr><td>4 hr</td><td>2 [1-4]</td><td>3 [1-5]</td></tr><tr><td>8 hr</td><td>1 [0-2]</td><td>1 [0-3]</td></tr><tr><td>16 hr</td><td>1 [0-2]</td><td>1 [0-3]</td></tr><tr><td>24 hr</td><td>1 [0-2]</td><td>1 [0-2]</td></tr></table>Patient satisfaction was evaluated at the 24th postoperative hour according to the following 5-grade scale: 1 = very satisfied, 2 = satisfied, 3 = neither satisfied nor dissatisfied, 4 = dissatisfied and 5 = strongly dissatisfied.
<table><tr><td></td><td>PCA n=20</td><td>continuous n=20</td></tr><tr><td>satisfied/very satisfied</td><td>N=19</td><td>N=18</td></tr><tr><td>neither</td><td>N=1</td><td>N=2</td></tr></table></td><td>Limitations
RoB
Selection bias (Random sequence generation) UNCL EAR (no detail given)
Selection Bias (Allocation concealment) UNCL EAR (no detail given)
Performance bias (Blinding of participants and personnel) HIGH (cannot blind to allocation)
Detection bias (Blinding of outcomes) HIGH (subjective questionnaire completed by patient aware of allocation)
Attrition bias (incomplete outcome data) LOW
Reporting bias (selective reporting) UNCLEA R (no protocol available)</td></tr>
</table>

<table>
<tr><th>Study details</th><th>Participants</th><th>Interventions</th><th>Methods</th><th>Outcomes and Results</th><th>Comments</th></tr>
<tr>
<td>1131021

Country/ies where the study was carried out

Turkey

Study type
RCT

Aim of the study
compare analgesic efficacy, drug consumption and patient satisfaction with the IV patient-controlled and continuous infusion modes of administration of tramadol

Study dates
Not reported

Source of funding</td>
<td></td>
<td>VAS score was >3).</td>
<td></td>
<td>
<table>
<tr><td>dissatisfied/very dissatisfied</td><td>N=0</td><td>N=0</td></tr>
</table>
Nausea/vomiting (verbal descriptive scale for nausea, where 0 = none, 1 = mild, 2 = moderate and 3 = severe nausea).
<table>
<tr><td>Nausea (mild/moderate/severe)</td><td>PCA n=20</td><td>continuous n=20</td></tr>
<tr><td>PACU</td><td>N=8</td><td>N=6</td></tr>
<tr><td>1 hr</td><td>N=4</td><td>N=3</td></tr>
<tr><td>2 hr</td><td>N=2</td><td>N=2</td></tr>
<tr><td>4 hr</td><td>N=0</td><td>N=1</td></tr>
<tr><td>8 hr</td><td>N=0</td><td>N=2</td></tr>
<tr><td>16 hr</td><td>N=0</td><td>N=0</td></tr>
<tr><td>24 hr</td><td>N=0</td><td>N=0</td></tr>
</table>
</td>
<td>Other biases NONE IDENTIFIED

Other information</td>
</tr>
</table>

<table>
<tr><th>Study details</th><th>Participants</th><th>Interventions</th><th>Methods</th><th>Outcomes and Results</th><th>Comments</th></tr>
<tr><td>Not reported</td><td></td><td></td><td></td><td></td><td></td></tr>
<tr>
<td>Full citation

Ffrench-O'Carroll, R., Steinhaeuser, H., Duff, S., Close, J., McNamara, J., Ahmed, N., Murray, M., Rice, T., Immanni, S., A randomized controlled trial comparing tapentadol with oxycodone in non-breastfeeding women post elective cesarean section, Current Medical Research and Opinion, 35, 975-981, 2019

Ref Id

1174250

Country/ies where the</td>
<td>Sample size
N=68; 35 in oxycodone, 33 in tapentadol

Characteristics
<table>
<tr><td>mean [SD]</td><td>Oxycodone N=35</td><td>Tapentadol N=33</td></tr>
<tr><td>age (years)</td><td>32.1 (3.56)</td><td>31.8 (5.34)</td></tr>
<tr><td>para</td><td>2.17 (0.79)</td><td>2.31 (2.56)</td></tr>
<tr><td>baseline pain (24hrs post-CS)</td><td>4.09 (2.83)</td><td>5.10 (2.67)</td></tr>
</table>
Inclusion criteria
full term pregnant women of American Society of Anesthesiologists (ASA) grade one or two undergoing elective cesarean section, who didn’t plan to breastfeed.

Exclusion criteria
patients undergoing emergency cesarean section, those with an intolerance to opioids, those with a history of chronic pain on opioids or tapentadol and those with an ASA status of three or more</td>
<td>Interventions
Tapentadol: 50mg (Palexia 50mg SR [Slow Release]) commencing 24 hours postoperatively.
Oxycodone: equivalent oxycodone controlled release 10mg 12 hourly commencing 24 hours postoperatively.</td>
<td>Details
Each woman received spinal anesthesia with 2.2 ml of 0.5% hyperbaric bupivicaine along with 15 mcg intrathecal fentanyl and 100 mcg intrathecal morphine.
It is standard practice in our institution for women to receive oxycodone 10mg 12 hourly post cesarean section for 48 hours. All women received 1 g paracetamol and 100mg diclofenac per rectum intraoperatively and were prescribed regular paracetamol and diclofenac postoperatively unless there was a specific contraindication. Administration of intraoperative antiemetics was at the discretion of the anesthetists.</td>
<td>Results
PAIN numerical rating scale (NRS) from 0=no pain to 10=worst pain imaginable
SPID: sum of pain intensity difference (SPID48 is calculated as “difference in pain intensity from 24 to 48 hours postoperatively” multiplied by 24.)
pain relief scores (score 0–4) (0=no relief, 4=complete relief).

patient satisfaction scores (score 1–5)
TOTPAR: total pain relief (difference in pain relief scores multiplied by the time period)
<table>
<tr><td>mean(SD) or n/N</td><td>Oxycodone N=35</td><td>Tapentadol N=33</td></tr>
<tr><td>SPID 36hrs post-op</td><td>32.57 (35.11)</td><td>28.36 (36.59)</td></tr>
<tr><td>SPID 48hrs post-op</td><td>65.14 (70.23)</td><td>74.54 (77.97)</td></tr>
<tr><td>TOTPAR 36</td><td>-4.8 (16.26)</td><td>3.75 (32.32)</td></tr>
<tr><td>TOTPAR 48</td><td>-2.4 (22.88)</td><td>3.63 (31.82)</td></tr>
<tr><td>pain relief 36hrs</td><td>3.40 (0.88)</td><td>3.25 (1.16)</td></tr>
<tr><td>pain relief 48hrs</td><td>3.5 (0.90)</td><td>3.38 (1.10)</td></tr>
<tr><td>satisfaction 36</td><td>4.39 (0.88)</td><td>4.16 (1.19)</td></tr>
<tr><td>satisfaction 48</td><td>4.14 (0.84)</td><td>4.34 (1.21)</td></tr>
</table>
</td>
<td>Limitations
RoB
Selection bias (Random sequence generation) LOW
Selection Bias (Allocation concealment) LOW
Performance bias (Blinding of participants and personnel) LOW
Detection bias (Blinding of outcomes) LOW
Attrition bias (incomplete outcome data) LOW
Reporting bias (selective reporting) UNCLEAR (no protocol available)
Other biases NONE IDENTIFIED

Other information</td>
</tr>
</table>

Study details	Participants	Interventions	Methods	Outcomes and Results	Comments
study was carried out Ireland **Study type** RCT **Aim of the study** The objective of this study was to compare the efficacy and side effect profile of tapentadol with oxycodone in patients who received spinal anesthesia for elective cesarean section **Study dates** Not reported **Source of funding** Grunenthal Pharma Ltd provided			Rescue medications postoperatively were administered as oxycodone (OxyNorm 5–10 mg) and tapentadol (Palexia 50mg FC [Film Coated]). These could be requested at any time by study participants postoperatively. There were no additional rescue doses of paracetamol or diclofenac prescribed.	<table><tr><td>nausea</td><td>9/35</td><td>10/33</td></tr><tr><td>vomiting</td><td>5/35</td><td>6/33</td></tr><tr><td>constipation (absence of bowel movement @48hrs)</td><td>23/35</td><td>27/33</td></tr><tr><td>pruritus (itching)</td><td>24/35</td><td>19/33</td></tr></table>modified intention to treat study population	

<table>
<tr><th>Study details</th><th>Participants</th><th>Interventions</th><th>Methods</th><th>Outcomes and Results</th><th>Comments</th></tr>
<tr><td>financial support for initial independent statistical analysis for power calculations for this study</td><td></td><td></td><td></td><td></td><td></td></tr>
<tr><td>Full citation

Makela, Katja, Palomaki, Outi, Pokkinen, Satu, Yli-Hankala, Arvi, Helminen, Mika, Uotila, Jukka, Oral versus patient-controlled intravenous administration of oxycodone for pain relief after cesarean section, Archives of Gynecology and Obstetrics, 300, 903-909, 2019</td><td>Sample size
270 randomised; 133 to PCA, 137 to oral analgesia

Characteristics
<table><tr><td>median [range]</td><td>IV PCA N=133</td><td>Oral N=137</td></tr><tr><td>age (years)</td><td>32 [19-46]</td><td>33 [20-43]</td></tr><tr><td>GA (days)</td><td>274 [208-295]</td><td>274 [228-295]</td></tr><tr><td>prior CS</td><td>48/133</td><td>53/137</td></tr></table>
Inclusion criteria
women scheduled for elective or acute CS.

Exclusion criteria
Patients who underwent emergency CS or were unable to understand the Finnish language</td><td>Interventions
IV PCA group: the patients received an intravenous PCA device (CADD Legacy PCA, Smiths Medical MD, Inc., St. Paul, MN, USA) with oxycodone 1 mg/ml, using oxycodone bolus doses of 2 mg and a lockout time of 10 min. Patients were taught to use the pump in the operating theatre, and they were recommended to use it for at least 24 h.
Oral analgesia group: patients were given an oxycodone 5 mg capsule upon request, the maximum dose</td><td>Details
All patients were operated on under spinal anaesthesia. Spinal anaesthesia was performed using a 27-gauge BD™ Quincke spinal needle at the L3–4 level. The patients were given intrathecal 0.5% hyperbaric bupivacaine 11 mg and fentanyl 10 µg. Non-invasive arterial blood pressure was maintained above − 10% of the preoperative value using an intravenous crystalloid fluid infusion and boluses of intravenous phenylepinephrine 0.05 mg.
The patients had either a</td><td>Results
Five patients requested to have the IV PCA discontinued after a few hours' use because of side effects like nausea. Respectively, six patients in the oral analgesia group switched to an IV PCA later on because of pain. Epidural analgesia was used for one patient in the IV PCA group, and two patients in the IV PCA group were given extra oxycodone for intolerable pain. The mean usage time of the IV PCA was 19 h postoperatively.
pain scale ranged from 0 (= no pain) to 10 (= worst pain imaginable);

• severe pain (at rest) NRS>/=7

satisfaction scale ranged from 0 (= completely dissatisfied) to 10 (= completely satisfied)

• dissatisfaction (NRS ≤ 3)

<table><tr><td>n/N</td><td>IV PCA N=133</td><td>Oral N=137</td></tr><tr><td>Severe pain 2hrs</td><td>10/119</td><td>4/124</td></tr><tr><td>severe pain 4hrs</td><td>26/123</td><td>30/126</td></tr></table></td><td>Limitations
RoB
Selection bias (Random sequence generation) UNCL
EAR (no detail given)
Selection Bias (Allocation concealment) LOW
Performance bias (Blinding of participants and personnel) HIGH (cannot blind to allocation)
Detection bias (Blinding of outcomes) HIGH (subjective questionnaire completed by patient aware of allocation)
Attrition bias (incomplete outcome data) LOW
Reporting bias (selective reporting) UNCLEA</td></tr>
</table>

<table>
<tr><th>Study details</th><th>Participants</th><th>Interventions</th><th>Methods</th><th>Outcomes and Results</th><th>Comments</th></tr>
<tr>
<td>Ref Id

1174278

Country/ies where the study was carried out

Finland

Study type
RCT

Aim of the study
primary objective of this study was to assess whether oral oxycodone provides the same or better pain control and satisfaction with pain relief as oxycodone given intravenously using a patient-controlled analgesia (PCA)</td>
<td></td>
<td>being 60 mg in 24 h.</td>
<td>Pfannenstiel incision (263 patients) or a lower midline incision (3 patients in the IV PCA group and 4 in oral group). Patients in both groups received extended-release oxycodone/naloxone 10/5 mg (OX/NAL) (oxycodone hydrochloride10 mg + naloxone hydrochloride 5 mg), ibuprofen 600 mg, and paracetamol 1 g orally 1 h after surgery. Thereafter, an OX/NAL dose was given every 12 h, and ibuprofen and paracetamol were given every 8 h.</td>
<td>
<table>
<tr><td>severe pain 8hrs</td><td>9/120</td><td>8/121</td></tr>
<tr><td>severe pain 24hrs</td><td>5/106</td><td>0/111</td></tr>
<tr><td>dissatisfaction 2hrs</td><td>6/115</td><td>6/118</td></tr>
<tr><td>dissatisfaction 4hrs</td><td>4/111</td><td>7/119</td></tr>
<tr><td>dissatisfaction 8hrs</td><td>3/118</td><td>9/117</td></tr>
<tr><td>dissatisfaction 24hrs</td><td>3/103</td><td>1/108</td></tr>
<tr><td>nausea 4hrs</td><td>19/121</td><td>4/125</td></tr>
<tr><td>nausea 8hrs</td><td>11/121</td><td>6/120</td></tr>
<tr><td>nausea 24hrs</td><td>5/105</td><td>6/110</td></tr>
<tr><td>vomiting 4hrs</td><td>6/105</td><td>2/109</td></tr>
<tr><td>vomiting 8hrs</td><td>11/108</td><td>2/108</td></tr>
<tr><td>vomiting 24hrs</td><td>4/94</td><td>0/97</td></tr>
</table>
</td>
<td>R (no protocol available)
Other biases NONE IDENTIFIED

Other information</td>
</tr>
</table>

<table>
<tr><th>Study details</th><th>Participants</th><th>Interventions</th><th>Methods</th><th>Outcomes and Results</th><th>Comments</th></tr>
<tr><td>infusion device.
The secondary objectives were to compare the gastrointestinal symptoms and postsurgical recovery of the two groups.

Study dates
Feb 2015 - June 2017

Source of funding
Not reported</td><td></td><td></td><td></td><td></td><td></td></tr>
<tr><td>Full citation

Niklasson, B., Arnelo, C., Georgsson Ohman, S., Segerdahl, M., Blanck, A., Oral oxycodone for pain after caesarean section: A</td><td>Sample size
80 randomised; 40 per group
analysed: OXY n=38, Morphine/codeine n=39

Characteristics<table><tr><td>median [range]</td><td>oxycodone N=38</td><td>IV morphine/codeine N=39</td></tr><tr><td>age (years)</td><td>33.5 [23-42]</td><td>34.0 [21-44]</td></tr></table></td><td>Interventions
Oxycodone group: Before leaving the operating room, women received 20 mg long acting OXY (OxyContin®, Mundipharma, Sweden). Thereafter, 10 mg OxyContin® was given every 12 h for minimum 48 h.</td><td>Details
One hour preoperatively patients received 2 g oral paracetamol(Alvedon®, AstraZeneca, Sweden) as a bolus dose according to local routines. Spinal anaesthesia was administered using 1.8–2.6 ml(body</td><td>Results
Pain (at rest) (NRS) (0–10, where 0 depicts “no pain” and 10 “worst pain imaginable”)<table><tr><td>mean[SD]</td><td>oral oxycodone N=38</td><td>IV morphine/codeine N=39</td></tr><tr><td>pain (0-6hrs)</td><td>3.80±1.52</td><td>4.96±1.49</td></tr><tr><td>pain (0-24hrs)</td><td>3.43±1.74</td><td>3.93±1.30</td></tr></table></td><td>Limitations
RoB
Selection bias (Random sequence generation) LOW
Selection Bias (Allocation concealment) LOW
Performance bias (Blinding of participants and personnel) HIGH (cannot blind to allocation)</td></tr>
</table>

Study details	Participants	Interventions	Methods	Outcomes and Results	Comments
randomized comparison with nurse-administered IV morphine in a pragmatic study, Scandinavian Journal of Pain, 7, 17-24, 2015 **Ref Id** 697118 **Country/ies where the study was carried out** Sweden **Study type** RCT **Aim of the study** evaluate if an oral oxycodone (OXY) regimen can be at least equally effective and as safe for postoperative analgesia	previous CS: 19/38 0.5[1-4] / 22/39 0.5[1-3] **Inclusion criteria** Healthy women, 18–50 years old, planned for CS from 38 fullweeks of gestation, having the intention to breastfeed and whohad sufficient understanding of the Swedish language **Exclusion criteria** ongoing participation in another clinical trial, treatment for chronic pain, drug abuse,mental illness, patients treated with antidepressants, known intolerance or allergy towards any of the study drugs, maternal disease that could affect pregnancy and foetal complications e.g. large for gestational age or intrauterine growth retardation	Rescue medication was given as an oral dose of 5 mg immediate release OXY (OxyNorm®, Mundipharma, Sweden). In the case of severe breakthrough pain, 1–5 mg of i.v. OXY (OxyNorm®, Mundipharma, Sweden); 10 mg/ml, 1 ml diluted with 9 ml saline solution (Natriumklorid 9 mg/ml, Fresenius, Sweden) were given. Occasionally, short acting OXY was given before mobilization. All patients in this group received 1 g oral paracetamol every 6 h until discharged, longer if needed. IV morphine/codeine group: For 24 h, morphine (Morfin MEDA® 10 mg/ml, MEDA, Sweden), diluted in saline (Natriumklorid 9 mg/ml, Fresenius, Sweden) was nurse-	height depending) bupivacaine (Marcain Tung®5 mg/ml,AstraZeneca , Sweden) plus 15 g (0.3 ml) fentanyl (Fentanyl®50 g/ml, Meda AB, Sweden) through a 27 G Sproutte spinal needle at L2–L3 or L3–L4 with the woman in sitting position. Immediately after surgery, before leaving the operating room, all patients received oral ibuprofen 400 mg (Brufen®, Abbott Laboratories,Sweden). During the rest of the hospital stay, and longer if needed,all patients continuously received 200 mg ibuprofen every 6 h. Oral paraffin emulsion (30 ml) was given twice daily to diminish constipation.	pain (25-48hrs): 2.89±1.88 / 3.80±1.83	Detection bias (Blinding of outcomes) LOW Attrition bias (incomplete outcome data) LOW Reporting bias (selective reporting) UNCLEAR (no protocol available) Other biases NONE IDENTIFIED **Other information**

Study details	Participants	Interventions	Methods	Outcomes and Results	Comments
after caesarean section (CS) as a standard of care program using nurse-administered intravenous morphine (IVM), followed by oral codeine. **Study dates** November 2010 to August 2012 **Source of funding** grant from the Stockholm County Council (grant no.2006023) and funding from Sophiahemmet University, Stockholm. Mundipharma provided financial support for the OXY		administered by slow i.v. injection until an adequate response, NRS < 4/10, was obtained (if more than 10 mg the responsible physician was contacted). After 24 h, morphine and paracetamol were substituted by a combination treatment of paracetamol 500 mg plus codeine 30 mg (Citodon®, BioPhausia, Sweden), two tablets every 6 h for up to at least 48 h.			

<table>
<tr><th>Study details</th><th>Participants</th><th>Interventions</th><th>Methods</th><th>Outcomes and Results</th><th>Comments</th></tr>
<tr><td>analyses atthe Department of Clinical Pharmacology, Karolinska University Hospital, Huddinge.</td><td></td><td></td><td></td><td></td><td></td></tr>
<tr><td>Full citation

Sammour, Rami N., Ohel, Gonen, Cohen, Max, Gonen, Ron, Oral naproxen versus oral tramadol for analgesia after cesarean delivery, International journal of gynaecology and obstetrics: the official organ of the International Federation of Gynaecology and Obstetrics, 113, 144-7, 2011

Ref Id</td><td>Sample size
120; 30 to each group - only 2 groups relevant to this review

Characteristics<table><tr><td></td><td>fixed interval N=30</td><td>on request N=30</td></tr><tr><td>spinal</td><td>29/30</td><td>29/30</td></tr><tr><td>previous CS</td><td>17/30</td><td>20/30</td></tr></table>Inclusion criteria
planned or urgent (defined as any cesarean delivery performed urgently during labor owing to signs of fetal distress or non-progressive labor) cesarean

Exclusion criteria
hypersensitivity to 1 of the study drugs, concurrent use of anticoagulant drugs, chronic use of narcotic drugs, emergency cesarean delivery (where no time is available for</td><td>Interventions
fixed interval: oral tramadol (100 mg; Tramadex, Dexel, Or-Akiva, Israel) at fixed intervals every 6 hours request: oral tramadol (100 mg); no additional drug was administered before an interval of 6 hours had elapsed</td><td>Details
In the recovery room, immediately after surgery, participants received parenteral morphine from the attending nurse who was unaware of the allocation. Women were transferred to the maternity unit 2 hours after surgery. On admission, oral treatment with 1 of the treatment regimens was initiated according to the result of the randomization. In women receiving drugs on request, no additional drug was administered before an interval of 6 hours had elapsed in the case of tramadol.
If a participant required an</td><td>Results
Pain VAS of 0–10, where 0 was equal to no pain, and 10 was equal to the worst pain imaginable<table><tr><td>mean[SD]</td><td>fixed N=30</td><td>request N=30</td></tr><tr><td>pain 6hrs</td><td>5.4±2.5</td><td>4.9±2.2</td></tr><tr><td>pain 12hrs</td><td>4.1±2.6</td><td>4.9±2.3</td></tr><tr><td>pain 24hrs</td><td>3.7±2.5</td><td>3.4±2.3</td></tr><tr><td>pain 48hrs</td><td>2.8±2.0</td><td>3.3±2.1</td></tr><tr><td>pain average</td><td>4.0</td><td>4.2</td></tr></table></td><td>Limitations
RoB
Selection bias (Random sequence generation) LOW
Selection Bias (Allocation concealment) LOW
Performance bias (Blinding of participants and personnel) HIGH (cannot blind to allocation)
Detection bias (Blinding of outcomes) LOW
Attrition bias (incomplete outcome data) LOW
Reporting bias (selective reporting) UNCLEAR (no protocol available)
Other biases NONE IDENTIFIED</td></tr>
</table>

Study details	Participants	Interventions	Methods	Outcomes and Results	Comments
1160795 **Country/ies where the study was carried out** Israel **Study type** RCT **Aim of the study** compare the efficacies of oral tramadol for pain relief after cesarean delivery at fixed intervals versus on request. **Study dates** 7th August 2006 - 23rd March 2009 **Source of funding** Not reported	recruitment), peptic ulcer disease, and preeclampsia treated with magnesium sulfate.		additional pain relief medication during the 48 hours of the study before the above-mentioned interval had elapsed, she was given oral paracetamol–propoxyphene and this was recorded in her medical file. If a participant wished to withdraw from the trial, this was recorded in her medical file, but pain score was nevertheless obtained because the analysis was performed according to intention to treat		**Other information**

<table>
<tr><th>Study details</th><th>Participants</th><th>Interventions</th><th>Methods</th><th>Outcomes and Results</th><th>Comments</th></tr>
<tr>
<td>Full citation

Saracoglu, A., Saracoglu, K. T., Umuroglu, T., But, A., The effectivity of fentanyl versus tramadol as intravenous patient-controlled analgesia after cesarean section, Advances in Clinical and Experimental Medicine, 19, 739-743, 2010

Ref Id

1040944

Country/ies where the study was carried out

Turkey

Study type
RCT</td>
<td>Sample size
60; 30 per group

Characteristics
All had general anaesthetic
<table>
<tr><th>mean [SD]</th><th>fentanyl N=30</th><th>tramadol N=30</th></tr>
<tr><td>age (years)</td><td>26.32 ± 8.69</td><td>28.06 ± 11.47</td></tr>
<tr><td>ASA1</td><td>76%</td><td>80%</td></tr>
</table>
Inclusion criteria
elective cesarean surgery for pregnancy

Exclusion criteria
patient refusal to join the study, allergy to opioids, a history of chronic pain, an American Society of Anesthesiologists (ASA) physical status grade more than 3,
inability to understand how to use the PCA device, age less than 18 years, and extreme obesity (body mass index > 40)</td>
<td>Interventions
IV PCA fentanyl (Group F, n = 30) : Postoperatively, patients in Group F received an initial dose of 1 µg kg–1 fentanyl IV. For the PCA, 1 mg of fentanyl was diluted in 100 ml of isotonic saline. The PCA boluses were 20 mcg, and the lockout interval was 8 minutes without an infusion rate.
IV PCA tramadol (Group T, n = 30) : Patients in Group T received 1 mg kg–1 tramadol as an initial dose, and 1 g of tramadol was diluted in 100 ml of isotonic saline for the PCA device. The demand dose was 20 mg; the lockout interval was 8 minutes without basal infusion. The patients began to receive analgesic medication via PCA immediately</td>
<td>Details
All the patients were premedicated with atropin 0.01 mg kg–1 im 45 minutes before the surgical procedure. The use of the PCA system and a standard visual analogue scale (VAS) for pain was explained to the patients the day before the operation
General anesthesia was induced by propofol 2 mg kg–1 and atracurium 0.4 mg kg–1. The patients' lungs were mechanically ventilated and ventilation was adjusted to maintain endexpiratory CO2 between 32–36 mm Hg. After the baby was born, anesthesia was maintained by sevoflurane with an end-tidal concentration of 1.5% in oxygen–nitrous oxide (FIO2 = 0.5). Isotonic saline was</td>
<td>Results
Pain 100-point VAS. If the VAS score>30, the physician in charge could give a 2-cc bolus via PCA without changing the bolus dose and lockout interval
<table>
<tr><th>mean [sd]</th><th>fentanyl N=30</th><th>tramadol N=30</th></tr>
<tr><td>post-op 0hrs</td><td>50 ± 15.3</td><td>52.6 ± 10.48</td></tr>
<tr><td>post-op 1hrs</td><td>31.6 ± 14.8</td><td>36.6 ± 15.3</td></tr>
<tr><td>post-op 2hrs</td><td>20.3 ± 16.5</td><td>28.6 ± 14.07</td></tr>
<tr><td>post-op 4hrs</td><td>19 ± 10.2</td><td>22 ± 13.2</td></tr>
<tr><td>post-op 8hrs</td><td>24 ± 13.5</td><td>20.6 ± 11.7</td></tr>
<tr><td>post-op 12hrs</td><td>28 ± 15.8</td><td>22.6 ± 10.1</td></tr>
<tr><td>post-op 24hrs</td><td>15.3 ± 7.7</td><td>11.3 ± 10.0</td></tr>
</table>
side effects like pruritus, nausea and vomiting: 0 = no episode; 1 = at least one episode: no difference</td>
<td>Limitations
RoB
Selection bias (Random sequence generation) LOW
Selection Bias (Allocation concealment) LOW
Performance bias (Blinding of participants and personnel) LOW
Detection bias (Blinding of outcomes) LOW
Attrition bias (incomplete outcome data) LOW
Reporting bias (selective reporting) UNCLEAR (no protocol available)
Other biases NONE IDENTIFIED

Other information</td>
</tr>
</table>

<table>
<tr><th>Study details</th><th>Participants</th><th>Interventions</th><th>Methods</th><th>Outcomes and Results</th><th>Comments</th></tr>
<tr><td>Aim of the study
compare postoperative pain scores and analgesic requirements for both kinds of opioids in patients following cesarean section

Study dates

Source of funding
not reported</td><td></td><td>after the initial doses.</td><td>used for intraoperative fluid maintenance.</td><td></td><td></td></tr>
<tr><td>Full citation

Saracoglu, Kemal Tolga, Saracoglu, Ayten, Cakar, Kubra, Fidan, Vural, Ay, Binnaz, Comparative study of intravenous opioid consumption in the</td><td>Sample size
60 patients undergoing general anaesthesia

Characteristics
all had general anesthestic
<table><tr><td>mean[sd]</td><td>fentanyl</td><td>tramadol</td></tr><tr><td>age (years)</td><td>29. ± 9.3</td><td>29 ± 11.8</td></tr><tr><td>ASA1</td><td>82%</td><td>76%</td></tr></table></td><td>Interventions
IV PCA tramadol (n=30)
IV PCA fentanyl (n=30)
Postoperatively, patients received a PCA setting of a bolus of 20 µg fentanyl or 20 mg tramadol with a 10 min lockout interval time without basal infusion.</td><td>Details
All GA patients were premedicated with atropine 0.5 mg in 45 min before the surgical procedure. GA was induced by thiopental 5 mgkg–1 and atracurium 0.5 mg kg–1. Fentanyl 2 µg kg–1 was given IV and anesthesia was maintained by</td><td>Results
(VAS) for pain, the day before the surgery. 0 meant “No pain” and 100 meant “Worst possible pain imagined”.
<table><tr><td>mean[sd]</td><td>fentanyl N=30</td><td>tramadol N=30</td></tr><tr><td>pain 1hr</td><td>31.6 ± 14.8</td><td>32.4±11.5</td></tr><tr><td>pain 2hrs</td><td>20.3 ± 16.5</td><td>22.1±7.9</td></tr><tr><td>pain 4hrs</td><td>19.0 ± 10.2</td><td>18.9±13.7</td></tr></table></td><td>Limitations
RoB
Selection bias (Random sequence generation) UNCLEAR
Selection Bias (Allocation concealment) UNCLEAR
Performance bias (Blinding of participants and personnel) UNCLEAR</td></tr>
</table>

Study details	Participants	Interventions	Methods	Outcomes and Results	Comments
postoperative period, Biomedical papers of the Medical Faculty of the University Palacky, Olomouc, Czechoslovakia, 156, 48-51, 2012 **Ref Id** 1160797 **Country/ies where the study was carried out** Turkey **Study type** RCT **Aim of the study** compare fentanyl and tramadol with IV PCA after spinal anesthesia (SA) and general anesthesia (GA) following	**Inclusion criteria** undergoing elective C/S (who elected to have general anaestheisa) **Exclusion criteria** contraindications to neuraxial anesthesia (patient refusal, coagulation defects, intracranial masses, use of acetylsalicylic acid in the last ten days, skin infection on interprice location, lumbar disc herniation, peripheral neuropathy), allergy to local anesthetics or opioids, history of chronic pain, American Society of Anesthesiologists (ASA) ≥ 3, inability to understand how to use the PCA device, age < 18 years		sevoflurane with an end-tidal concentration 1.5% in oxygen–nitrous oxide (FIO2 = 0.5). Isotonic saline infusion was used for intraoperative fluid maintenance Postoperatively, patients received a PCA setting of a bolus of 20 µg fentanyl or 20 mg tramadol with a 10 min lockout interval time without basal infusion. The solution was prepared as 1 mg of fentanyl or 1000 mg of tramadol diluted in 100 ml of isotonic saline. During follow up, if the VAS score of the patient was above 30, the physician in charge gave a bolus of 2 ml solution without changing the bolus dose and lockout interval time of the PCA set.	<table><tr><td>pain 8hrs</td><td>24.0 ± 13.5</td><td>23.3±11.8</td></tr><tr><td>pain 12hrs</td><td>28.0 ± 15.8</td><td>26.4±9.6</td></tr><tr><td>pain 24hrs</td><td>12.3 ± 7.7</td><td>12.8±14.7</td></tr></table>Side-effects such as pruritus, nausea and vomiting were recorded: 0= no episode; 1= at least one episode: Postoperative nausea and vomiting scores were similar (P>0.05).	Detection bias (Blinding of outcomes) LOW Attrition bias (incomplete outcome data) LOW Reporting bias (selective reporting) UNCLEAR (no protocol available) Other biases NONE IDENTIFIED **Other information**

<table>
<tr><th>Study details</th><th>Participants</th><th>Interventions</th><th>Methods</th><th>Outcomes and Results</th><th>Comments</th></tr>
<tr><td>cesarean section (C/S) - only data relevant to GA used for this review

Study dates
Not reported

Source of funding
Not reported</td><td></td><td></td><td></td><td></td><td></td></tr>
<tr><td>Full citation

Snell,P., Hicks,C., An exploratory study in the UK of the effectiveness of three different pain management regimens for post-caesarean section women, Midwifery, 22, 249-261, 2006

Ref Id

60926</td><td>Sample size
66 (groups 2 and 3 only); midwife-oral n=33, midwife-oral+IM n=33

Characteristics
<table>
<tr><td>mean [sd]</td><td>oral only N=33</td><td>oral+IM N=33</td></tr>
<tr><td>age (years)</td><td>29.5 [6.8]</td><td>30.9 [5.4]</td></tr>
<tr><td>breastfeeding</td><td>10/33</td><td>17/33</td></tr>
<tr><td>primiparous</td><td>3/33</td><td>14/33</td></tr>
</table>
Inclusion criteria
elective caesarean section; subarachnoid anaesthesia; aged 18 years or over; and</td><td>Interventions
Midwife-oral: midwife-administered oral analgesia (morphine, Codydramol and diclofenac)
Midwife-oral+IM: midwife-administered intramuscular morphine, plus oral Codydramol and diclofenac.</td><td>Details
After elective caesarean section under subarachnoid anaesthesia, diclofenac 100 mg was given, per rectum, to all participants. Immediately after surgery, all groups were prescribed oral diclofenac and Co-dydramol; these drugs were administered by the midwife. In addition, oral morphine was prescribed for the midwife-oral group, whereas, for</td><td>Results
Pain VAS scale of 0–10, Pain was measured once per day, between 9.30 and 11.30 am
Nausea & vomiting NRS (three-point ordinal scale: 0 for no nausea or vomiting, 1 for nausea and 2 for vomiting) completed daily by the women
Satisfaction with pain relief: self-completed on day 2
<table>
<tr><td>mean[sd] or n/N</td><td>oral only N=33</td><td>oral+IM N=33</td></tr>
<tr><td>Pain day1</td><td>54.2 [19.5]</td><td>49.0 [13.1]</td></tr>
<tr><td>Pain day2</td><td>39.9 [21.4]</td><td>35.2 [12.5]</td></tr>
<tr><td>Nausea only day1</td><td>6/33</td><td>6/33</td></tr>
<tr><td>Nausea only day2</td><td>1/33</td><td>0/33</td></tr>
</table></td><td>Limitations
RoB
Selection bias (Random sequence generation) UNCLEAR
Selection Bias (Allocation concealment) UNCLEAR
Performance bias (Blinding of participants and personnel) HIGH (cannot blind to allocation)
Detection bias (Blinding of outcomes) LOW
Attrition bias (incomplete outcome data) LOW</td></tr>
</table>

Study details	Participants	Interventions	Methods	Outcomes and Results	Comments
Country/ies where the study was carried out UK **Study type** RCT **Aim of the study** compare the effects of three types of analgesic administration after elective caesarean section on a number of clinical outcome measures. Supplementary aims of the study were to determine the acceptability of, and satisfaction with, the different regimens	ability to read, write and speak English; primiparous and multiparous women **Exclusion criteria** • contraindications to morphine, diclofenac or Co-dydramol; • history of drug abuse		midwife-oral+IM, intramuscular morphine was prescribed. After delivery, and in order to establish effective analgesia, all participants were prescribed a single, midwife-administered dose of intramuscular morphine. In the postnatal ward, the midwife administered the prescribed analgesia either at set drug round times or when requested by the woman.	Vomiting day1 5/33 5/33 Vomiting day2 3/33 0/33 satisfaction >7 12/14 25/26	Reporting bias (selective reporting) UNCLEAR (no protocol available) Other biases NONE IDENTIFIED **Other information**

<table>
<tr><th>Study details</th><th>Participants</th><th>Interventions</th><th>Methods</th><th>Outcomes and Results</th><th>Comments</th></tr>
<tr><td>Study dates
Not reported

Source of funding
Not reported</td><td></td><td></td><td></td><td></td><td></td></tr>
<tr><td>Full citation

Yefet, E., Taha, H., Salim, R., Hasanein, J., Carmeli, Y., Schwartz, N., Nachum, Z., Fixed time interval compared with on-demand oral analgesia protocols for post-caesarean pain: a randomised controlled trial, BJOG, 124, 1063-1070, 2017

Ref Id

1033932

Country/ies where the</td><td>Sample size
214 randomised: 108 to fixed time interval group, 106 to on-demand group
200 analysed; 100 per group

Characteristics<table><tr><td>mean [sd]</td><td>on-demand N=100</td><td>fixed interval N=100</td></tr><tr><td>age (years)</td><td>31.5 [5.3]</td><td>31.5 [5.1]</td></tr><tr><td>GA (weeks)</td><td>38.5 [1.0]</td><td>38.4 [1.3]</td></tr><tr><td>previous CS</td><td>2.2 [1.1]</td><td>2.2 [1.0]</td></tr><tr><td>first CS</td><td>26/100</td><td>30/100</td></tr></table>Inclusion criteria
CS delivery with regional anaesthesia

Exclusion criteria
women who suffered from chronic pain, women using chronic pain medications, known allergy to any drug used in the study, women</td><td>Interventions
Fixed time interval group – once the patient arrived at the maternity ward she received intravenous tramadol hydrochloride 100 mg (the only time an intravenous medication was used), a tablet of paracetamol 500 mg and a tablet of diclofenac 100 mg. Six hours after patient arrival and every 6 h the patient received two tablets of Zaldiar (each tablet contained paracetamol 325 mg and tramadol 35.5 mg). The patient also received a tablet of diclofenac 100 mg 12, 24 and 48 h from arrival.</td><td>Details
All the study participants received spinal anaesthesia with fentanyl 25 lg and Bupivacaine 10 mg (isobaric) for the surgery. In the recovery ward, the patients received one tablet of Percocet (oxycodone 5 mg and paracetamol 325 mg).
In both groups, if the patients required additional pain relievers, they were given a tablet of Percocet (oxycodone 5 mg and paracetamol 325 mg) as necessary up to four times per day. In the ‘on-demand’ group, this treatment was</td><td>Results
Pain intensity (taken at rest) self-reporting VAS 0=no pain and 10=the worst pain
Satisfaction VAS (0-10) 0=least satisfied, 10=most satisfied<table><tr><td>mean[sd]</td><td>on-demand N=100</td><td>fixed time interval N=100</td></tr><tr><td>satisfaction (0-10)</td><td>N=99
8.3 [1.5]</td><td>N=91
9.1 [1.2]</td></tr><tr><td>Pain VAS average</td><td>N=100
4.12 [0.48]</td><td>N=100
2.81 [0.84]</td></tr><tr><td>Pain 0-6hrs</td><td>4.11 (0.89)</td><td>3.11 (0.97)</td></tr><tr><td>Pain 6-12hrs</td><td>4.10 (0.84)</td><td>2.86 (1.27)</td></tr><tr><td>Pain 12-18hrs</td><td>4.29 (0.83)</td><td>2.97 (1.58)</td></tr><tr><td>Pain 18-24hrs</td><td>4.16 (0.83)</td><td>2.80 (1.36)</td></tr><tr><td>Pain 24-30hrs</td><td>4.04 (0.91)</td><td>2.28 (1.41)</td></tr><tr><td>Pain 30-36hrs</td><td>4.13 (0.88)</td><td>2.18 (1.61)</td></tr></table></td><td>Limitations
RoB
Selection bias (Random sequence generation) LOW
Selection Bias (Allocation concealment) LOW
Performance bias (Blinding of participants and personnel) HIGH (cannot blind to allocation)
Detection bias (Blinding of outcomes) LOW
Attrition bias (incomplete outcome data) LOW
Reporting bias (selective reporting) UNCLEAR (no protocol available)
Other biases NONE IDENTIFIED</td></tr>
</table>

Study details	Participants	Interventions	Methods	Outcomes and Results	Comments
study was carried out Israel **Study type** RCT **Aim of the study** compare the efficacy, safety and satisfaction from two modes of oral analgesia administration for the treatment of post-caesarean pain in the first 48 h following surgery: on-demand versus fixed time interval administration **Study dates** February to December 2013	who were scheduled or eventually underwent general anaesthesia during the surgery, who delivered vaginally, or women with abnormal liver functions.	'On-demand' group – patients allocated to this group received the same medications in the same combinations and order as described in the 'fixed time interval' group protocol, only patients in this group received pain treatment only following demand, and the time intervals described above were considered as the minimal time for giving the next combination of drugs.	given if the patient requested additional pain relievers prior to 6 h past the last treatment	Pain 36-42hrs | 3.95 (0.96) | 1.98 (1.52)	**Other information**

<table>
<tr><th>Study details</th><th>Participants</th><th>Interventions</th><th>Methods</th><th>Outcomes and Results</th><th>Comments</th></tr>
<tr><td>Source of funding
None</td><td></td><td></td><td></td><td></td><td></td></tr>
<tr><td>Full citation

Yost,N.P., Bloom,S.L., Sibley,M.K., Lo,J.Y., McIntire,D.D., Leveno,K.J., A hospital-sponsored quality improvement study of pain management after cesarean delivery, American Journal of Obstetrics and Gynecology, 190, 1341-1346, 2004

Ref Id

117360

Country/ies where the study was carried out

USA</td><td>Sample size
2644 allocated;
IM meperidine n=306
PCA meperidine n=319
IM morphine n=322
PCA morphine n=309

Characteristics
<table>
<tr><th>mead[sd]</th><th>IM meperidine</th><th>PCA mep</th><th>IM morphine</th><th>PCA morph</th></tr>
<tr><td>age (years)</td><td>25.9 [5.6]</td><td>26.2 [5.4]</td><td>26 [5.7]</td><td>26.3 [5.8]</td></tr>
<tr><td>primiparous</td><td>109/306</td><td>115/319</td><td>109/322</td><td>107/309</td></tr>
<tr><td>previous CS</td><td>156/306</td><td>151/319</td><td>159/322</td><td>160/309</td></tr>
<tr><td>general anaesthesia</td><td>29/306</td><td>25/319</td><td>23/322</td><td>29/309</td></tr>
</table>
Inclusion criteria
women with caesarean deliveries</td><td>Interventions
(1) intramuscular (IM) meperidine,
(2) patient-controlled analgesia (PCA) meperidine,
(3) IM morphine sulfate,
(4) PCA morphine sulfate
Abbott-Lifecare 4100 (Abbott Laboratories, Chicago, Ill) pumps were used for the PCA study groups.</td><td>Details
Each ward used 1 of these pain management protocols for a 3-month period and then rotated such that each of the pain regimens was measured on each ward
Each woman was given meperidine 25 mg intravenously every 5 min up to 100 mg maximum or morphine 2 mg every 5 min up to 10 mg in the recovery room after cesarean delivery with the goal of a VAS score of 4 or less.
Postpartum ward (first 24 h after surgery):

• Study group 1. IM meperidine, 50-75 mg every</td><td>Results
Pain VAS 0-10 (>4 is moderate severe)
<table>
<tr><th></th><th>IM mep</th><th>PCA mep</th><th>IM morph</th><th>PCA morph</th></tr>
<tr><td>Pain VAS >4 day1 (mod/severe)</td><td>132/306</td><td>100/319</td><td>70/322</td><td>62/309</td></tr>
<tr><td>satisfied with pain relief (satisfied/strongly)</td><td>252/306</td><td>266/319</td><td>290/322</td><td>254/309</td></tr>
<tr><td>breastfeeding discontinued</td><td>8/306</td><td>6/319</td><td>1/322</td><td>1/309</td></tr>
<tr><td>breastfeeding</td><td>231/306</td><td>233/319</td><td>243/322</td><td>246/309</td></tr>
</table>
Fewer women given morphine stopped breastfeeding (0.4% vs 3%, P=.02, for morphine vs meperidine, respectively).</td><td>Limitations
RoB
Selection bias (Random sequence generation) HIGH (not randomised, allocation by ward/hospital)
Selection Bias (Allocation concealment) HIGH (not randomised, allocation by ward/hospital)
Performance bias (Blinding of participants and personnel) HIGH (cannot blind to allocation)
Detection bias (Blinding of outcomes) HIGH (not randomised, allocation by ward/hospital)
Attrition bias (incomplete outcome data) LOW
Reporting bias (selective reporting) UNCLEAR (no protocol available)</td></tr>
</table>

Study details	Participants	Interventions	Methods	Outcomes and Results	Comments
Study type cluster RCT (by hospital ward per 3 month period) **Aim of the study** evaluate patient-controlled pain relief versus use of intermittent nurse-administered intramuscular (IM) injections of meperidine or morphine sulfate **Study dates** August 1999 - July 2000 **Source of funding** This study was supported, in part, from a grant from	**Exclusion criteria** Not reported		3-4 h as needed. • Study group 2. PCA intravenous meperidine, 10 mg with a 6-min lockout interval and maximum dose of 200 mg in 4-h as needed. An additional 25 mg ''booster'' dose was permitted for a maximum of 2 doses. • Study group 3. IM morphine, 10-15 mg every 3-4 h as needed. • Study group 4. PCA intravenou		Other biases NONE IDENTIFIED **Other information**

Study details	Participants	Interventions	Methods	Outcomes and Results	Comments
the National Institute of Child Health and Human Development no. 2 U10 HD 34116.			s morphine, 1 mg with a 6-min lockout interval and a maximum dose of 30 mg in 4-h as needed. An additional 2 mg ‘‘booster’’ dose was permitted for a maximum of 2 doses. Each postpartum ward regimen also included promethazine 25 mg intravenously every 6 h as needed for nausea.		

Appendix E – Forest plots

Forest plots for review question: Are opioids safe and effective for pain management after caesarean birth?

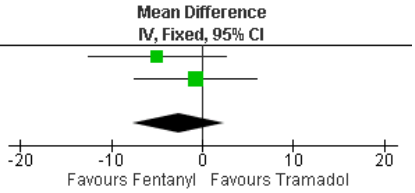
This section includes forest plots only for outcomes that are meta-analysed. Outcomes from single studies are not presented here, but the quality assessment for these outcomes is provided in the GRADE profiles in appendix F.

Comparison 2. Fentanyl (IV PCA) versus tramadol (IV PCA)

2.1 Pain 1hr

	Opiate (Fentanyl)			Part-opioid (Tramadol)				Mean Difference
Study or Subgroup	Mean	SD	Total	Mean	SD	Total	Weight	IV, Fixed, 95% CI
Saracoglu 2010	31.6	14.8	30	36.6	15.3	30	43.7%	-5.00 [-12.62, 2.62]
Saracoglu 2012	31.6	14.8	30	32.4	11.5	30	56.3%	-0.80 [-7.51, 5.91]
Total (95% CI)			**60**			**60**	**100.0%**	**-2.63 [-7.67, 2.40]**

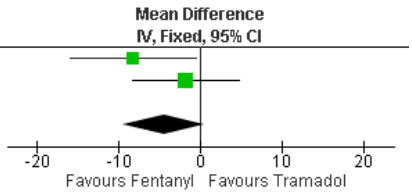
Heterogeneity: Chi² = 0.66, df = 1 (P = 0.42); I² = 0%
Test for overall effect: Z = 1.03 (P = 0.31)



2.2 Pain 2hrs

	Opiate (Fentanyl)			Part-opioid (Tramadol)				Mean Difference
Study or Subgroup	Mean	SD	Total	Mean	SD	Total	Weight	IV, Fixed, 95% CI
Saracoglu 2010	20.3	16.5	30	28.6	14.07	30	41.6%	-8.30 [-16.06, -0.54]
Saracoglu 2012	20.3	16.5	30	22.1	7.9	30	58.4%	-1.80 [-8.35, 4.75]
Total (95% CI)			**60**			**60**	**100.0%**	**-4.50 [-9.51, 0.50]**

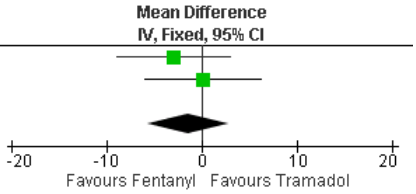
Heterogeneity: Chi² = 1.57, df = 1 (P = 0.21); I² = 36%
Test for overall effect: Z = 1.76 (P = 0.08)



2.3 Pain 4hrs

	Opiate (Fentanyl)			Part-opioid (Tramadol)				Mean Difference
Study or Subgroup	Mean	SD	Total	Mean	SD	Total	Weight	IV, Fixed, 95% CI
Saracoglu 2010	19	10.2	30	22	13.2	30	51.2%	-3.00 [-8.97, 2.97]
Saracoglu 2012	19	10.2	30	18.9	13.7	30	48.8%	0.10 [-6.01, 6.21]
Total (95% CI)			**60**			**60**	**100.0%**	**-1.49 [-5.76, 2.78]**

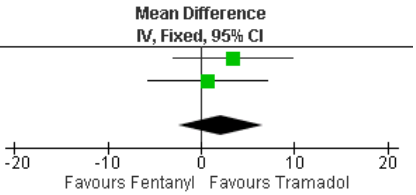
Heterogeneity: Chi² = 0.51, df = 1 (P = 0.48); I² = 0%
Test for overall effect: Z = 0.68 (P = 0.50)



2.4 Pain 8hrs

	Opiate (Fentanyl)			Part-opioid (Tramadol)				Mean Difference
Study or Subgroup	Mean	SD	Total	Mean	SD	Total	Weight	IV, Fixed, 95% CI
Saracoglu 2010	24	13.5	30	20.6	11.7	30	50.2%	3.40 [-2.99, 9.79]
Saracoglu 2012	24	13.5	30	23.3	11.8	30	49.8%	0.70 [-5.72, 7.12]
Total (95% CI)			**60**			**60**	**100.0%**	**2.05 [-2.47, 6.58]**

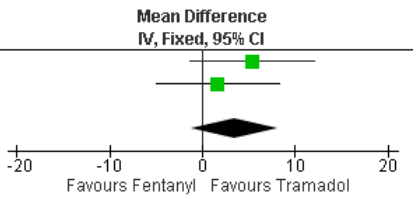
Heterogeneity: Chi² = 0.34, df = 1 (P = 0.56); I² = 0%
Test for overall effect: Z = 0.89 (P = 0.37)



2.5 Pain 12hrs

	Opiate (Fentanyl)			Part-opioid (Tramadol)				Mean Difference
Study or Subgroup	Mean	SD	Total	Mean	SD	Total	Weight	IV, Fixed, 95% CI
Saracoglu 2010	28	15.8	30	22.6	10.1	30	49.3%	5.40 [-1.31, 12.11]
Saracoglu 2012	28	15.8	30	26.4	9.6	30	50.7%	1.60 [-5.02, 8.22]
Total (95% CI)			**60**			**60**	**100.0%**	**3.47 [-1.24, 8.18]**

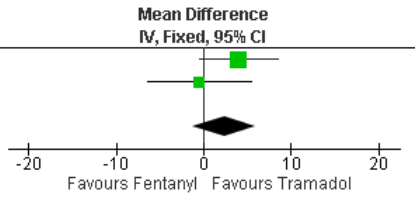
Heterogeneity: Chi² = 0.62, df = 1 (P = 0.43); I² = 0%
Test for overall effect: Z = 1.44 (P = 0.15)



2.6 Pain 24hrs

Study or Subgroup	Opiate (Fentanyl) Mean	SD	Total	Part-opioid (Tramadol) Mean	SD	Total	Weight	Mean Difference IV, Fixed, 95% CI
Saracoglu 2010	15.3	7.7	30	11.3	10	30	63.4%	4.00 [-0.52, 8.52]
Saracoglu 2012	12.3	7.7	30	12.8	14.7	30	36.6%	-0.50 [-6.44, 5.44]
Total (95% CI)			**60**			**60**	**100.0%**	**2.35 [-1.24, 5.95]**

Heterogeneity: Chi² = 1.40, df = 1 (P = 0.24); I² = 28%
Test for overall effect: Z = 1.28 (P = 0.20)

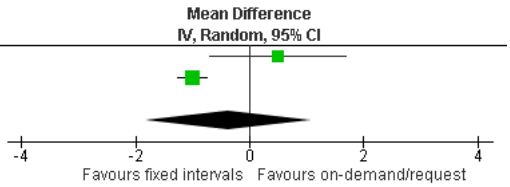


Comparison 7. Oral fixed timing versus oral on-demand (tramadol in both arms)

7.1 Pain 6hrs

Study or Subgroup	Fixed Mean	SD	Total	On-demand Mean	SD	Total	Weight	Mean Difference IV, Random, 95% CI
Sammour 2011	5.4	2.5	30	4.9	2.2	30	42.2%	0.50 [-0.69, 1.69]
Yefet 2017	3.11	0.97	100	4.11	0.89	100	57.8%	-1.00 [-1.26, -0.74]
Total (95% CI)			**130**			**130**	**100.0%**	**-0.37 [-1.82, 1.08]**

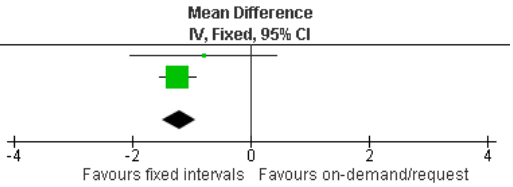
Heterogeneity: Tau² = 0.93; Chi² = 5.81, df = 1 (P = 0.02); I² = 83%
Test for overall effect: Z = 0.50 (P = 0.62)



7.2 Pain 12hrs

Study or Subgroup	Fixed Mean	SD	Total	On-demand Mean	SD	Total	Weight	Mean Difference IV, Fixed, 95% CI
Sammour 2011	4.1	2.6	30	4.9	2.3	30	5.5%	-0.80 [-2.04, 0.44]
Yefet 2017	2.86	1.27	100	4.1	0.84	100	94.5%	-1.24 [-1.54, -0.94]
Total (95% CI)			**130**			**130**	**100.0%**	**-1.22 [-1.51, -0.93]**

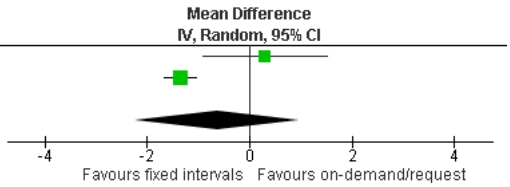
Heterogeneity: Chi² = 0.46, df = 1 (P = 0.50); I² = 0%
Test for overall effect: Z = 8.21 (P < 0.00001)



7.4 Pain 24hrs

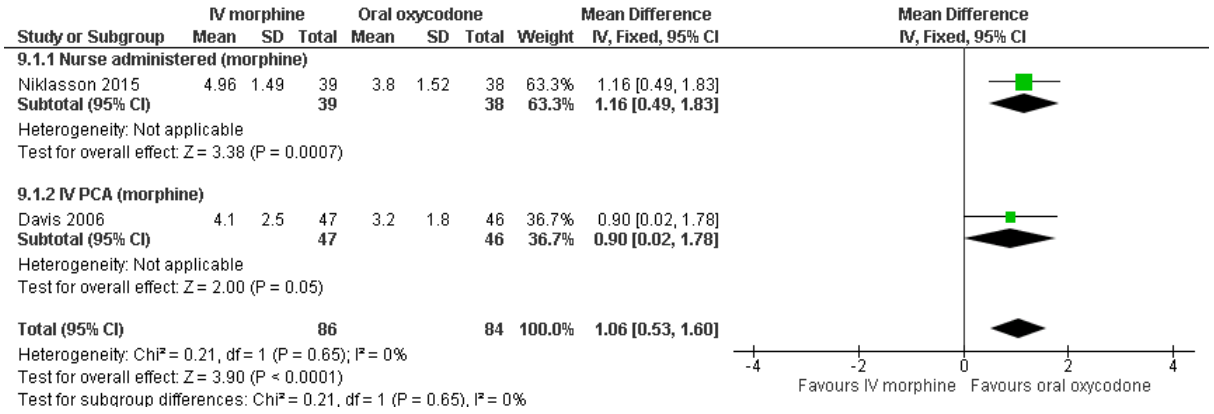
Study or Subgroup	Fixed Mean	SD	Total	On-demand Mean	SD	Total	Weight	Mean Difference IV, Random, 95% CI
Sammour 2011	3.7	2.5	30	3.4	2.3	30	43.5%	0.30 [-0.92, 1.52]
Yefet 2017	2.8	1.36	100	4.16	0.83	100	56.5%	-1.36 [-1.67, -1.05]
Total (95% CI)			**130**			**130**	**100.0%**	**-0.64 [-2.25, 0.97]**

Heterogeneity: Tau² = 1.17; Chi² = 6.72, df = 1 (P = 0.010); I² = 85%
Test for overall effect: Z = 0.78 (P = 0.44)

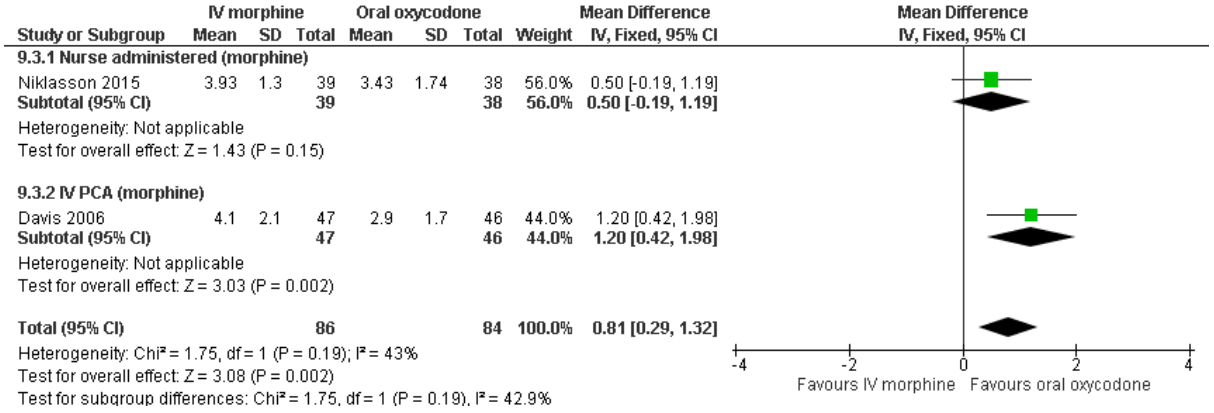


Comparison 9. IV morphine vs oral oxycodone

9.1 Pain 6hrs



9.3 Pain 24hrs



Appendix F – GRADE tables

GRADE tables for review question: Are opioids safe and effective for pain management after caesarean birth?

PHARMACOLOGICAL INTERVENTIONS

Comparison 1: Oxycodone (oral) versus tapentadol (oral) for post-caesarean birth

Quality assessment							No of patients		Effect		Quality	Importance
No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Opioid (oxycodone)	Part-opioid (tapendatol)	Relative (95% CI)	Absolute		
Pain relief 36hrs (measured with: pain relief scores (score 0–4) (0=no relief, 4=complete relief); Better indicated by higher values)												
1 (Ffrench-O'Carroll 2019)	randomised trials	no serious risk of bias	no serious inconsistency	no serious indirectness	serious[1]	none	35	33	-	MD 0.15 higher (0.34 lower to 0.64 higher)	MODERATE	CRITICAL
Pain relief 48hrs (measured with: pain relief scores (score 0–4) (0=no relief, 4=complete relief); Better indicated by higher values)												
1 (Ffrench-O'Carroll 2019)	randomised trials	no serious risk of bias	no serious inconsistency	no serious indirectness	serious[2]	none	35	33	-	MD 0.12 higher (0.36 lower to 0.6 higher)	MODERATE	CRITICAL
Satisfaction 36hrs (measured with: patient satisfaction scores (score 1–5); Better indicated by higher values)												
1 (Ffrench-O'Carroll 2019)	randomised trials	no serious risk of bias	no serious inconsistency	no serious indirectness	serious[3]	none	35	33	-	MD 0.23 higher (0.27 lower to 0.73 higher)	MODERATE	IMPORTANT
Satisfaction 48hrs (measured with: patient satisfaction scores (score 1–5); Better indicated by higher values)												
1 (Ffrench-O'Carroll 2019)	randomised trials	no serious risk of bias	no serious inconsistency	no serious indirectness	serious[4]	none	35	33	-	MD 0.2 lower (0.7 lower to 0.3 higher)	MODERATE	IMPORTANT
Nausea												
1 (Ffrench-O'Carroll 2019)	randomised trials	no serious risk of bias	no serious inconsistency	no serious indirectness	very serious[5]	none	9/35 (25.7%)	10/33 (30.3%)	RR 0.85 (0.39 to 1.82)	45 fewer per 1000 (from 185 fewer to 248 more)	LOW	IMPORTANT

Quality assessment							No of patients		Effect		Quality	Importance
No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Opioid (oxycodone)	Part-opioid (tapendatol)	Relative (95% CI)	Absolute		
Vomiting												
1 (Ffrench-O'Carroll 2019)	randomised trials	no serious risk of bias	no serious inconsistency	no serious indirectness	very serious[5]	none	5/35 (14.3%)	6/33 (18.2%)	RR 0.79 (0.26 to 2.33)	38 fewer per 1000 (from 135 fewer to 242 more)	LOW	IMPORTANT
Constipation 48hrs												
1 (Ffrench-O'Carroll 2019)	randomised trials	no serious risk of bias	no serious inconsistency	no serious indirectness	serious[6]	none	23/35 (65.7%)	27/33 (81.8%)	RR 0.8 (0.6 to 1.07)	164 fewer per 1000 (from 327 fewer to 57 more)	MODERATE	IMPORTANT
Pruritus (itching)												
1 (Ffrench-O'Carroll 2019)	randomised trials	no serious risk of bias	no serious inconsistency	no serious indirectness	serious[6]	none	24/35 (68.6%)	19/33 (57.6%)	RR 1.19 (0.82 to 1.72)	109 more per 1000 (from 104 fewer to 415 more)	MODERATE	IMPORTANT

[1] *95%CI crosses one MID boundary; MID=+/-0.5*1.16 (SD in tapentadol group)*
[2] *95%CI crosses one MID boundary; MID=+/-0.5*1.1 (SD in tapentadol group)*
[3] *95%CI crosses one MID boundary; MID=+/-0.5*1.19 (SD in tapentadol group)*
[4] *95%CI crosses one MID boundary; MID=+/-0.5*1.21 (SD in tapentadol group)*
[5] *95%CI crosses two MID boundaries (0.8 to 1.25)*
[6] *95%CI crosses one MID boundary (0.8 to 1.25)*

Comparison 2: Fentanyl (IV PCA) versus tramadol (IV PCA) for post-caesarean birth (all following general anaesthetic)

Quality assessment							No of patients		Effect			
No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Opiate (fentanyl)	Part-opioid (tramadol)	Relative (95% CI)	Absolute	Quality	Importance
Pain 1hr (measured with: VAS: 0 =“No pain” to 100 = “Worst possible pain imagined”.; Better indicated by lower values)												
2 (Saracoglu 2010; Saracoglu 2012)	randomised trials	serious[1]	no serious inconsistency	no serious indirectness	serious[2]	none	60	60	-	MD 2.63 lower (7.67 lower to 2.4 higher)	LOW	CRITICAL
Pain 2hrs (measured with: VAS: 0 =“No pain” to 100 = “Worst possible pain imagined”.; Better indicated by lower values)												
2 (Saracoglu 2010; Saracoglu 2012)	randomised trials	serious[1]	no serious inconsistency	no serious indirectness	serious[3]	none	60	60	-	MD 4.5 lower (9.51 lower to 0.5 higher)	LOW	CRITICAL
Pain 4hrs (measured with: VAS: 0 =“No pain” to 100 = “Worst possible pain imagined”.; Better indicated by lower values)												
2 (Saracoglu 2010; Saracoglu 2012)	randomised trials	serious[1]	no serious inconsistency	no serious indirectness	no serious imprecision[4]	none	60	60	-	MD 1.49 lower (5.76 lower to 2.78 higher)	MODERATE	CRITICAL
Pain 8hrs (measured with: VAS: 0 =“No pain” to 100 = “Worst possible pain imagined”.; Better indicated by lower values)												
2 (Saracoglu 2010; Saracoglu 2012)	randomised trials	serious[1]	no serious inconsistency	no serious indirectness	serious[5]	none	60	60	-	MD 2.05 higher (2.47 lower to 6.58 higher)	LOW	CRITICAL
Pain 12hrs (measured with: VAS: 0 =“No pain” to 100 = “Worst possible pain imagined”.; Better indicated by lower values)												
2 (Saracoglu 2010; Saracoglu 2012)	randomised trials	serious[1]	no serious inconsistency	no serious indirectness	serious[6]	none	60	60	-	MD 3.47 higher (1.24 lower to 8.18 higher)	LOW	CRITICAL
Pain 24hrs (measured with: VAS: 0 =“No pain” to 100 = “Worst possible pain imagined”.; Better indicated by lower values)												
2 (Saracoglu 2010; Saracoglu 2012)	randomised trials	serious[1]	no serious inconsistency	no serious indirectness	no serious imprecision[7]	none	60	60	-	MD 2.35 higher (1.24 lower to 5.95 higher)	MODERATE	CRITICAL

[1] *Unclear ROB in multiple domains in one study*

[2] *95%CI crosses one MID boundary; MID=+/-0.5*13.4 (SD in Tramadol group)*

[3] *95%CI crosses one MID boundary; MID=+/-0.5*10.985 (SD in Tramadol group)*

[4] *MID=+/-0.5*13.45 (SD in Tramadol group)*
[5] *95%CI crosses one MID boundary; MID=+/-0.5*11.75 (SD in Tramadol group)*
[6] *95%CI crosses one MID boundary; MID=+/-0.5*9.85 (SD in Tramadol group)*
[7] *MID=+/-0.5*12.35 (SD in Tramadol group)*

Comparison 3: Morphine (IM or IV PCA) versus meperidine (IM or IV PCA) for post-caesarean birth (10% general anaesthetic)

Quality assessment							No of patients		Effect		Quality	Importance
No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Opiate (morphine)	Opioid (meperidine)	Relative (95% CI)	Absolute		
Pain >4/10 (moderate/severe)												
1 (Yost 2004)	randomised trials	very serious[1]	no serious inconsistency	no serious indirectness	serious[2]	none	132/631 (20.9%)	232/625 (37.1%)	RR 0.56 (0.47 to 0.68)	163 fewer per 1000 (from 119 fewer to 197 fewer)	VERY LOW	CRITICAL
Breastfeeding established												
1 (Yost 2004)	randomised trials	very serious[1]	no serious inconsistency	no serious indirectness	serious[2]	none	489/631 (77.5%)	464/625 (74.2%)	RR 1.04 (0.98 to 1.11)	30 more per 1000 (from 15 fewer to 82 more)	VERY LOW	IMPORTANT
Breastfeeding discontinued												
1 (Yost 2004)	randomised trials	very serious[1]	no serious inconsistency	no serious indirectness	serious[2]	none	2/631 (0.32%)	14/625 (2.2%)	RR 0.14 (0.03 to 0.62)	19 fewer per 1000 (from 9 fewer to 22 fewer)	VERY LOW	IMPORTANT
Satisfaction (satisfied/strongly)												
1 (Yost 2004)	randomised trials	very serious[1]	no serious inconsistency	no serious indirectness	serious[2]	none	544/631 (86.2%)	518/625 (82.9%)	RR 1.04 (0.99 to 1.09)	33 more per 1000 (from 8 fewer to 75 more)	VERY LOW	IMPORTANT

[1] *High ROB in multiple domains*

[2] *Downgraded once for cluster randomisation without adjustment information*

MODE OF DELIVERY

Comparison 4: IV PCA versus continuous infusion (tramadol in both arms) for post-caesarean birth (all following general anaesthetic)

Quality assessment							No of patients		Effect		Quality	Importance
No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	IV PCA	IV continuous	Relative (95% CI)	Absolute		
Pain 1hr (measured with: VAS 0 = total absence of pain to 10 = most intolerable pain imaginable; Better indicated by lower values) presented as median [range]												
1 (Demirel 2014)	randomised trials	very serious [1]	no serious inconsistency	no serious indirectness	very serious[2]	none	20 3 [2-5]	20 4 [2-7]	-	median difference 1.00 lower	VERY LOW	CRITICAL
Pain 2hrs (measured with: VAS 0 = total absence of pain to 10 = most intolerable pain imaginable; Better indicated by lower values) presented as median [range]												
1 (Demirel 2014)	randomised trials	very serious [1]	no serious inconsistency	no serious indirectness	very serious[2]	none	20 3 [2-4]	20 3 [1-5]	-	median difference 0.00 higher	VERY LOW	CRITICAL
Pain 4hrs (measured with: VAS 0 = total absence of pain to 10 = most intolerable pain imaginable; Better indicated by lower values) presented as median [range]												
1 (Demirel 2014)	randomised trials	very serious [1]	no serious inconsistency	no serious indirectness	very serious[2]	none	20 2 [1-4]	20 3 [1-5]	-	median difference 1.00 lower	VERY LOW	CRITICAL
Pain 8hrs (measured with: VAS 0 = total absence of pain to 10 = most intolerable pain imaginable; Better indicated by lower values) presented as median [range]												
1 (Demirel 2014)	randomised trials	very serious [1]	no serious inconsistency	no serious indirectness	very serious[2]	none	20 1 [0-2]	20 1 [0-3]	-	median difference 0.00 higher	VERY LOW	CRITICAL
Pain 16hrs (measured with: VAS 0 = total absence of pain to 10 = most intolerable pain imaginable; Better indicated by lower values) presented as median [range]												
1 (Demirel 2014)	randomised trials	very serious [1]	no serious inconsistency	no serious indirectness	very serious[2]	none	20 1 [0-2]	20 1 [0-3]	-	median difference 0.00 higher	VERY LOW	CRITICAL
Pain 24hrs (measured with: VAS 0 = total absence of pain to 10 = most intolerable pain imaginable; Better indicated by lower values) presented as median [range]												
1 (Demirel 2014)	randomised trials	very serious [1]	no serious inconsistency	no serious indirectness	very serious[2]	none	20 1 [0-2]	20 1 [0-2]	-	median difference 0.00 higher	VERY LOW	CRITICAL
Satisfaction (satisfied/very)												
1 (Demirel 2014)	randomised trials	very serious [1]	no serious inconsistency	no serious indirectness	serious[3]	none	19/20 (95%)	18/20 (90%)	RR 1.06 (0.88 to 1.26)	54 more per 1000 (from 108 fewer to 234 more)	VERY LOW	IMPORTANT
Nausea 1hr												

Quality assessment							No of patients		Effect		Quality	Importance
No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	IV PCA	IV continuous	Relative (95% CI)	Absolute		
1 (Demirel 2014)	randomised trials	very serious [1]	no serious inconsistency	no serious indirectness	very serious [4]	none	4/20 (20%)	3/20 (15%)	RR 1.33 (0.34 to 5.21)	50 more per 1000 (from 99 fewer to 632 more)	VERY LOW	IMPORTANT
Nausea 2hrs												
1 (Demirel 2014)	randomised trials	very serious [1]	no serious inconsistency	no serious indirectness	very serious [4]	none	2/20 (10%)	2/20 (10%)	RR 1 (0.16 to 6.42)	0 fewer per 1000 (from 84 fewer to 542 more)	VERY LOW	IMPORTANT
Nausea 4hrs												
1 (Demirel 2014)	randomised trials	very serious [1]	no serious inconsistency	no serious indirectness	very serious [4]	none	0/20 (0%)	1/20 (5%)	POR 0.14 (0 to 6.82) [5]	43 fewer per 1000 (from 50 fewer to 214 more)	VERY LOW	IMPORTANT
Nausea 8hrs												
1 (Demirel 2014)	randomised trials	very serious [1]	no serious inconsistency	no serious indirectness	very serious [4]	none	0/20 (0%)	2/20 (10%)	POR 0.13 (0.01 to 2.13) [5]	86 fewer per 1000 (from 99 fewer to 91 more)	VERY LOW	IMPORTANT
Nausea 16hrs												
1 (Demirel 2014)	randomised trials	very serious [1]	no serious inconsistency	no serious indirectness	very serious [2]	none	0/20 (0%)	0/20 (0%)	RD = 0 (-0.09, 0.09)	0 more per 1000 (from 90 fewer to 90 more) [6]	VERY LOW	IMPORTANT
Nausea 24hrs												
1 (Demirel 2014)	randomised trials	very serious [1]	no serious inconsistency	no serious indirectness	very serious [2]	none	0/20 (0%)	0/20 (0%)	RD = 0 (-0.09, 0.09)	0 more per 1000 (from 90 fewer to 90 more) [6]	VERY LOW	IMPORTANT

[1] *High and unclear ROB in multiple domains*
[2] *Optimal Information Size (OIS) <300; No relative measure CI for assessment, sample size <300*
[3] *95%CI crosses one MID boundary (0.8 to 1.25)*
[4] *95%CI crosses two MID boundaries (0.8 to 1.25)*
[5] *Peto OR (POR) used due to low event rate (0 cases in one arm)*
[6] *calculated from risk difference (RD) due to low event rate (0 cases in both arms)*

Comparison 5: IV PCA versus oral (oxycodone in both arms) for post-caesarean birth

Quality assessment							No of patients		Effect		Quality	Importance
No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	IV PCA	Oral	Relative (95% CI)	Absolute		
Pain >7/10 (at rest) 2hrs (severe)												
1 (Makela 2019)	randomised trials	very serious[1]	no serious inconsistency	no serious indirectness	serious[2]	none	10/119 (8.4%)	4/124 (3.2%)	RR 2.61 (0.84 to 8.08)	52 more per 1000 (from 5 fewer to 228 more)	VERY LOW	CRITICAL
Pain >7/10 (at rest) 4hrs (severe)												
1 (Makela 2019)	randomised trials	very serious[1]	no serious inconsistency	no serious indirectness	very serious[3]	none	26/123 (21.1 %)	30/126 (23.8%)	RR 0.89 (0.56 to 1.41)	26 fewer per 1000 (from 105 fewer to 98 more)	VERY LOW	CRITICAL
Pain >7/10 (at rest) 8hrs (severe)												
1 (Makela 2019)	randomised trials	very serious[1]	no serious inconsistency	no serious indirectness	very serious[3]	none	9/120 (7.5%)	8/121 (6.6%)	RR 1.13 (0.45 to 2.84)	9 more per 1000 (from 36 fewer to 122 more)	VERY LOW	CRITICAL
Pain >7/10 (at rest) 24hrs (severe)												
1 (Makela 2019)	randomised trials	very serious[1]	no serious inconsistency	no serious indirectness	no serious imprecision	none	5/106 (4.7%)	0/111 (0%)	POR 8.05 (1.37 to 47.27)[4]	50 more per 1000 (from 0 more to 90 more)[5]	LOW	CRITICAL
Dissatisfaction 2hrs (NRS<3/10)												
1 (Makela 2019)	randomised trials	very serious[1]	no serious inconsistency	no serious indirectness	very serious[3]	none	6/115 (5.2%)	6/118 (5.1%)	RR 1.03 (0.34 to 3.09)	2 more per 1000 (from 34 fewer to 106 more)	VERY LOW	IMPORTANT
Dissatisfaction 4hrs (NRS<3/10)												
1 (Makela 2019)	randomised trials	very serious[1]	no serious inconsistency	no serious indirectness	very serious[3]	none	4/111 (3.6%)	7/119 (5.9%)	RR 0.61 (0.18 to 2.04)	23 fewer per 1000 (from 48 fewer to 61 more)	VERY LOW	IMPORTANT
Dissatisfaction 8hrs (NRS<3/10)												
1 (Makela 2019)	randomised trials	very serious[1]	no serious inconsistency	no serious indirectness	serious[2]	none	3/118 (2.5%)	9/117 (7.7%)	RR 0.33 (0.09 to 1.19)	52 fewer per 1000 (from 70 fewer to 15 more)	VERY LOW	IMPORTANT
Dissatisfaction 24hrs (NRS<3/10)												
1 (Makela 2019)	randomised trials	very serious[1]	no serious inconsistency	no serious indirectness	very serious[3]	none	3/103 (2.9%)	1/108 (0.93%)	RR 3.15 (0.33 to 29.76)	20 more per 1000 (from 6 fewer to 266 more)	VERY LOW	IMPORTANT
Nausea 4hrs												

Quality assessment							No of patients		Effect		Quality	Importance
No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	IV PCA	Oral	Relative (95% CI)	Absolute		
1 (Makela 2019)	randomised trials	very serious[1]	no serious inconsistency	no serious indirectness	no serious imprecision	none	19/121 (15.7%)	4/125 (3.2%)	RR 4.91 (1.72 to 14.01)	125 more per 1000 (from 23 more to 416 more)	LOW	IMPORTANT
Nausea 8hrs												
1 (Makela 2019)	randomised trials	very serious[1]	no serious inconsistency	no serious indirectness	very serious[3]	none	11/121 (9.1%)	6/120 (5%)	RR 1.82 (0.69 to 4.76)	41 more per 1000 (from 16 fewer to 188 more)	VERY LOW	IMPORTANT
Nausea 24hrs												
1 (Makela 2019)	randomised trials	very serious[1]	no serious inconsistency	no serious indirectness	very serious[3]	none	5/105 (4.8%)	6/110 (5.5%)	RR 0.87 (0.27 to 2.77)	7 fewer per 1000 (from 40 fewer to 97 more)	VERY LOW	IMPORTANT
Vomiting 4hrs												
1 (Makela 2019)	randomised trials	very serious[1]	no serious inconsistency	no serious indirectness	very serious[3]	none	6/105 (5.7%)	2/109 (1.8%)	RR 3.11 (0.64 to 15.09)	39 more per 1000 (from 7 fewer to 259 more)	VERY LOW	IMPORTANT
Vomiting 8hrs												
1 (Makela 2019)	randomised trials	very serious[1]	no serious inconsistency	no serious indirectness	no serious imprecision	none	11/108 (10.2%)	2/108 (1.9%)	RR 5.5 (1.25 to 24.23)	83 more per 1000 (from 5 more to 430 more)	LOW	IMPORTANT
Vomiting 24hrs												
1 (Makela 2019)	randomised trials	very serious[1]	no serious inconsistency	no serious indirectness	serious[2]	none	4/94 (4.3%)	0/97 (0%)	POR 7.88 (1.09 to 56.85)[4]	40 more per 1000 (from 0 more to 90 more)[5]	VERY LOW	IMPORTANT

[1] *High and unclear ROB in multiple domains*
[2] *95%CI crosses one MID boundary (0.8 to 1.25)*
[3] *95%CI crosses two MID boundaries (0.8 to 1.25)*
[4] *Peto OR (POR) used due to rare event rate (0 cases in one arm)*
[5] *calculated from risk difference (RD) as 0 cases in control arm*

Comparison 6: IV PCA versus intramuscular (IM) (meperidine or morphine) for post-caesarean birth (10% general anaesthetic)

Quality assessment							No of patients		Effect		Quality	Importance
No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	IV PCA	IM	Relative (95% CI)	Absolute		
Pain >4/10 (moderate/severe)												
1 (Yost 2004)	randomised trials	very serious [1]	no serious inconsistency	no serious indirectness	very serious[2,3]	none	162/628 (25.8%)	202/628 (32.2%)	RR 0.80 (0.67 to 0.96)	64 fewer per 1000 (from 13 fewer to 106 fewer)	VERY LOW	CRITICAL
Breastfeeding established												
1 (Yost 2004)	randomised trials	very serious [1]	no serious inconsistency	no serious indirectness	serious[2]	none	479/628 (76.3%)	474/628 (75.5%)	RR 1.01 (0.95 to 1.08)	8 more per 1000 (from 38 fewer to 60 more)	VERY LOW	IMPORTANT
Breastfeeding discontinued												
1 (Yost 2004)	randomised trials	very serious [1]	no serious inconsistency	no serious indirectness	very serious[2,4]	none	7/628 (1.1%)	9/628 (1.4%)	RR 0.78 (0.29 to 2.08)	3 fewer per 1000 (from 10 fewer to 15 more)	VERY LOW	IMPORTANT
Satisfaction (satisfied/strongly)												
1 (Yost 2004)	randomised trials	very serious [1]	no serious inconsistency	no serious indirectness	serious[3]	none	520/628 (82.8%)	542/628 (86.3%)	RR 0.96 (0.92 to 1.01)	35 fewer per 1000 (from 69 fewer to 9 more)	VERY LOW	IMPORTANT

[1] *High ROB in multiple domains*
[2] *Downgraded once for cluster randomisation without adjustment information*
[3] *95%CI crosses one MID boundary (0.8 to 1.25)*
[4] *95%CI crosses two MID boundaries (0.8 to 1.25)*

Comparison 7: Oral fixed timimg versus oral on-demand (tramadol in both arms) for post-caesarean birth

Quality assessment							No of patients		Effect		Quality	Importance
No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Oral fixed	Oral on-demand/ request	Relative (95% CI)	Absolute		
Pain 6hrs (Better indicated by lower values) VAS 0-10												
2 (Sammour 2011; Yefet 2017)	randomised trials	serious[1]	very serious[2]	no serious indirectness	very serious[3]	none	130	130	-	MD 0.37 lower (1.82 lower to 1.08 higher)[4]	VERY LOW	CRITICAL
Pain 12hrs (Better indicated by lower values) VAS 0-10												
2 (Sammour 2011; Yefet 2017)	randomised trials	serious[1]	no serious inconsistency	no serious indirectness	no serious imprecision[5]	none	130	130	-	MD 1.22 lower (1.51 to 0.93 lower)	MODERATE	CRITICAL
Pain 18hrs (Better indicated by lower values) VAS 0-10												
1 (Yefet 2017)	randomised trials	serious[1]	no serious inconsistency	no serious indirectness	no serious imprecision[6]	none	100	100	-	MD 1.32 lower (1.67 to 0.97 lower)	MODERATE	CRITICAL
Pain 24hrs (Better indicated by lower values) VAS 0-10												
2 (Sammour 2011; Yefet 2017)	randomised trials	serious[1]	very serious[7]	no serious indirectness	very serious[8]	none	130	130	-	MD 0.64 lower (2.25 lower to 0.97 higher)[4]	VERY LOW	CRITICAL
Pain 30hrs (Better indicated by lower values) VAS 0-10												
1 (Yefet 2017)	randomised trials	serious[1]	no serious inconsistency	no serious indirectness	no serious imprecision[9]	none	100	100	-	MD 1.76 lower (2.09 to 1.43 lower)	MODERATE	CRITICAL
Pain 36hrs (Better indicated by lower values) VAS 0-10												

Quality assessment							No of patients		Effect		Quality	Importance
No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Oral fixed	Oral on-demand/ request	Relative (95% CI)	Absolute		
1 (Yefet 2017)	randomised trials	serious[1]	no serious inconsistency	no serious indirectness	no serious imprecision[10]	none	100	100	-	MD 1.95 lower (2.31 to 1.59 lower)	MODERATE	CRITICAL
Pain 42hrs (Better indicated by lower values) VAS 0-10												
1 (Yefet 2017)	randomised trials	serious[1]	no serious inconsistency	no serious indirectness	no serious imprecision[11]	none	100	100	-	MD 1.97 lower (2.32 to 1.62 lower)	MODERATE	CRITICAL
Pain 48hrs (Better indicated by lower values) VAS 0-10												
1 (Sammour 2011)	randomised trials	serious[1]	no serious inconsistency	no serious indirectness	serious[12]	none	30	30	-	MD 0.5 lower (1.54 lower to 0.54 higher)	LOW	CRITICAL
Satisfaction (Better indicated by higher values) VAS 0-10												
1 (Yefet 2017)	randomised trials	serious[1]	no serious inconsistency	no serious indirectness	serious[13]	none	91	99	-	MD 0.8 higher (0.42 to 1.18 higher)	LOW	IMPORTANT

[1] High and unclear ROB in one domain in each study
[2] i2=83% (random effects model)
*[3] 95%CI crosses two MID boundaries; MID=+/-0.5*1.545 (SD in on-demand group)*
[4] random effects model
*[5] MID=+/-0.5*1.57 (SD in on-demand group)*
*[6] MID=+/-0.5*0.83 (SD in on-demand group)*
[7] i2=85% (random effects model)
*[8] 95%CI crosses two MID boundaries; MID=+/-0.5*1.565 (SD in on-demand group)*
*[9] MID=+/-0.5*0.91 (SD in on-demand group)*
*[10] MID=+/-0.5*0.88 (SD in on-demand group)*
*[11] MID=+/-0.5*0.96 (SD in on-demand group)*

[12] *95%CI crosses one MID boundary; MID=+/-0.5*2.1 (SD in on-demand group)*
[13] *95%CI crosses one MID boundary; MID=+/-0.5*1.5 (SD in on-demand group)*

Comparison 8: Oral versus IM (morphine in both arms) for post-caesarean birth

Quality assessment							No of patients		Effect		Quality	Importance
No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Oral	IM	Relative (95% CI)	Absolute		
Pain day 1 (Better indicated by lower values) VAS 0-10												
1 (Snell 2006)	randomised trials	very serious [1]	no serious inconsistency	no serious indirectness	serious[2]	none	33	33	-	MD 5.2 higher (2.82 lower to 13.22 higher)	VERY LOW	CRITICAL
Pain day 2 (Better indicated by lower values) VAS 0-10												
1 (Snell 2006)	randomised trials	very serious [1]	no serious inconsistency	no serious indirectness	serious[3]	none	33	33	-	MD 4.7 higher (3.76 lower to 13.16 higher)	VERY LOW	CRITICAL
Satisfaction >7/10												
1 (Snell 2006)	randomised trials	very serious [1]	no serious inconsistency	no serious indirectness	serious[4]	none	12/14 (85.7 %)	25/26 (96.2%)	RR 0.89 (0.71 to 1.12)	106 fewer per 1000 (from 279 fewer to 115 more)	VERY LOW	IMPORTANT
Nausea day 1												
1 (Snell 2006)	randomised trials	very serious [1]	no serious inconsistency	no serious indirectness	very serious[5]	none	6/33 (18.2 %)	6/33 (18.2%)	RR 1 (0.36 to 2.78)	0 fewer per 1000 (from 116 fewer to 324 more)	VERY LOW	IMPORTANT
Nausea day 2												
1 (Snell 2006)	randomised trials	very serious [1]	no serious inconsistency	no serious indirectness	very serious[5]	none	1/33 (3%)	0/33 (0%)	POR 7.39 (0.15 to 372.38)[6]	30 more per 1000 (from 50 fewer to 110 more)[7]	VERY LOW	IMPORTANT
Vomiting day 1												
1 (Snell 2006)	randomised trials	very serious [1]	no serious inconsistency	no serious indirectness	very serious[5]	none	5/33 (15.2 %)	5/33 (15.2%)	RR 1 (0.32 to 3.13)	0 fewer per 1000 (from 103 fewer to 323 more)	VERY LOW	IMPORTANT
Vomiting day 2												
1 (Snell 2006)	randomised trials	very serious [1]	no serious inconsistency	no serious indirectness	very serious[5]	none	3/33 (9.1%)	0/33 (0%)	POR 7.87 (0.79 to 78.44)[6]	90 more per 1000 (from 20 fewer to 200 more)[7]	VERY LOW	IMPORTANT

[1] *High and unclear ROB in multiple domains*
[2] *95%CI crosses one MID boundary; MID=+/-0.5*13.1 (SD in IM group)*
[3] *95%CI crosses one MID boundary; MID=+/-0.5*12.5 (SD in IM group)*

[4] *95%CI crosses one MID boundary (0.8 to 1.25)*
[5] *95%CI crosses two MID boundaries (0.8 to 1.25)*
[6] *Peto OR (POR) used due to rare event (0 cases in one arm)*
[7] *calculated using risk difference as 0 cases in control arm*

COMPLEX (MULTIPLE) INTERVENTIONS

Comparison 9: IV morphine versus oral oxycodone for post-caesarean birth

Quality assessment							No of patients		Effect			
No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	IV opiate-morphine	Oral opioid-oxycodone	Relative (95% CI)	Absolute	Quality	Importance
Pain 6hrs (measured with: VAS/NRS 0-10 (0 no pain, 10 worst pain); Better indicated by lower values)												
2 (Davis 2006; Niklasson 2015)	randomised trials	very serious[1]	no serious inconsistency	no serious indirectness	serious[2]	none	86	84	-	MD 1.06 higher (0.53 to 1.6 higher)	VERY LOW	CRITICAL
SUBGROUP: Pain 6hrs - Nurse administered (morphine) (measured with: VAS/NRS 0-10 (0 no pain, 10 worst pain); Better indicated by lower values)												
1 (Niklasson 2015)	randomised trials	serious[3]	no serious inconsistency	no serious indirectness	serious[4]	none	39	38	-	MD 1.16 higher (0.49 to 1.83 higher)	LOW	CRITICAL
SUBGROUP: Pain 6hrs - IV PCA (morphine) (measured with: VAS/NRS 0-10 (0 no pain, 10 worst pain); Better indicated by lower values)												
1 (Davis 2006)	randomised trials	serious[3]	no serious inconsistency	no serious indirectness	serious[5]	none	47	46	-	MD 0.9 higher (0.02 to 1.78 higher)	LOW	CRITICAL
Pain 24hrs (measured with: VAS/NRS 0-10 (0 no pain, 10 worst pain); Better indicated by lower values)												
2 (Davis 2006; Niklasson 2015)	randomised trials	very serious[1]	no serious inconsistency	no serious indirectness	serious[6]	none	86	84	-	MD 0.81 higher (0.29 to 1.32 higher)	VERY LOW	CRITICAL
SUBGROUP: Pain 24hrs - Nurse administered (morphine) (measured with: VAS/NRS 0-10 (0 no pain, 10 worst pain); Better indicated by lower values)												
1 (Niklasson 2015)	randomised trials	serious[3]	no serious inconsistency	no serious indirectness	serious[7]	none	39	38	-	MD 0.5 higher (0.19 lower to 1.19 higher)	LOW	CRITICAL
SUBGROUP: Pain 24hrs - IV PCA (morphine) (measured with: VAS/NRS 0-10 (0 no pain, 10 worst pain); Better indicated by lower values)												
1 (Davis 2006)	randomised trials	serious[3]	no serious inconsistency	no serious indirectness	serious[8]	none	47	46	-	MD 1.2 higher (0.42 to	LOW	CRITICAL

Quality assessment							No of patients		Effect			
No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	IV opiate-morphine	Oral opioid-oxycodone	Relative (95% CI)	Absolute	Quality	Importance
										1.98 higher)		
Pain 48hrs - Nurse administered (morphine) (measured with: VAS/NRS 0-10 (0 no pain, 10 worst pain); Better indicated by lower values)												
1 (Niklasson 2015)	randomised trials	serious[3]	no serious inconsistency	no serious indirectness	serious[9]	none	39	38	-	MD 0.91 higher (0.08 to 1.74 higher)	LOW	CRITICAL
Nausea 6hrs - IV PCA (morphine) (measured with: VAS 0-10; Better indicated by lower values)												
1 (Davis 2006)	randomised trials	serious[3]	no serious inconsistency	no serious indirectness	no serious imprecision [10]	none	47	46	-	MD 1.8 higher (0.79 to 2.81 higher)	MODERATE	IMPORTANT
Nausea 24hrs - IV PCA (morphine) (measured with: VAS 0-10; Better indicated by lower values)												
1 (Davis 2006)	randomised trials	serious[3]	no serious inconsistency	no serious indirectness	serious[11]	none	47	46	-	MD 0.7 lower (1.4 lower to 0 higher)	LOW	IMPORTANT
Pruritus 6hrs - IV PCA (morphine) (measured with: VAS 0-10; Better indicated by lower values)												
1 (Davis 2006)	randomised trials	serious[3]	no serious inconsistency	no serious indirectness	serious[12]	none	47	46	-	MD 0.8 higher (0.1 lower to 1.7 higher)	LOW	IMPORTANT
Pruritus 24hrs - IV PCA (morphine) (measured with: VAS 0-10; Better indicated by lower values)												
1 (Davis 2006)	randomised trials	serious[3]	no serious inconsistency	no serious indirectness	no serious imprecision [13]	none	47	46	-	MD 0.1 higher (0.74 lower to 0.94 higher)	MODERATE	IMPORTANT

[1] *High and unclear ROB in at least one domain in all studies*
[2] *95%CI crosses one MID boundary; MID=+/-0.5*1.66 (SD in oral oxycodone group)*
[3] *High and unclear ROB in one domain*
[4] *95%CI crosses one MID boundary; MID=+/-0.5*1.52 (SD in oral oxycodone group)*
[5] *95%CI crosses one MID boundary; MID=+/-0.5*1.8 (SD in oral oxycodone group)*
[6] *95%CI crosses one MID boundary; MID=+/-0.5*1.66 (SD in oral oxycodone group)*
[7] *95%CI crosses one MID boundary; MID=+/-0.5*1.74 (SD in oral oxycodone group)*
[8] *95%CI crosses one MID boundary; MID=+/-0.5*1.7 (SD in oral oxycodone group)*

[9] *95%CI crosses one MID boundary; MID=+/-0.5*1.88 (SD in oral oxycodone group)*
[10] *MID=+/-0.5*0.9 (SD in oral oxycodone group)*
[11] *95%CI crosses one MID boundary; MID=+/-0.5*2.3 (SD in oral oxycodone group)*
[12] *95%CI crosses one MID boundary; MID=+/-0.5*1.9 (SD in oral oxycodone group)*
[13] *MID=+/-0.5*2.3 (SD in oral oxycodone group)*

Comparison 10: IV PCA meperidine versus IM morphine for post-caesarean birth (10% general anaesthetic)

Quality assessment							No of patients		Effect		Quality	Importance
No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	IV PCA opioid (meperidine)	IM opiate (morphine)	Relative (95% CI)	Absolute		
Pain >4/10 (moderate/severe)												
1 (Yost 2004)	randomised trials	very serious[1]	no serious inconsistency	no serious indirectness	very serious[2,3]	none	100/319 (31.3%)	70/322 (21.7%)	RR 1.44 (1.11 to 1.88)	96 more per 1000 (from 24 more to 191 more)	VERY LOW	CRITICAL
Breastfeeding established												
1 (Yost 2004)	randomised trials	very serious[1]	no serious inconsistency	no serious indirectness	serious[2]	none	233/319 (73%)	243/322 (75.5%)	RR 0.97 (0.88 to 1.06)	23 fewer per 1000 (from 91 fewer to 45 more)	VERY LOW	IMPORTANT
Breastfeeding discontinued												
1 (Yost 2004)	randomised trials	very serious[1]	no serious inconsistency	no serious indirectness	very serious[2,4]	none	6/319 (1.9%)	1/322 (0.31%)	RR 6.06 (0.73 to 50.02)	16 more per 1000 (from 1 fewer to 152 more)	VERY LOW	IMPORTANT
Satisfaction (satisfied/strongly)												
1 (Yost 2004)	randomised trials	very serious[1]	no serious inconsistency	no serious indirectness	serious[2]	none	266/319 (83.4%)	290/322 (90.1%)	RR 0.93 (0.87 to 0.98)	63 fewer per 1000 (from 18 fewer to 117 fewer)	VERY LOW	IMPORTANT

[1] *High ROB in multiple domains*
[2] *Downgraded once for cluster randomisation without adjustment information*
[3] *95%CI crosses one MID boundary (0.8 to 1.25)*
[4] *95%CI crosses two MID boundaries (0.8 to 1.25)*

Comparison 11: IV PCA morphine versus IM meperidine for post-caesarean birth (10% general anaesthetic)

Quality assessment							No of patients		Effect		Quality	Importance
No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	IV PCA opiate (morphine)	IM opioid (meperidine)	Relative (95% CI)	Absolute		
Pain >4/10 (moderate/severe)												
1 (Yost 2004)	randomised trials	very serious[1]	no serious inconsistency	no serious indirectness	serious[2]	none	62/309 (20.1%)	132/306 (43.1%)	RR 0.47 (0.36 to 0.6)	229 fewer per 1000 (from 173 fewer to 276 fewer)	VERY LOW	CRITICAL
Breastfeeding established												
1 (Yost 2004)	randomised trials	very serious[1]	no serious inconsistency	no serious indirectness	serious[2]	none	246/309 (79.6%)	231/306 (75.5%)	RR 1.05 (0.97 to 1.15)	38 more per 1000 (from 23 fewer to 113 more)	VERY LOW	IMPORTANT
Breastfeeding discontinued												
1 (Yost 2004)	randomised trials	very serious[1]	no serious inconsistency	no serious indirectness	very serious[2,3]	none	1/309 (0.32%)	8/306 (2.6%)	RR 0.12 (0.02 to 0.98)	23 fewer per 1000 (from 1 fewer to 26 fewer)	VERY LOW	IMPORTANT
Satisfaction (satisfied/strongly)												
1 (Yost 2004)	randomised trials	very serious[1]	no serious inconsistency	no serious indirectness	serious[2]	none	254/309 (82.2%)	252/306 (82.4%)	RR 1 (0.93 to 1.07)	0 fewer per 1000 (from 58 fewer to 58 more)	VERY LOW	IMPORTANT

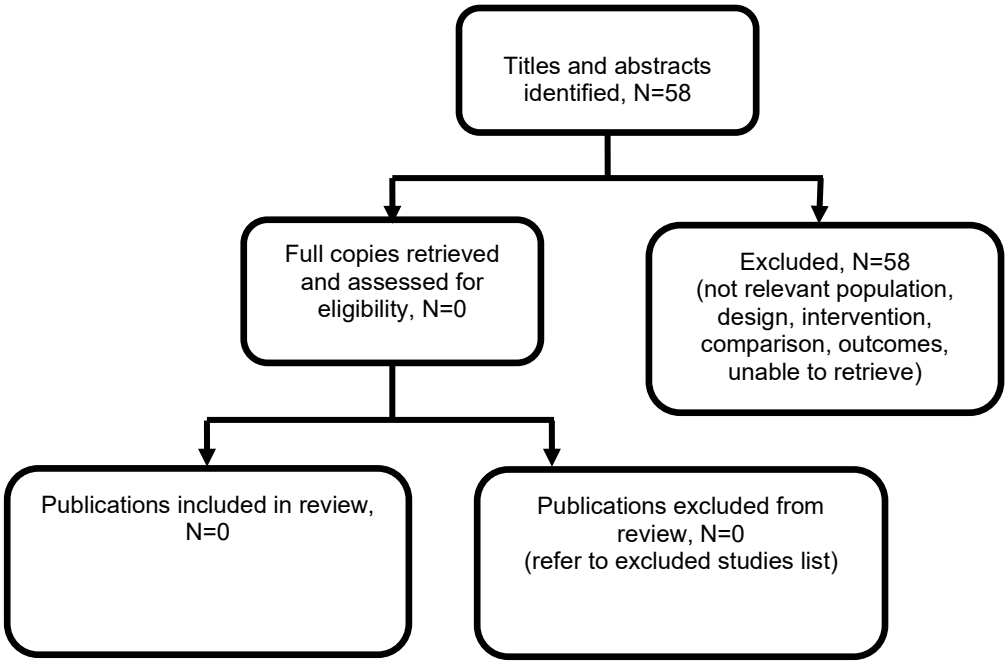
[1] *High ROB in multiple domains*
[2] *Downgraded once for cluster randomisation without adjustment information*
[3] *95%CI crosses one MID boundary (0.8 to 1.25)*

Appendix G – Economic evidence study selection

Economic evidence study selection for review question: Are opioids safe and effective for pain management after caesarean birth?

No economic evidence was identified which was applicable to this review question.

Figure 2: Flow diagram of economic article selection



Appendix H – Economic evidence tables

Economic evidence tables for review question: Are opioids safe and effective for pain management after caesarean birth?

No economic evidence was identified which was applicable to this review question.

Appendix I – Economic evidence profiles

Economic evidence profiles for review question: Are opioids safe and effective for pain management after caesarean birth?

No economic evidence was identified which was applicable to this review question.

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Appendix J – Economic analysis

Economic evidence analysis for review question: Are opioids safe and effective for pain management after caesarean birth?

No health economic analysis was conducted for this review question.

Appendix K – Excluded studies

Excluded studies for review question: Are opioids safe and effective for pain management after caesarean birth?

Clinical studies

Table 5: Excluded studies and reasons for their exclusion

Study	Reason for Exclusion
Abdallah, F. W., Halpern, S. H., Margarido, C. B., Transversus abdominis plane block for postoperative analgesia after Caesarean delivery performed under spinal anaesthesia? A systematic review and meta-analysis, British Journal of Anaesthesia, 109, 679-687, 2012	Systematic review: analyses cannot be used in entirety, included studies checked for inclusion
Abdallah, F. W., Laffey, J. G., Halpern, S. H., Brull, R., Duration of analgesic effectiveness after the posterior and lateral transversus abdominis plane block techniques for transverse lower abdominal incisions: a meta-analysis, British Journal of Anaesthesia, 111, 721-735, 2013	Systematic review: analyses cannot be used in entirety, included studies checked for inclusion
Adeniji, Adetunji Oladeni, Atanda, Oluseyi Olaboyede A., Randomized comparison of effectiveness of unimodal opioid analgesia with multimodal analgesia in post-cesarean section pain management, Journal of pain research, 6, 419-24, 2013	Non-OECD country (Nigeria)
Bang, U., Kristensen, B. S., Pankoke, M., Greisen, J. R., Patient-controlled analgesia (PCA) after caesarean section. Oral morphine vs. intravenous fentanyl. A randomized controlled study, Acta Anaesthesiologica Scandinavica, Supplement, 53, 60, 2009	Conference abstract
Bonnal, A., Dehon, A., Nagot, N., Macloce, V., Nogue, E., Morau, E., Patient-controlled oral analgesia versus nurse-controlled parenteral analgesia after caesarean section: A randomised controlled trial, Anaesthesia, 71, 535-543, 2016	Does not assess opioids for analgesia - paracetamol (acetaminophen), ketoprofen, nefopam only
Caughey, A. B., Wood, S. L., Macones, G. A., Wrench, I. J., Huang, J., Norman, M., Pettersson, K., Fawcett, W. J., Shalabi, M. M., Metcalfe, A., Gramlich, L., Nelson, G., Wilson, R. D., Guidelines for intraoperative care in cesarean delivery: Enhanced Recovery After Surgery Society Recommendations (Part 2), American Journal of Obstetrics and Gynecology, 219, 533-544, 2018	Narrative review and recommendations
Cheung, C. W., Wong, S. S. C., Qiu, Q., Wang, X., Oral oxycodone for acute postoperative pain: A review of clinical trials, Pain Physician, 20, SE33-SE52, 2017	Unavailable at full text
Chi, Xiaohui, Li, Man, Mei, Wei, Liao, Mingfeng, Comparison of patient-controlled intravenous	Non-OECD country (China)

Study	Reason for Exclusion
analgesia with sufentanil versus tramadol in post-cesarean section pain management and lactation after general anesthesia - a prospective, randomized, double-blind, controlled study, Journal of Pain Research, 10, 1521-1527, 2017	
Dieterich, Max, Muller-Jordan, Katja, Stubert, Johannes, Kundt, Gunther, Wagner, Klaus, Gerber, Bernd, Pain management after cesarean: a randomized controlled trial of oxycodone versus intravenous piritramide, Archives of Gynecology and Obstetrics, 286, 859-65, 2012	Compares piritramide to oxycodone (piritramide not listed in protocol, not available in UK)
Duan, Guangyou, Bao, Xiaohang, Yang, Guiying, Peng, Jing, Wu, Zhuoxi, Zhao, Peng, Zuo, Zhiyi, Li, Hong, Patient-controlled intravenous tramadol versus patient-controlled intravenous hydromorphone for analgesia after secondary cesarean delivery: a randomized controlled trial to compare analgesic, anti-anxiety and anti-depression effects, Journal of Pain Research, 12, 49-59, 2019	Non-OECD country (China)
Ebneshahidi, A., Akbari, M., Mohseni, M., Eskandari, S., Mobasherizadeh, S., Heshmati, B., Patient-controlled versus nurse-controlled analgesia after caesarean section, Pain Practice, 12, 127, 2012	Conference abstract
Ebneshahidi, A., Akbari, M., Mohseni, M., Heshmati, B., Morphine, methadone and fentanyl on post-cesarean section pain, European Journal of Pain Supplements, 5, 279-280, 2011	Conference abstract
Eslamian, Laleh, Kabiri-Nasab, Motahareh, Agha-Husseini, Marzieh, Azimaraghi, Omid, Barzin, Gilda, Movafegh, Ali, Adding Sufentanil to TAP Block Hyperbaric Bupivacaine Decreases Post-Cesarean Delivery Morphine Consumption, Acta Medica Iranica, 54, 185-90, 2016	Non-OECD country (Iran)
Gulhas, N., Ozgul, U., Erdil, F., Sanli, M., Nakir, H., Yologlu, S., Durmus, M., Ersoy, M. O., The effect of low-dose ketamine on ephedrine requirement following spinal anesthesia in cesarean sections: A randomised controlled trial, HealthMED, 6, 2870-2876, 2012	Unavailable
Ismail, S., Afshan, G., Monem, A., Ahmed, A., Postoperative analgesia after caesarean section: Comparison of patient controlled analgesia with continuous infusion of pethidine, International Journal of Obstetric Anesthesia, 20, S46, 2011	Conference abstract
Jaafarpour, Molouk, Vasigh, Aminolah, Khajavikhan, Javaher, Khani, Ali, Effect of Ketofol on Pain and Complication after Caesarean Delivery under Spinal Anaesthesia: A Randomized Double-blind Clinical Trial,	Non-OECD country (Iran)

Study	Reason for Exclusion
Journal of clinical and diagnostic research : JCDR, 11, UC04-UC07, 2017	
Jabalameli, M., Aram, S., Parvaresh, M., Comparison of intranasal versus intravenous pethidine for pain relief after cesarean section, Pain Practice, 9, 145, 2009	Conference abstract
Jabalameli, Mitra, Rouholamin, Safoura, Gourtanian, Fatemeh, A comparison of the effects of fentanyl and remifentanil on nausea, vomiting, and pain after cesarean section, Iranian Journal of Medical Sciences, 36, 183-7, 2011	Non-OECD country (Iran)
Javaherforoosh, F., Akhondzadeh, R., Aein, K. B., Olapour, A., Samimi, M., Effects of tramadol on shivering post spinal anesthesia in elective cesarean section, Pakistan journal of medical sciences, 25, 12â□□17, 2009	Non-OECD country (Iran)
John, Roshan, Ranjan, R. V., Ramachandran, T. R., George, Sagiev Koshy, Analgesic Efficacy of Transverse Abdominal Plane Block after Elective Cesarean Delivery - Bupivacaine with Fentanyl versus Bupivacaine Alone: A Randomized, Double-blind Controlled Clinical Trial, Anesthesia, essays and researches, 11, 181-184, 2017	Non-OECD country (India)
Lema, Girmay Fitiwi, Gebremedhn, Endale Gebreegziabher, Gebregzi, Amare Hailekiros, Desta, Yilkal Tadesse, Kassa, Adugna Aregawi, Efficacy of intravenous tramadol and low-dose ketamine in the prevention of post-spinal anesthesia shivering following cesarean section: a double-blinded, randomized control trial, International journal of women's health, 9, 681-688, 2017	Non-OECD country (Ethiopia)
Menkiti, I. D., Desalu, I., Kushimo, O. T., Low-dose intravenous ketamine improves postoperative analgesia after caesarean delivery with spinal bupivacaine in African parturients, International Journal of Obstetric Anesthesia, 21, 217-221, 2012	Non-OECD country (Nigeria)
Mkontwana, Nondumiso, Novikova, Natalia, Oral analgesia for relieving post-caesarean pain, Cochrane Database of Systematic Reviews, 2015	Systematic review: analyses cannot be used in entirety, included studies checked for inclusion - two additional papers located but excluded as non-OECD
Naghibi, K., Lotfi, A., Shafiei, M., Preemptive analgesia using intravenous fentanyl for elective cesarean section under general anesthesia does not have side effects on newborn Apgar, Pain Practice, 9, 128, 2009	Conference abstract
Ngan Kee, W. D., Khaw, K. S., Wong, E. L., Randomised double-blind comparison of morphine vs. a morphine-alfentanil combination for patient-controlled analgesia, Anaesthesia, 54, 629â□□633, 1999	Non-OECD country (China)

Study	Reason for Exclusion
Nie, J. J., Sun, S., Huang, S. Q., Effect of oxycodone patient-controlled intravenous analgesia after cesarean section: A randomized controlled study, Journal of Pain Research, 10, 2649-2655, 2017	Non-OECD (China)
Ortner, C. M., Kimberger, O., Gustorff, B., Patient-controlled oral analgesia following cesarean section: tramadol versus a combination of tramadol and acetaminophen, Acta Obstetricia et Gynecologica Scandinavica, 90, 925â□□926, 2011	Tramadol in both groups; intervention of interest was additional acetaminophen (paracetamol)
Prabhu, M., Dubois, H., James, K., Leffert, L. R., Riley, L. E., Bateman, B. T., Henderson, M., Implementation of a quality improvement initiative to decrease opioid prescribing after cesarean delivery, Obstetrics and Gynecology, 132, 631â□□636, 2018	Focus on counselling, with shared decision making, for patient controlled analgesia
Rahmanian, M., Leysi, M., Hemmati, A. A., Mirmohammadkhani, M., The effect of low-dose intravenous ketamine on postoperative pain following cesarean section with spinal anesthesia: A randomized clinical trial, Oman Medical Journal, 30, 11-16, 2015	Non-OECD country (Iran)
Safavi, M., Honarmand, A., Postoperative analgesia after caesarean section: intermittent intramuscular versus subcutaneous morphine boluses, Acute pain, 9, 215â□□219, 2007	Non-OECD country (Iran)
Schoenwald, Anthony, Windsor, Carol, Gosden, Edward, Douglas, Clint, Nurse practitioner led pain management the day after caesarean section: A randomised controlled trial and follow-up study, International journal of nursing studies, 78, 1-9, 2018	Irrelevant comparison; compares oral drug administered immediately vs slow release. Intervention arm also includes additional education for the patient
Shahraki, Azar Danesh, Jabalameli, Mitra, Ghaedi, Somayeh, Pain relief after cesarean section: Oral methadone vs. intramuscular pethidine, Journal of research in medical sciences : the official journal of Isfahan University of Medical Sciences, 17, 143-7, 2012	Non-OECD country (Iran)
Sharawi, Nadir, Carvalho, Brendan, Habib, Ashraf S., Blake, Lindsay, Mhyre, Jill M., Sultan, Pervez, A Systematic Review Evaluating Neuraxial Morphine and Diamorphine-Associated Respiratory Depression After Cesarean Delivery, Anesthesia and Analgesia, 127, 1385-1395, 2018	Review of prevalence and incidence reporting in all studies using neuraxial morphine/ diamorphine in c-section. Relevant references checked for inclusion.
Singh, V., Singh, V. P., Shankar, R. R., POST OPERATIVE PAIN RELIEF IN CAESAREAN SECTION, Medical journal, Armed Forces India, 57, 31-4, 2001	Non-OECD country (India)
Sunshine, A., Olson, N. Z., Zighelboim, I., De Castro, A., Ketoprofen, acetaminophen plus oxycodone, and acetaminophen in the relief of postoperative pain, Clinical Pharmacology and Therapeutics, 54, 546â□□555, 1993	Study conducted in non-OECD country (Venezuela)

Study	Reason for Exclusion
Sunshine, A., Olson, N. Z., Zighelboim, I., DeCastro, A., Minn, F. L., Analgesic oral efficacy of tramadol hydrochloride in postoperative pain, Clinical Pharmacology and Therapeutics, 51, 740â□□746, 1992	Study conducted in non-OECD country (Venezuela)

Economic studies

No economic evidence was identified for this review.

Appendix L – Research recommendations

Research recommendations for review question: Are opioids safe and effective for pain management after caesarean birth?

No research recommendations were made for this review question.